

Accelerated corneal cross-linking with photoactivated chromophore (PACK-CXL) for moderate therapy-resistant infectious keratitis

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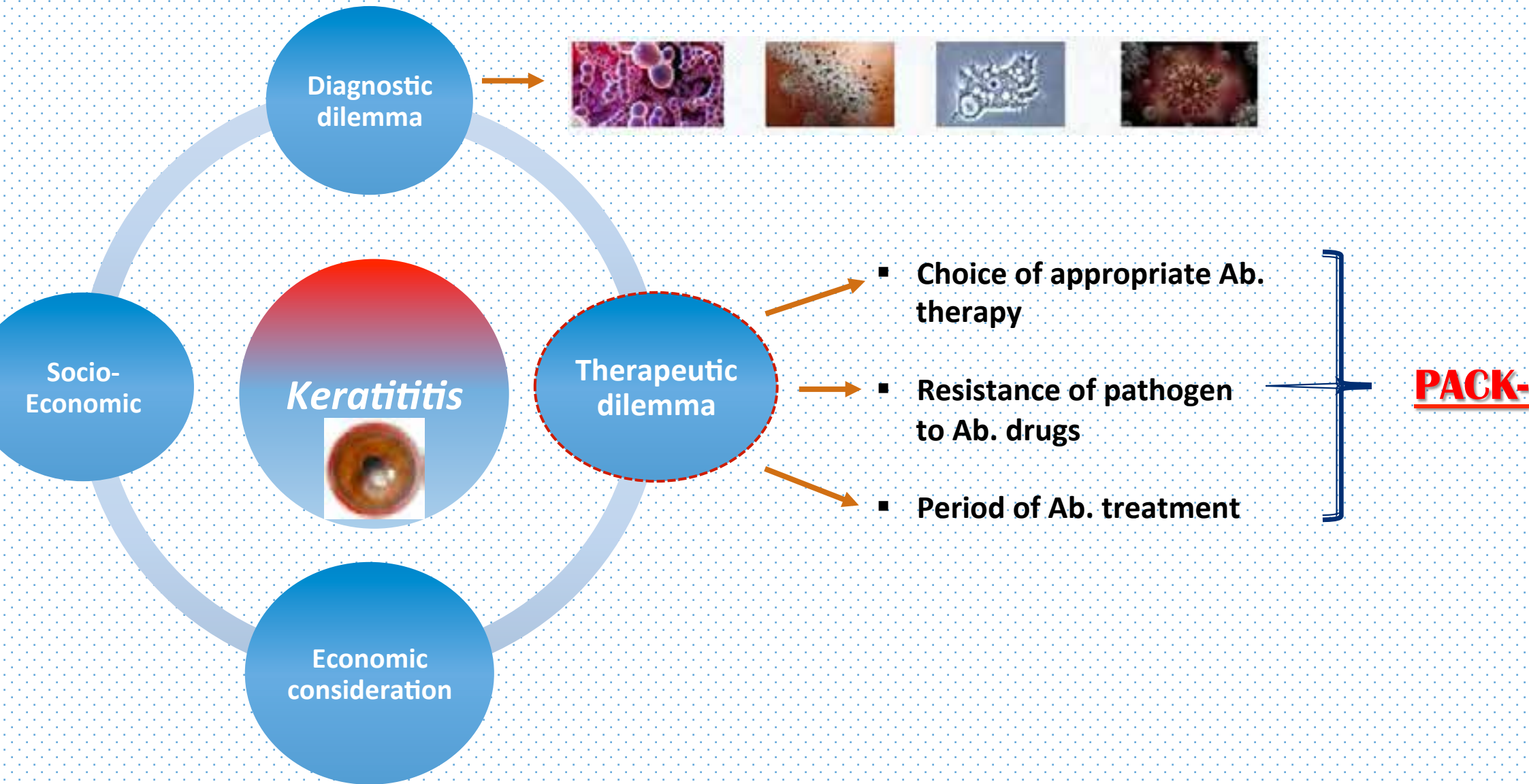
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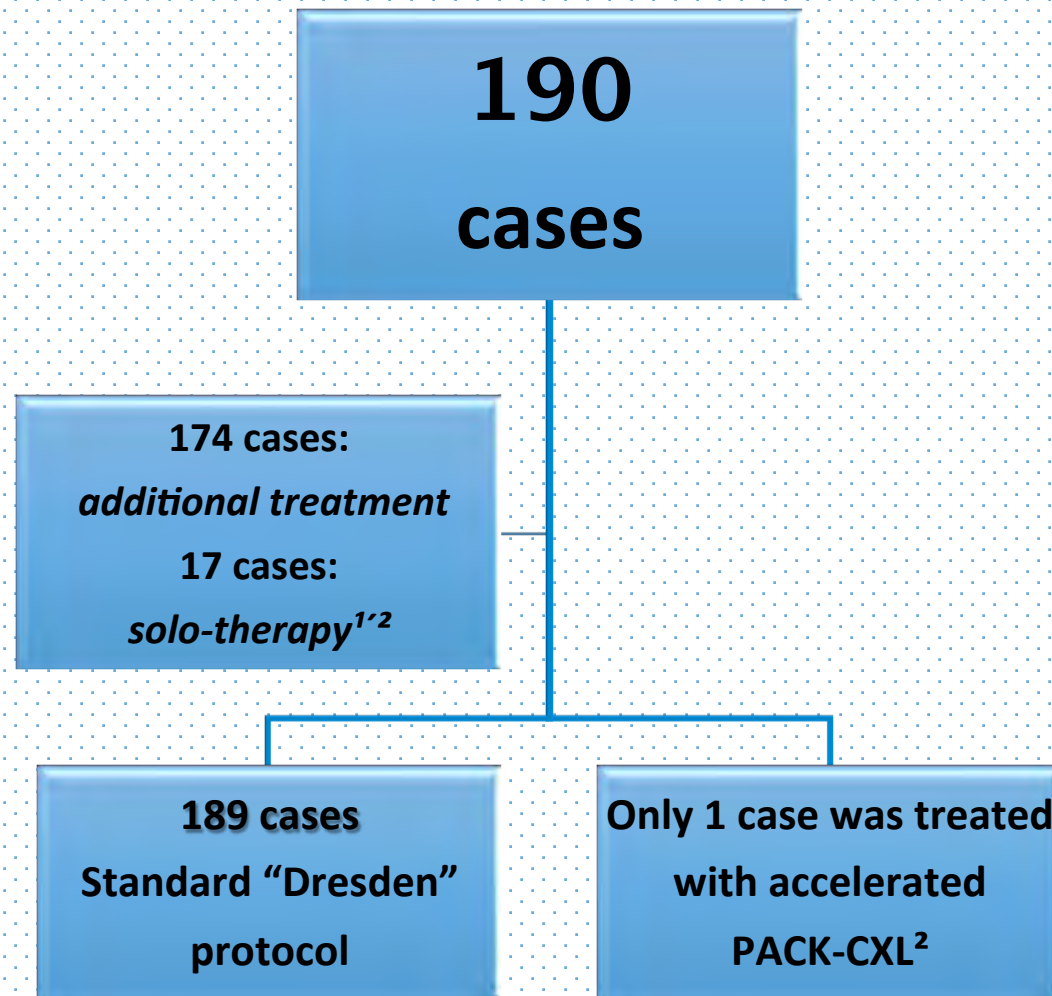


