

# CORNEAL CROSSLINKING- WHAT SHOULD AN OPTOMETRIST KNOW

Pinakin Davey OD, PhD, FAAO, FOWNS  
Professor Of Optometry  
WesternU Director of Clinical Research

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## LEARNING OBJECTIVES

- Recollect basics of Keratoconus
- Know cornea signs of Keratoconus
- Understand the principles behind crosslinking
- Understand the FDA approved protocols
- Understand research behind crosslinking - epithelium off versus epithelium on
- Understand the accelerated protocol

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## RISK FACTORS

- Down syndrome
- relatives of affected patients especially if they are young
- ocular allergy
- ethnic factors
- mechanical factors, eg, eye rubbing
- floppy eyelid syndrome
- atopy
- connective tissue disorders (Marfan syndrome)
- Ehlers-Danlos syndrome
- Leber congenital amaurosis

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## DISCLOSURES

Has a relevant financial relationship with Sanofi, Optovue, ZeaVision, Haag Streit, Vector Vision/ Guardian Health and Innova systems as a speaker or research / consultant

The content and format of this course is presented without commercial bias and does not claim superiority and commercial product or service.

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## KERATOCONUS

- Keratoconus is a
  - progressive
  - bilateral ("true unilateral keratoconus does not exist." Global consensus)
  - asymmetric
  - ectatic disease
  - progressive corneal thinning
  - protrusion of the cornea leading to irregular astigmatism
  - visual deterioration
- Incidence 1 in 2000 (probably underestimated)
- Prevalence 0.054% USA Worldwide Big range 0.0003% to 2.3%

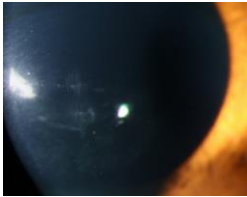
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## SPOT THE PATHOLOGY



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**NAME THE PATHOLOGY**



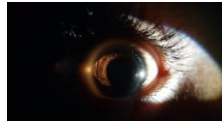
**Vogt's striae**

- Stress lines in deep stroma and Descemet's membrane
- Can disappear upon application of mild pressure to lower eyelid



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**NAME THE SIGN**



Rizzuti's sign

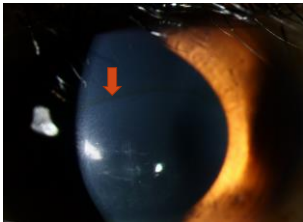
Sharply focused beam of light near nasal limbus

Usually, advanced keratoconus



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**NAME THE SIGN**



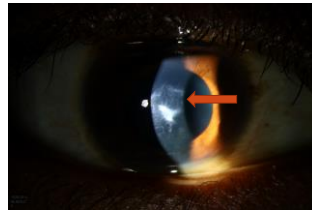
**Fleisher's ring**

- Iron deposit on epithelium
- Cobalt blue filter might help identifying subtle lines



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**WHAT IS THIS?**



- Opacities/scars
- Ruptures in Bowmans produces subepithelial or anterior stromal scars



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**NAME THE SIGN**

**Charlouex's oil droplet reflex**

- Total internal reflection in conical cornea
- Dark shadow around mid periphery
- The dark shadow separates central bright red fundus reflex from red reflex in periphery
- Don't confuse it with galactosemia cataract-oil droplet opacity in lens



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**KERATOCONUS PATIENT ON SLIT LAMP**



- Thin cornea at apex
- Increased endothelial reflection



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### NAME THE SIGN

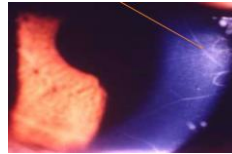
▪ Munson's sign



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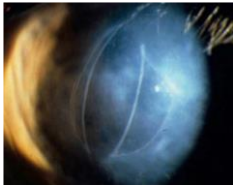
### WHAT'S THIS?

