

# CORNEAL CROSS LINKING FOR MICROBIAL KERATITIS

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## INTRODUCTION

- THE CURRENT MAINSTAY OF MICROBIAL KERATITIS TREATMENT IS THE USE OF LOCAL ANTIBIOTICS
- HOWEVER THE TREATMENT TAKES TIME AND IS ASSOCIATED WITH POTENTIALLY SERIOUS OCULAR SURFACE TOXICITY AND MICROBIAL RESISTANCE
- SINCE 2000, THE USE OF CXL HAS BEEN EXTENDED TO THE TREATMENT OF MICROBIAL KERATITIS AS FORM OF ADJUNCTIVE TREATMENT – PHOTOACTIVATED CHROMOPHORES FOR CROSS-LINKING (PACK-CXL)

## PRINCIPLE:

- THE PHOTODYNAMIC PROCEDURE OF RIBOFLAVIN WITH UV-A HAS BEEN USED TO **INACTIVATE VIRUSES, BACTERIA AND PARASITES** IN THE MEDICAL FIELD FOR SOME TIME

( GOODRICH ET AL. 2006; MARSCHNER & GOODRICH 2011).

- PHOTOACTIVATED RIBOFLAVIN CAN INDUCE **CHROMOSOMAL DAMAGES** IN MICRO-ORGANISMS THROUGH OXIDATIVE PROCESSES

(KUMAR ET AL. 2004; RUANE ET AL. 2004).

- MOREOVER, THE ULTRAVIOLET IRRADIATION ITSELF HAS **SPORICIDAL** AND **VIRUCIDAL** EFFECTS

(RUSSEL 1999).

## MAJOR QUESTIONS :

- WHAT IS THE **BASIS** FOR USE OF CXL IN CORNEAL INFECTIONS?
- CAN IT BE USED AS **SOLE** TREATMENT OR IN **COMBINATION** WITH ANTIBIOTICS ?
- ASSESSING ITS **EFFICACY** AND **SAFETY** ?
- WHAT **TYPE** OF MICROBIAL KERATITIS CAN BE TREATED WITH PACK-CXL?
- WHEN IS THE **OPTIMUM TIME** FOR TREATING MICROBIAL KERATITIS WITH PACK-CXL?

## WHAT IS THE BASIS FOR THE USE OF CXL IN CORNEAL INFECTIONS?

**MECHANISM OF ACTION:** NOT FULLY KNOWN

- PHOTO-ACTIVATION OF A CHROMOPHORE CAN RELEASE **REACTIVE OXYGEN** SPECIES AND ACTS AS DISINFECTANT.
- **OXIDATION** OF PATHOGEN DNA AND RNA
- **ROS** DAMAGE OF PATHOGEN **CELL WALLS**
- INCREASED CORNEAL **STIFFNESS** AND RESISTANCE TO ENZYMATIC DIGESTION
- KILLING OF INFLAMMATORY AND **IMMUNE CELLS** (APOPTOSIS)

## TECHNIQUE:

- **STANDARD DRESDEN PROTOCOL** MOST COMMONLY USED
- **EPITHELIUM-OFF**
- APPLICATION OF ISOTONIC RIBOFLAVIN FOR **30 MINUTES** (5 MINUTE INTERVALS)
- 365-NM UVA LIGHT EXPOSURE (3MW/CM<sup>2</sup>) FOR 30 MINUTES
- **ANTERIOR SEGMENT OCT** IS A USEFUL DIAGNOSTIC TOOL FOR ASSESSING **INFILTRATE DEPTH** BEFORE TREATMENT AND MONITORING AFTERWARD
- A MINIMAL CORNEAL THICKNESS OF **400 M** IS REQUIRED TO PREVENT ANY ENDOTHELIAL DAMAGE FROM CXL

## IMPORTANT CONSIDERATIONS

- INTRAOPERATIVE **PACHYMETRY** AND **HYPOTONIC RIBOFLAVIN** MAY HELP ENSURE SUFFICIENT ENDOTHELIAL PROTECTION IN BORDERLINE THIN CORNEAS.
- USE OF RIBOFLAVIN/UV-A SHOULD BE AVOIDED IN HERPES SIMPLEX.
- FLUORESCEIN STAIN SHOULD BE AVOIDED BEFORE USE OF PHOTO-ACTIVATED RIBOFLAVIN, BECAUSE IT COMPETES FOR ABSORPTION OF UV-A LIGHT AND REDUCES ANTIMICROBIAL EFFICACY