- **FH: holds a patent on a UV light source**
 - **All others: none**

The problem in corneal infections are multiple



Summary of PACK-CXL in the literature.



1. Makdoui K. UVA-Riboflavin photochemical therapy of bacterial keratitis: a pilot study. *Graefes Arch Clin Exp Ophthalmol.* 2012;250:95-102.
2. Tabibian D. Accelerated PACK-CXL as a First-line and Sole Treatment in Early Fungal Keratitis. *JRS.* 2014; 30:855-857

Accelerated PACK-CXL ?

- Accelerated UVA irradiation at 365 nm and 9 mW/cm² for 10 minutes was reported in a single case report by Tabibian in 2014 as a successful first-line and sole treatment in early fungal

keratitis

PACK-CXL for Fungal Keratitis/Tabibian et al

After PACK-CXL

Untreated

Day 1

Day 30



REPORT

Accelerated Photoactivated Chromophore for Keratitis—Corneal Collagen Cross-linking as a First-line and Sole Treatment in Early Fungal Keratitis

David Tabibian, MD; Olivier Richez, MD; Arnaud Riut, MS; Jacques Schrenzel, MD; Farhad Hafezi, MD, PhD

ABSTRACT

PURPOSE: To report the use of accelerated photoactivated chromophore for keratitis—corneal collagen cross-linking (PACK-CXL) as a first-line treatment in a patient with an atypical fungal keratitis.