▪ Prominent corneal nerves



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### OCCURRED SUDDENLY

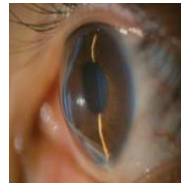


Acute hydrops

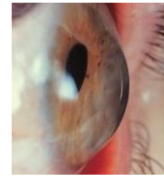
- Rupture of Descemet's membrane
- Sudden onset of redness and pain
- Sudden imbibition of aqueous humor into cornea
- Stromal edema

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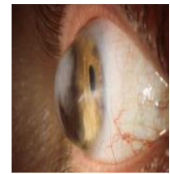
### TYPES OF CONE



Round cone



Oval cone



Globus cone

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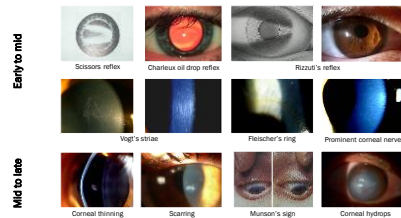
### NATURAL HISTORY

- Keratoconus natural history:
  - Scarring
    - Overall: 14%
    - CL wear: 17%
    - CL wear & K >52D: 38%
  - Hydrops: 2.5%
  - Keratoplasty: 15-21.6%



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### CLINICAL FINDINGS IN KERATOCONUS

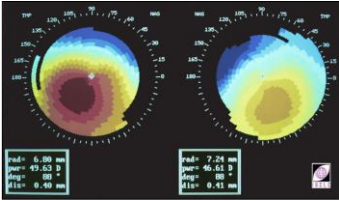


Picture: *Statens Eye Center, Oslo, NO*

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## CLINICAL FINDINGS IN KERATOCONUS

• Example topography findings



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## CLASSIFICATION SYSTEMS

### Various systems

1. **Amsler-Krumeich** (gives stages)
  - K-readings, corneal shape (e-value), refraction, pachymetry, corneal scarring
2. **Keratometry only** (gives stages)
  - K-readings and mire quality
3. **Morphology only** (gives description)
  - Cone shape
4. **Corneal topography** (gives likelihood of having KC)
  - Kerato-refractive indices and predictive analysis

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## CLASSIFICATION SYSTEMS

### 1. Amsler-Krumeich



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Stage	Findings
1	Eccentric steepening Myopia, induced astigmatism, or both <5.00 D K <sub>central</sub> <48.00 D
2	Myopia, induced astigmatism, or both from 5.00 to 8.00 D K <sub>central</sub> <53.00 D Absence of scarring Corneal thickness >400 microns
3	Myopia, induced astigmatism, or both from 8.00 to 10.00 D K <sub>central</sub> >53.00 D Absence of scarring Corneal thickness 300 - 400 microns
4	Refraction not measurable K <sub>central</sub> >55.00 D Central corneal scarring Corneal thickness < 200 microns

• Retinal-like changes of keratoconus from pigments  
Source: Amsler-Krumeich, Ophthalmologica, 1988; Fuchs  
Munich 1102-0298-011

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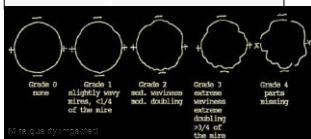
## CLASSIFICATION SYSTEMS

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## CLASSIFICATION SYSTEMS

### 2. Keratometry only

Stage	K <sub>central</sub> Findings
Mild	< 48.00 D
Moderate	48.00 D to 54.00 D
Severe	> 54.00 D



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### 3. Morphology only

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# CLASSIFICATION SYSTEMS

## 3. Morphology only

Description	Morphology Findings
Nipple cone	Central location, diameter < 5 mm
Oval (sagging) cone	Diameter 5 to 6 mm
Globus cone	Diameter > 6 mm

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# CORNEAL TOPOGRAPHY CLASSIFICATION SYSTEMS

• Rabinowitz (1999), KC screening

- K >47.20D
- I-S >1.40D
- AST >1.50D
- SRAX >21°
- KISA% >100%

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# CLASSIFICATION SYSTEMS

## 3. Corneal topography

• Rabinowitz (1999), KC screening

$$KISA\% = \frac{(K) \times (I - S) \times (AST) \times (SRAX) \times 100}{300}$$

- K = central keratometry value
- I - S = (inferior) minus (superior) diopter value
- SRAX = skewing of the radial axes
- AST = keratometric astigmatism ( $\Delta K$ )
- \*all values absolute

60-100 KC suspect  
> 100 highly sensitive in identifying KC

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# CLASSIFICATION SYSTEMS

## 3. Corneal topography

• Medmont E-300

Medmont output	What is it?	Abnormal
Axial curvature range	Flattest to steepest curvature range	>10.00D
e value	Corneal flattening from center to periphery	>0.80
I-S Index	Difference between average inferior and superior power	>1.40D
SAI	Surface Asymmetry Index (corneal power distribution)	>0.8
SRI	Surface Regularity Index (central corneal irregularity)	>1.0