## PROPOSED VARIATIONS TO STANDARD DRESDEN PROTOCOL

- **AVOID ENLARGING EPITHELIAL DEFECT** TO AVOID DELAYED HEALING  
VS **REMOVE EPITHELIUM** BEYOND AREA OF OBSERVED INFILTRATE TO IMPROVE RIBOFLAVIN PENETRATION
- **ALTER RIBOFLAVIN CONCENTRATION** TO IMPROVE KILLING EFFECT
  - \_\_\_ **HIGHER CONCENTRATION** (0.25 VS 0.1%) FOR ↑ **FUNGICIDAL** EFFECT
  - \_\_\_ **LOWER CONCENTRATIONS** (0.03 VS 0.09% WITH LONGER UVA EXPOSURE) FOR ↑ **BACTERICIDAL** EFFECT
- **PROLONGING RIBOFLAVIN INSTILLATION TIME** ↑ COLLAGEN COMPACTION, ↑ RESISTANCE TO ENZYMATIC DIGESTION
- MAY USE ACCELERATED PROTOCOL (16 MW/CM<sup>2</sup> FOR 5 MIN,  
36 MW/CM<sup>2</sup> FOR 2.5 MIN) –  
CONTROVERSIAL

## HOW SAFE AND EFFECTIVE IS PACK-CXL?

- OVERALL **87% SUCCESS RATE** WITH PACK-CXL FOR MICROBIAL KERATITIS (DEFINED AS COMPLETE RE-EPITHELIALIZATION AND INFILTRATE RESOLUTION)
- **70% TOPICAL ANTIBIOTIC THERAPY**,
- **SHORTEN RE-EPITHELIALIZATION** IN **EARLY** CASES (17 VS 24 DAYS)
- IN **ADVANCED** CASES, **NO RECURRENCES OR PERFORATIONS**

## WHAT TYPE OF MICROBIAL KERATITIS CAN BE TREATED WITH PACK-CXL?

- MAY HAVE ROLE IN **ANTIBIOTIC-RESISTANT CASES**
- HIGH SUCCESS RATES IN **BACTERIAL** AND **FUNGAL** KERATITIS
- ACANTHAMEBA** SHOWED EXCELLENT RESPONSE
- PRESENCE OF HYPOPION ASSOCIATED WITH LOWER SUCCESS RATE
- CONTRAINDICATED IN **VIRAL** ULCERS

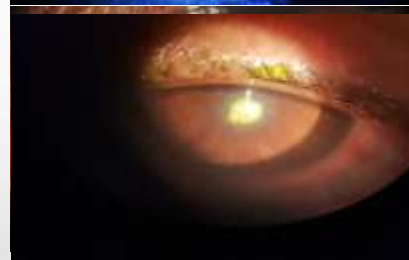
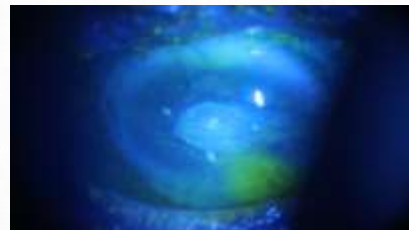
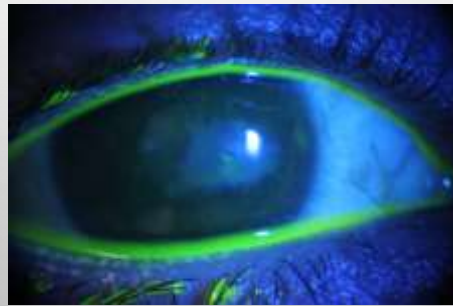
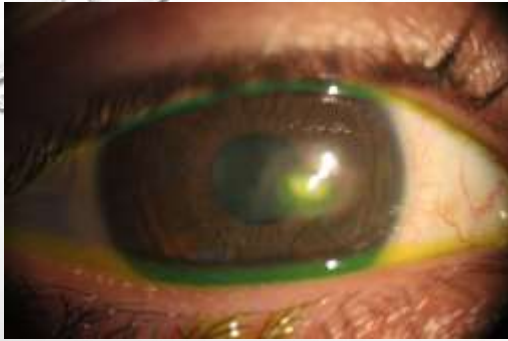
## OPTIMUM TREATMENT TIME POINT?

- A **BETTER TREATMENT RESPONSE** WITH SUPERFICIAL CORNEAL INFILTRATE INVOLVING **THE ANTERIOR THIRD** OF THE STROMA.
- DEPTH OF INFECTION SHOULD BE MONITORED VIA **ASOCT** (INFILTRATE DEPTH)
- **DEEPER** MICROBIAL PENETRATION ASSOCIATED WITH DISEASE **FLARES** AFTER PACK-CXL