METHODS: Case report and literature review.

RESULTS: A patient who presented with a painful peripheral corneal infiltrate underwent PACK-CXL with a local limited abrasion and accelerated ultraviolet-A irradiation at 365 nm and 9 mW/cm² for 10 minutes. Cultures grew *Aureobasidium pullulans*. The corneal epithelium closed completely within 3 days and the infiltrate was completely eradicated without administration of antibiotics.

CONCLUSIONS: Accelerated PACK-CXL was successfully used as a first-line and sole treatment in a case of early fungal keratitis caused by *Aureobasidium pullulans*. Further characterization of the antifungal effect of PACK-CXL is needed in prospective studies.

[J Refract Surg. 2014;30(12):855-857.]

Besides the established indication of corneal ectatic disorders, corneal collagen cross-linking (CXL) has more recently been used as photoac-

bell et al. published the first report on the PACK-CXL as a treatment in microbial ulcers resistant to conventional therapy in 2008. Two of the five presented were of fungal origin.¹ In 2012, Malhotra et al. observed 10 eyes of 16 patients with bacterial keratitis that received PACK-CXL as first-line treatment. Postoperatively, only 2 of the 16 eyes required additional topical antibiotic treatment and epithelial healing occurred within a mean of 7.1 days in the 16 cases.² These promising results encouraged others to explore PACK-CXL as a treatment for keratitis, both clinically^{3,4} and experimentally in animal models.⁵

We report successful PACK-CXL as a first-line and sole treatment in a patient with an atypical keratitis caused by *Aureobasidium pullulans*, a fungus rare occurrence in corneal infections.

CASE REPORT

A 27-year-old woman presented to our clinic in June 2014 complaining about a red, painful, and tearing right eye since the morning. She had worn daily soft contact lenses since 7 years of age and had no other relevant medical and ocular history. Corrected distance visual acuity (CDVA) was 0.1 logMAR (6/7.5 Snellen) in the right eye and 0.0 logMAR (6/6.0 Snellen) in the left eye (with -3.50 -0.75 × 174). Slit-lamp examination showed a marked conjunctival hyperemia, a round corneal stromal infiltrate with a diameter of 1 mm at the 2-o'clock position in the peripheral zone, surrounded by a mild localized corneal edema (Figure 1A). Minimum corneal thickness was 500 μm.

Accelerated PACK-CXL ?

Richotz O., Hafezi F. Antibacterial efficacy of accelerated corneal cross-linking with photoactivated chromophore (PACK-CXL).

J Refract Surg. 2014;30 :850-854.

ORIGINAL ARTICLE

Antibacterial Efficacy of Accelerated Photoactivated Chromophore for Keratolysis Corneal Collagen Cross-linking (PACK-CXL)

Olivier Richotz, MD; Sabine Kling, PhD; Florence Hoogwoud, MD; Arthur Hammer, MD; David Labbani, MD; Patrice Francois, PhD; Jacques Schranzel, MD; Tufhad Hafezi, MD

ABSTRACT

PURPOSE: To investigate whether optimized photoactivated chromophore for keratolysis-collagen cross-linking (PACK-CXL) increases efficacy, allow shortening treatment while maintaining antibacterial efficacy.

METHODS: *Staphylococcus aureus* and *Pseudomonas aeruginosa* strains were irradiated with ultraviolet A light of 365 nm fluence but different intensity settings (18 mW/cm² for 5 minutes and 36 mW/cm² for 2.5 minutes). The killing rate was determined by comparing the number of colony-forming units between cross-linked specimens and non-irradiated controls. The potential additional effect of 0.002% benzalkonium chloride was also investigated.

RESULTS: The killing rates for *Staphylococcus aureus* were 92.5% ± 5.5% (5 minutes at 18 mW/cm²) and 94.4% ± 2.0% (2.5 minutes at 36 mW/cm²). For *Pseudomonas aeruginosa*, the killing rates were 93.2% ± 8.3% (5 minutes at 18 mW/cm²) and 92.9% ± 5.0% (2.5 minutes at 36 mW/cm²). The presence of benzalkonium chloride in the treatment solution did not increase the killing rate significantly.

CONCLUSIONS: The accelerated efficacy of PACK-CXL allows the shorter fluence rate of reciprocity and can be maintained even when the irradiation intensity is considerably increased. These optimized settings may allow a shortened treatment time in the future for PACK-CXL and thus help facilitate the transition from the open-airing room to the slit lamp for treatment.