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# CLASSIFICATION SYSTEMS

## 3. Corneal topography

• Medmont E-300

Normalized Axial Curvature Range > 10.00 D indicates KC  
This cornea: ≈18.00D

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# CLASSIFICATION SYSTEMS

## 3. Corneal topography

• Zeiss Atlas 9000

- Pathfinder II module
- Evaluates cornea for several conditions, including KC
- Predictive analysis uses:
  - Corneal Irregularity Measurement
  - Toric Keratometric Mean
  - Shape factor (e-value square)

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## CROSS LINKING INDICATION

- Progressing keratoconus or post-LASIK ectasia
- Definition of progression is variable
  - Global consensus series
    - At least 2 of these
      - Steepening of the anterior corneal surface
      - Steepening of the posterior corneal surface
      - Thinning and/or an increase in the rate of corneal thickness change

Clinical trials have used these criteria

Steepest keratometry ( $K_{max}$ )	>1 D increase from baseline
Flattest keratometry ( $K_{min}$ )	>1 D increase from baseline
Mean keratometry ( $K_{mean}$ )	>0.75 D Increase from baseline
Corneal apex power	>1 D increase from baseline
Manifest spherical equivalent	>0.5 D difference from baseline
Central corneal thickness	>2% decrease from baseline

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## IDEAL CANDIDATE & WHO CAN WE RECOMMEND?

- Young patient (<30 years usually)
- Why ?
- BCVA worse than 20/20 (Spectacle or CL)
- Refraction:
  - Increase of  $\geq 1$  D in manifest cylinder
  - Increase of  $\geq 0.5$  D in manifest spherical equivalent
- Imaging:
  - Tomography: Steepening of anterior or posterior corneal surface, corneal thinning
  - OCT: evidence of progression in stromal thickness.

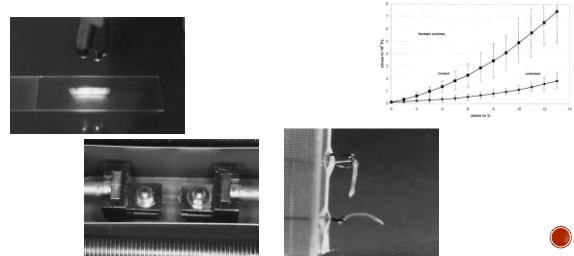
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## WHAT IS CROSSLINKING?

- The term "crosslink" derives from the assumption of creating new covalent links between collagen fibers in the stroma.
- Specifically, covalent chemical bonds between the amino terminals of the collagen side chains and the proteoglycans of the extracellular matrix.
- This can occur naturally in eye –glucose from aqueous humor along with exposure to sun

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## EFFECTS OF CROSSLINKING?



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**CROSSLINKING DRESDEN PROTOCOL-FDA APPROVED**

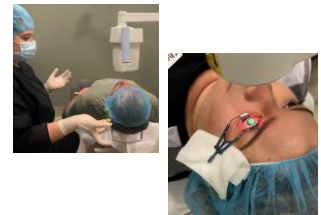
- Epithelium removal
- 8-10 mm

Video courtesy Dr. Amir Marvasti Coastal Vision

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## CROSSLINKING DRESDEN PROTOCOL-FDA APPROVED

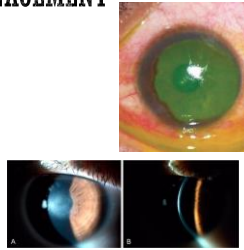
- Riboflavin 0.146% + 20% Dextran application before and during UVA radiation
- UVA radiation is 370 nm
- 3mW/cm<sup>2</sup>
- Exposure for 30 minutes
- Every 5-minutes apply (Riboflavin 0.146% + 20% Dextran )
- Total energy 5.4J/cm<sup>2</sup>



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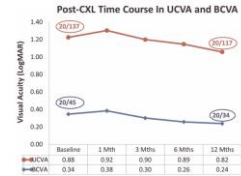
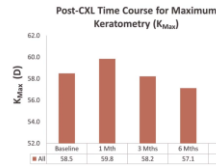
## POST OPERATIVE MANAGEMENT

- Epithelial healing
  - Delayed epithelial healing
  - Infectious keratitis
- Topical steroid
  - 1-2 month tapering schedule
  - Medical management of IOP if necessary
- Corneal haze
  - Up to 80% will have some degree of it
  - Typically resolves in 6-12 months



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## CROSSLINKING RESULTS



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## DOES IT ALL BECOME ALRIGHT?