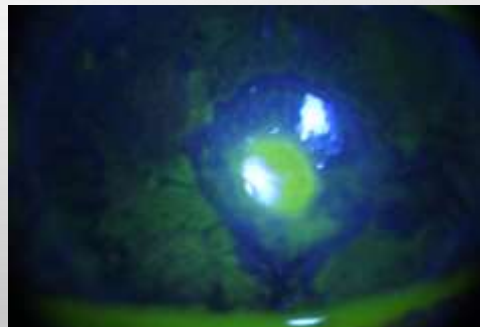
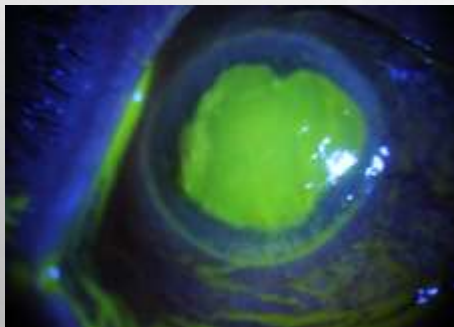
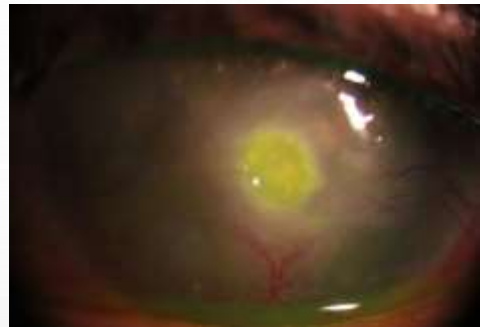
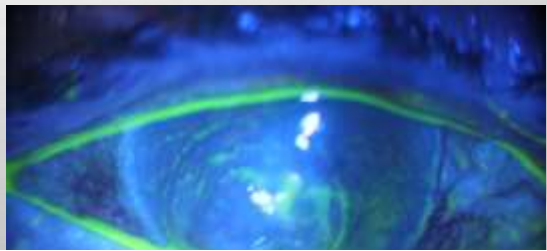
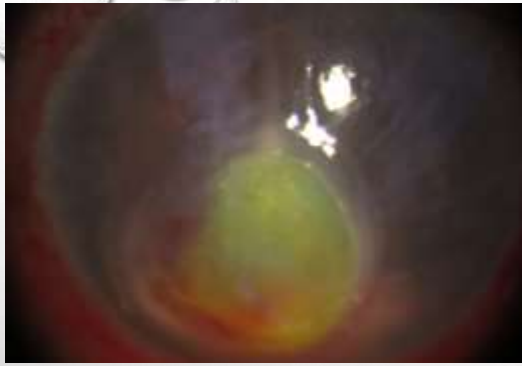
- WE VE COMPLETED **PROSPECTIVE COMPARATIVE TRIAL** COMPARING **CXL IN ADDITION TO** ANTIMICROBIAL STANDARD ANTIMICROBIAL **TREATMENT**(GROUP A) TO **TREATMENT ALONE** (GROUP B) FOR INFECTIOUS KERATITIS .
- **(GROUP A)** :**TEN EYES** WITH RECENT INFECTIVE KERATITIS UNDERWENT **CXL** WITH DRESDEN PROTOCOL AFTER DIRECT SMEAR AND CULTURES WERE DONE FOLLOWED BY TOPICAL SPECIFIC **TTT**.
- **(GROUP B)**: 12 EYES WITH RECENT INFECTIVE KERATITIS UNDERWENT SPECIFIC **TTT** .

	GROUP A...10 CASES	GROUP B...12 CASES
Staphylococcus aureus	3	2
Staphylococcus epidermidis	2	2
Streptococcus pneumoniae	1	2
Pseudomonas aeruginosa	0	1
Moraxella,	0	1
Fusarium	1	2
Aspergillus	2	1
Acanthamoeba	1	1

Groups	NO.	ULCER SIZE(MEAN)	ULCER DEPTH(MEAN)	TIME FOR HEALING	COMPLICATIONS
A(CXL AND TTT)	10	26.8mm	311.3M	17.8days	NO
B (TTT)	12	24.9mm	320.8M	26.8days	PERFORATION 1 RECURRENCE 2









## SUMMARY

- CORNEA COLLAGEN CROSS-LINKING IS A POTENTIALLY **USEFUL ADJUNCTIVE TREATMENT** FOR THE MANAGEMENT OF BACTERIAL, FUNGAL AND AMOEBIC KERATITIS

- TREATMENT EFFECTIVENESS IS LIMITED BY DEPTH OF CROSS-LINKING (250-300 MM). THEREFORE IT MAY BE POTENTIALLY **MORE USEFUL IN EARLY KERATITIS**

IT HAS ADVANTAGE OVER TOPICAL ANTIMICROBIAL TREATMENT WHEN THERE IS CONCERN ABOUT THE DEVELOPMENT OF ANTIMICROBIAL-RESISTANT ORGANISMS AND CORNEAL MELTING.  
PANDA ET AL. (2012)

**LARGE-SCALE RANDOMIZED CONTROL TRIALS** ARE WARRANTED TO FURTHER EVALUATE THE LONG-TERM EFFICACY AND SAFETY OF CXL FOR TREATMENT OF INFECTIOUS KERATITIS.

# THANK YOU