Severe visual impairment due to infection is a major cause of global blindness. In developed countries, the incidence varies between 100,000 to 1,000,000 contact lens wearers per year.^{1,2} In the United States, where approximately 30 million contact lenses, a central register reports 100,000 cases per year.³ In developing countries, infectious keratitis is a "silent epidemic." In India alone, the number of corneal ulcers is 2 million per year.⁴ Microbes are the most common underlying cause, associated with no access to an ophthalmologist, atypical pathogens. This configuration leads to legal blindness.

Although the underlying pathogens in infectious keratitis may be viruses, parasites, bacteria, and fungi, bacterial keratitis is the most common and responsible for most cases.⁵ Treatment of bacterial keratitis is challenging and costly, emerging fluoroquinolone resistance,⁶ even if it may not be enough to prevent corneal blindness.

The combination of riboflavin and ultraviolet A light (UVA) is clinical use as an antimicrobial adjuvant (ie, keratolysis medication).⁷ This combination translated into ophthalmology in 2008, when a pilot study showed that photoactivated riboflavin in cases of therapy-resistant infectious keratitis photoactivated chromophore for keratolysis-c-

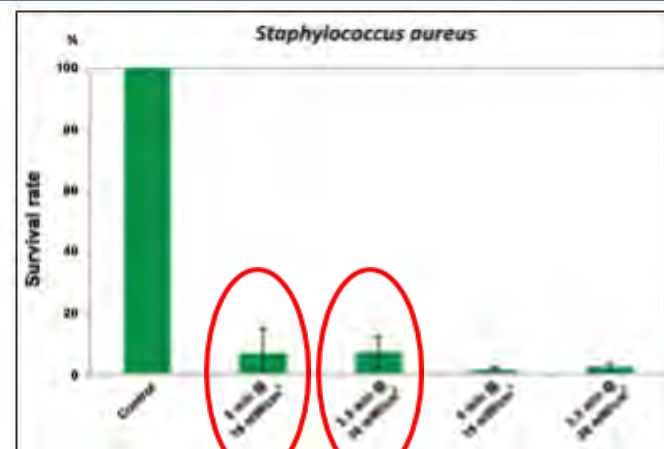
From the Department of Ophthalmology I/IV, Erlangen-Greifensee Research Lab, Division of Infectious Diseases, University Hospital, Erlangen-Nuremberg, Germany (O.R.); Department of Ophthalmology, University of Geneva, Geneva, Switzerland (O.R., F.H., J.S., T.H.); Department of Ophthalmology, University of Southern California, Los Angeles, California (A.H.); and the Department of Ophthalmology, University of Southern California, Los Angeles, California (D.L.).

TABLE 1

Mean Bacterial Killing Rate at Various Irradiance Settings in the Presence and Absence of BAC

Bacteria	Control	5 min @ 18 mW/cm ²	2.5 min @ 36 mW/cm ²	5 min @ 18 mW/cm ² with BAC	2.5 min @ 36 mW/cm ² with BAC
<i>Pseudomonas aeruginosa</i> (PA01)	100%	92.5% ± 5.5%	94.4% ± 2.0%	98.5% ± 1.6%	93.3% ± 6.8%
<i>Staphylococcus aureus</i> (SA564)	100%	93.2% ± 8.3%	92.9% ± 5.0%	98.5% ± 0.8%	97.7% ± 1.2%

BAC = benzalkonium chloride.



Purpose

To evaluate the effect of accelerated PACK-CXL (corneal cross-linking with photoactivated chromophore) as an additional treatment for therapy-resistant infectious keratitis.

Patients and Methods

- A retrospective, interventional, cohort study (may 2015-oct. 2016).

