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 microorganisms 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/CM2) 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/CM2 FOR 5 MIN, 36 MW/CM2 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 INFLTRATE INVOLVING THE ANTERIOR THIRD OF THE STROMA.**
- DEPTH OF INFECTION SHOULD BE MONITORED VIA ASOCT (INFLTRATE 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.
### Microbiological Analysis

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Group A...10 Cases</th>
<th>Group B...12 Cases</th>
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<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
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<td>2</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
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<td>1</td>
</tr>
<tr>
<td>Moraxella,</td>
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<td>1</td>
</tr>
<tr>
<td>Fusarium</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Acanthamoeba</td>
<td>1</td>
<td>1</td>
</tr>
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</table>

### Clinical Data

<table>
<thead>
<tr>
<th>Groups</th>
<th>NO.</th>
<th>ULCER SIZE(MEAN)</th>
<th>ULCER DEPTH(MEAN)</th>
<th>TIME FOR HEALING</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(CXL AND TTT)</td>
<td>10</td>
<td>26.8mm</td>
<td>311.3M</td>
<td>17.8days</td>
<td>NO</td>
</tr>
</tbody>
</table>
| B (TTT)    | 12  | 24.9mm           | 320.8M            | 26.8days        | PERFORATION 1 
RECURRANCE 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