### UCVA

- No change: 51%
- Improve: 31%
- Decline: 18%

### BCVA

- No change: 47%
- Improve: 45%
- Decline: 8%

### Kmax

- No change: 39%
- Decrease: 51%
- Increase: 10%

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## CONTRAINDICATIONS

- Acute hydrops
- Total corneal thickness < 365 microns
- Relative contraindications:
  - Herpetic keratitis
  - Significant scarring
  - Pregnancy
  - Lactation
  - Autoimmune disease

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## PATIENT EDUCATION

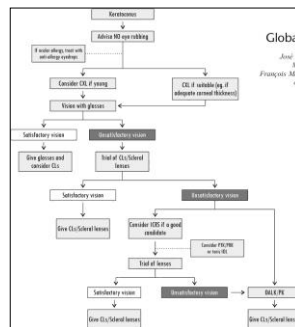
1. CXL will slow or stop the disease, it will not reverse it.
2. Glasses or contact lenses will still be needed after the procedure.
3. Vision might worsen before it improves.
4. Prescription might change up to 1 year after CXL.
5. You still need to be monitored after CXL for progression.



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## Global Consensus on Keratoconus and Ectatic Diseases

*Andr  A. P. Gomes, MD, PhD,\* Donald Tan, MD, PhD,† Christopher J. Rapuano, MD,‡ Michael W. Belin, MD,‡ Renato Ambrosio, Jr, MD, PhD,§ Joel L. Greer, MD,|| Francisco Maldonado, MD, PhD,\*\* Jorge Nickola, MD,†† and Vladimir S. Stojanovic, MD,‡‡ the Group of Panelists for the Global Digital Panel of Keratoconus and Ectatic Diseases*

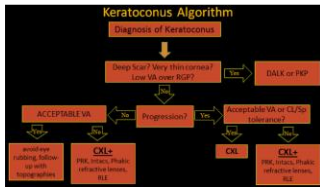


- ICRS intrastromal corneal rings
- DALK Deep anterior lamellar keratoplasty
- PK penetrating keratoplasty
- CL contact lenses
- SP spectacles

(Cornea 2015;34:359-369)

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## KERATOCONUS TREATMENT ALGORITHM



DALK Deep anterior lamellar keratoplasty  
 PKP penetrating keratoplasty  
 CL contact lenses  
 SP spectacles  
 PRK photorefractive keratectomy  
 RLE Refractive lens exchange

Optimised Ther (2017) 6:245-262

## ACCELERATED CROSS LINKING (NOT FDA APPROVED)

- Bunsen-Roscoe law of photochemical reciprocity
- Same photochemical effect can be achieved by delivering a similar total energy over a shorter period of time

- Avedro KXL
- 30mW/cm<sup>2</sup>
- 3 minute exposure
- Total energy on cornea 5.4J/cm<sup>2</sup>
- Effective at halting keratoconus
- Did not induce changes to corneal transparency
- Endothelial cell density
- Central foveal thickness

ORIGINAL ARTICLE

### Efficacy and Safety of Accelerated Corneal Cross-linking for Progressive Keratoconus: A 5-Year Follow-up Study

Ahmed M. Mousa, MD, Valentin M. Moshirfegh, MD, Maria Cristina Romano, MD, Dasha Kozlov, MD, Laura Breglio, MD, Luigi Fontana, MD, PhD

J Refract Surg. 2020;36(11):724-730.

## EPITHELIUM ON CROSSLINKING (NOT FDA APPROVED)

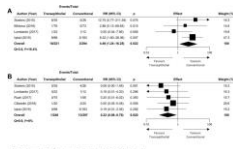
- Epithelium left intact, no pain
- Possibly prevents corneal crosslinking complications?
- BAK+ ethyldiaminetetraacetic acid+ tetracaine to increase riboflavin diffusion
- Iontophoresis assisted corneal crosslinking



Ophthalmology  
 Accepted March 20, 2020. © 2020

Transepithelial versus epithelium-off corneal collagen cross-linking for corneal ectasia: a systematic review and meta-analysis

Conclusions: The efficacy of transepithelial CXL remains inferior to the epithelium-off approach, although it is significantly safer.



A- Disease progression B -Complications