Inclusion criteria:

- Corneal ulcer of suspected bacterial origin >2mm
- No response to conventional Ab. treatment (Vancomycine+ Fortum)
- Signed informed consent

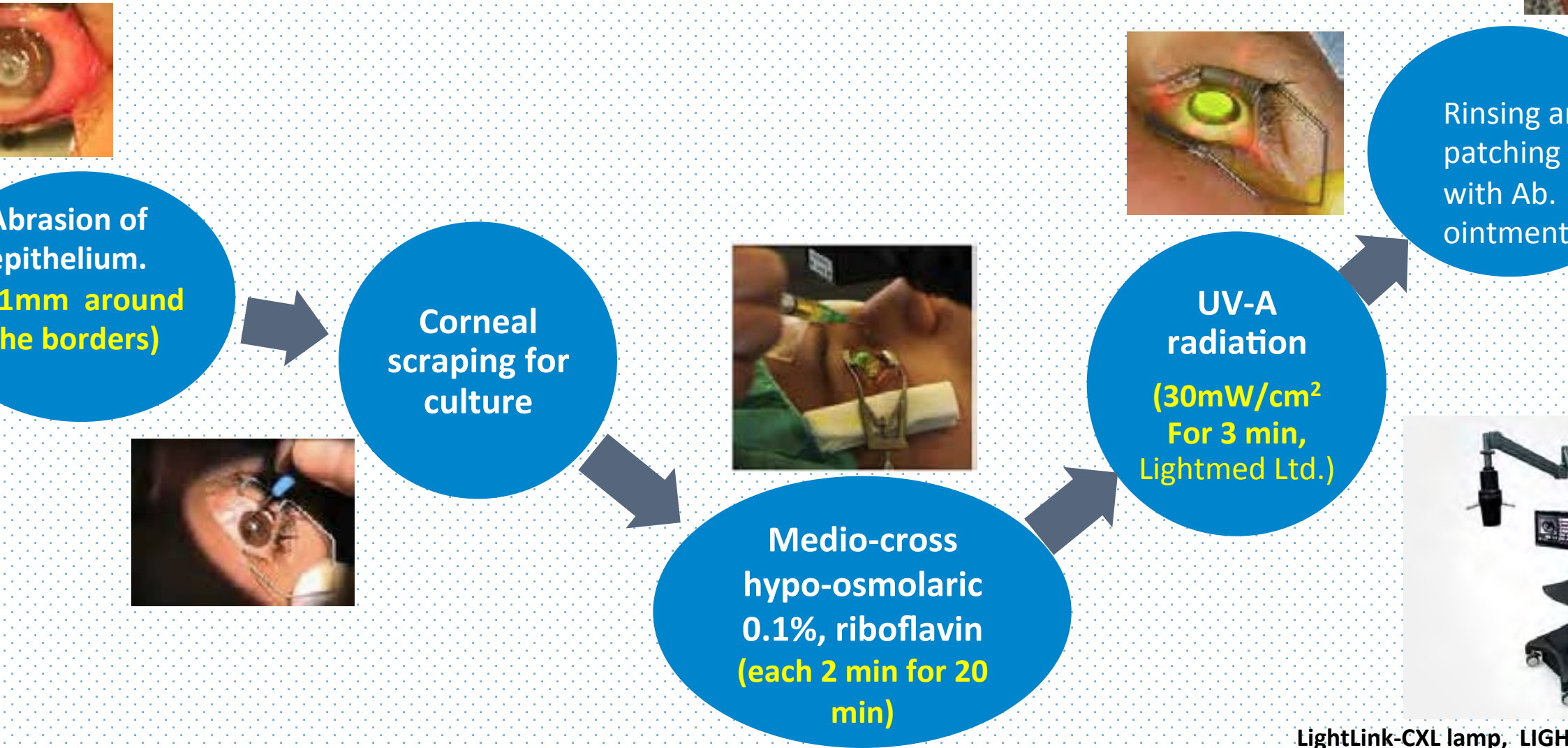
Exclusion criteria:

- Pregnancy or breast feeding
- Descemetocoele
- Corneal perforation
- Suspicion of non-infectious keratitis
- Endophthalmitis

Treatment endpoints:

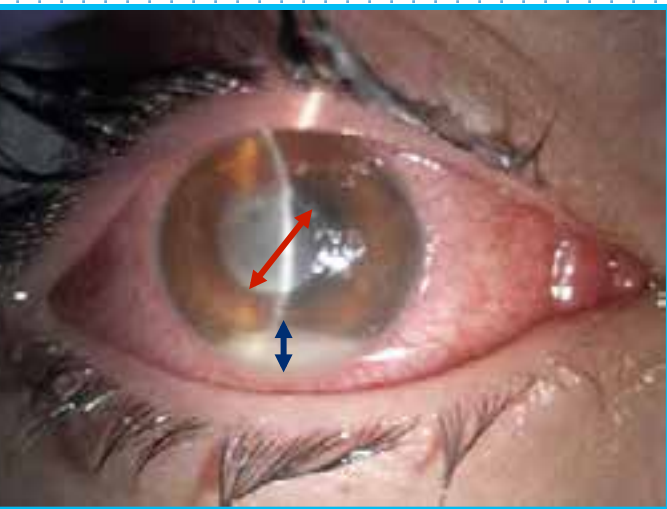
- Final UDCVA
- Day of re-epithelialization
- Rate of emergency PKP

Accelerated PAKK-CXL



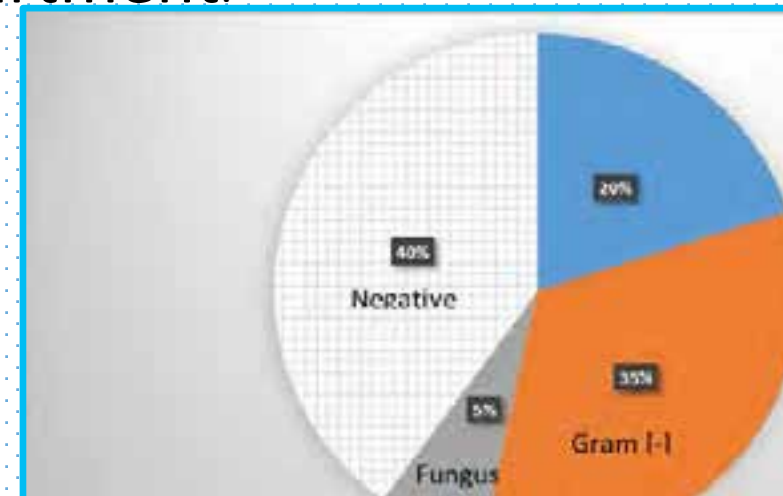
Results

Twenty eyes from **20 patients** (11 males/ 9 females) with an average age 54.5 ± 27.9 years have been included in study.



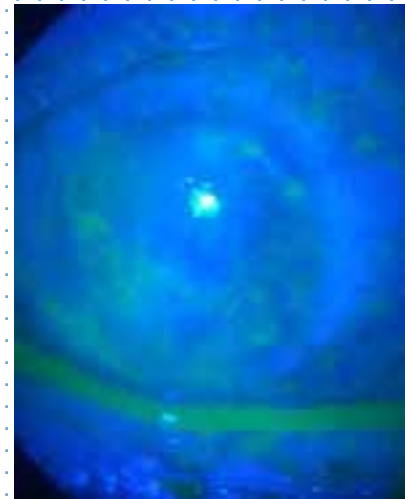
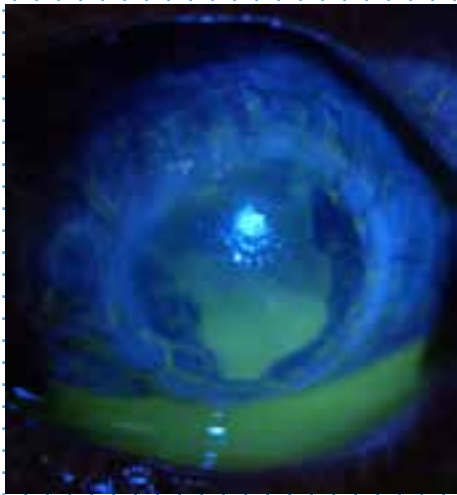
- The initial mean ulcer diameter was 3.5 ± 1.3 mm.
- Five patients (25%) presented with a hypopyon at admission to our department.

The pathogens were identified in 12 (60%) patients of study population.

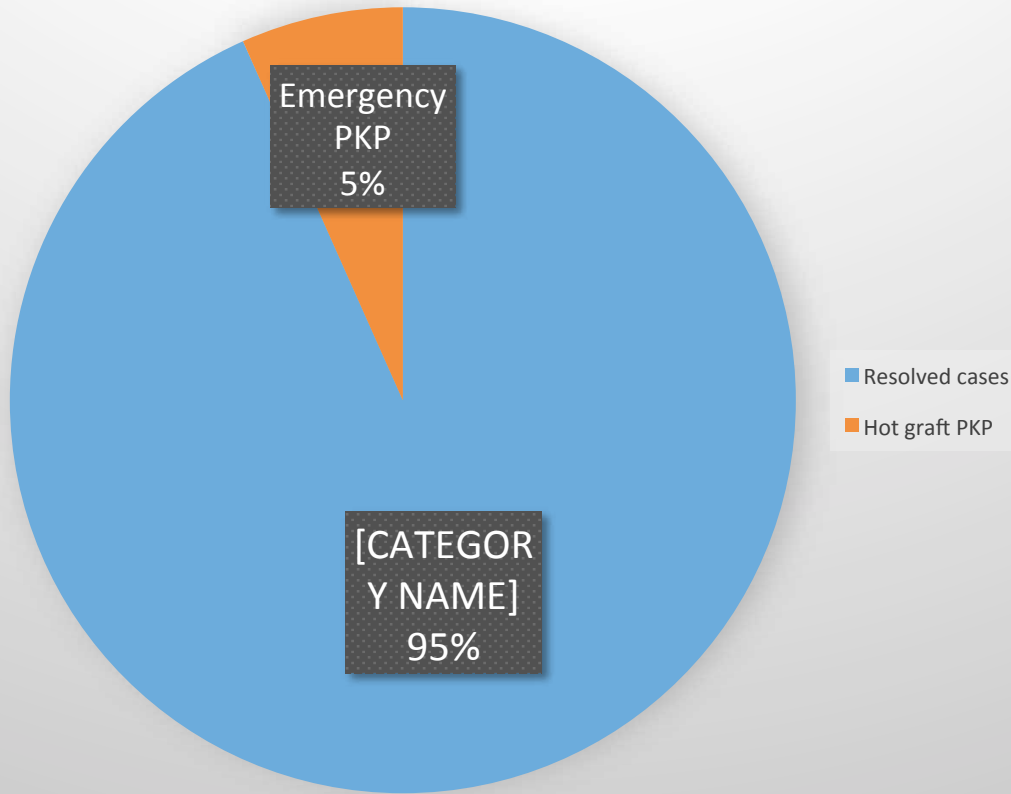


Results

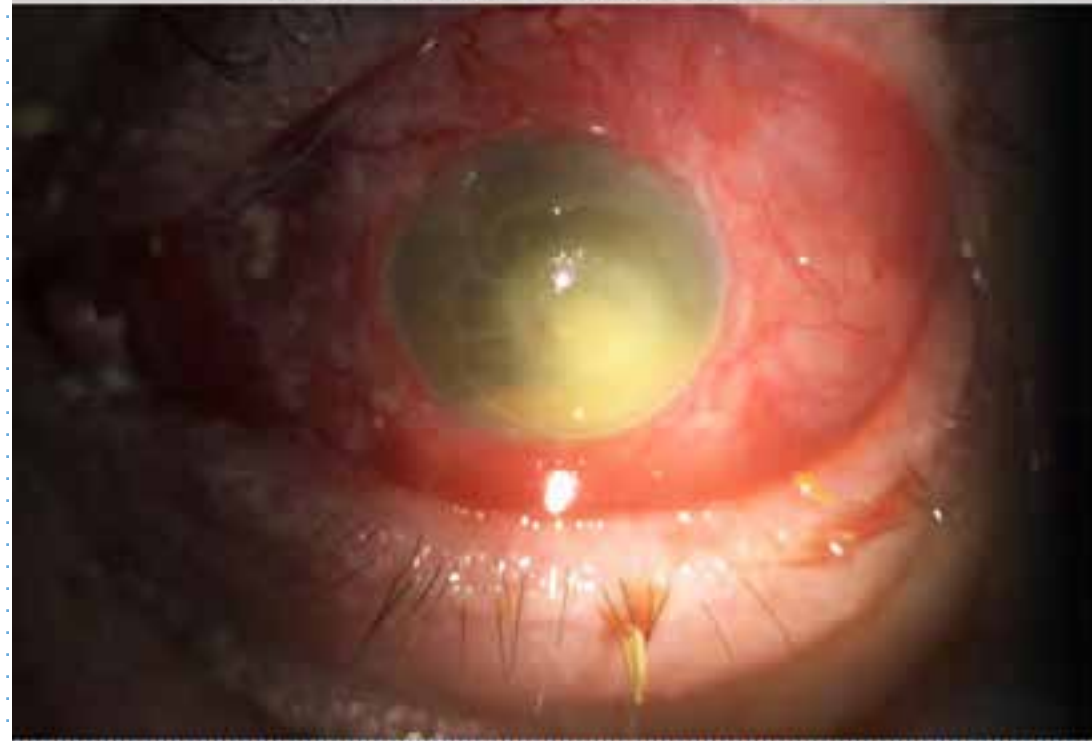
- **Initial UDVA** was 2.1 ± 0.96 (HM) and **finally UCVA** 1.26 ± 0.83 (6/120m)
- The mean duration to **complete re-epithelization** was 11.3 ± 7.7 days



Surgical treatment after PAKK-CXL

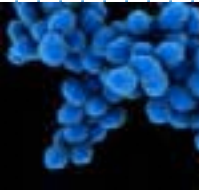


64 y.o. patient with a *Proteus Mirabilis* and *Candida Parapsilosis* corneal abscess.



Accelerated PACK-CXL in Gram (+)

- Staphylococcus epidermidis.



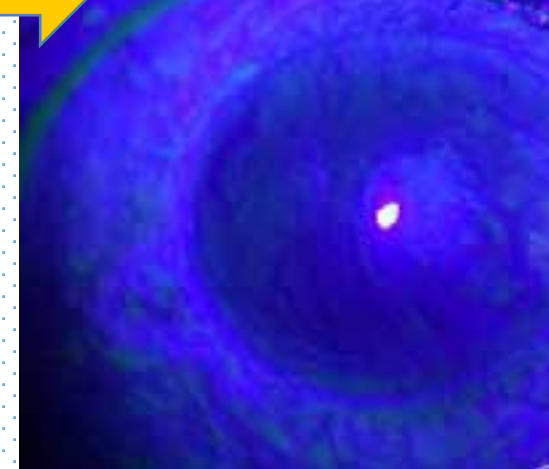
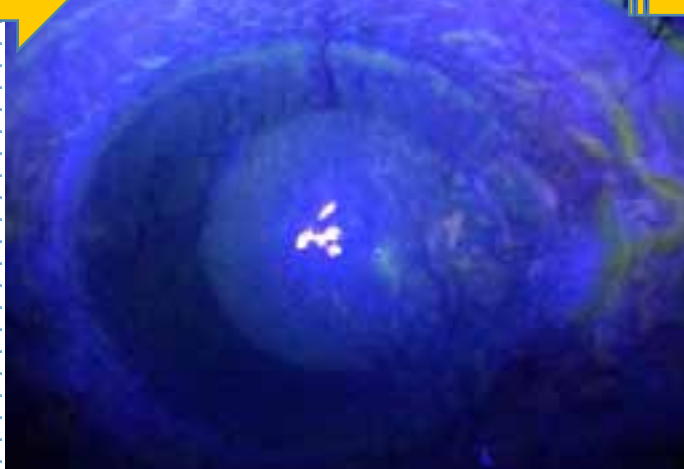
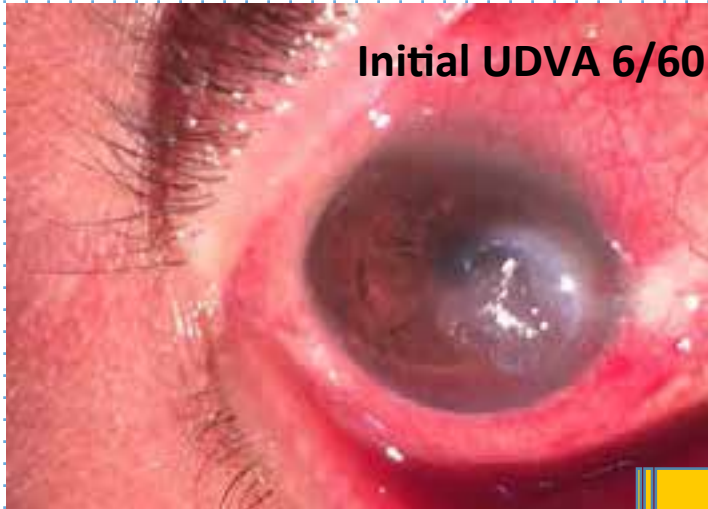
before PACK-CXL

S/P 5 Days

S/P 2 weeks

Initial UDVA 6/60

Final UDVA 6/15



Pre and Post accelerated PACK-CXL in Gram (-)

Streptococcus pneumoniae, *Pseudomonas Aeruginosa* and *Serratia Morganella*



before PACK-CXL

S/P 3 Days

S/P 2 weeks



initial UCVA= CF 1 m

final UCVA= 6/24

Accelerated PACK-CXL in Gram (-)

Klebsiella Pneumonia

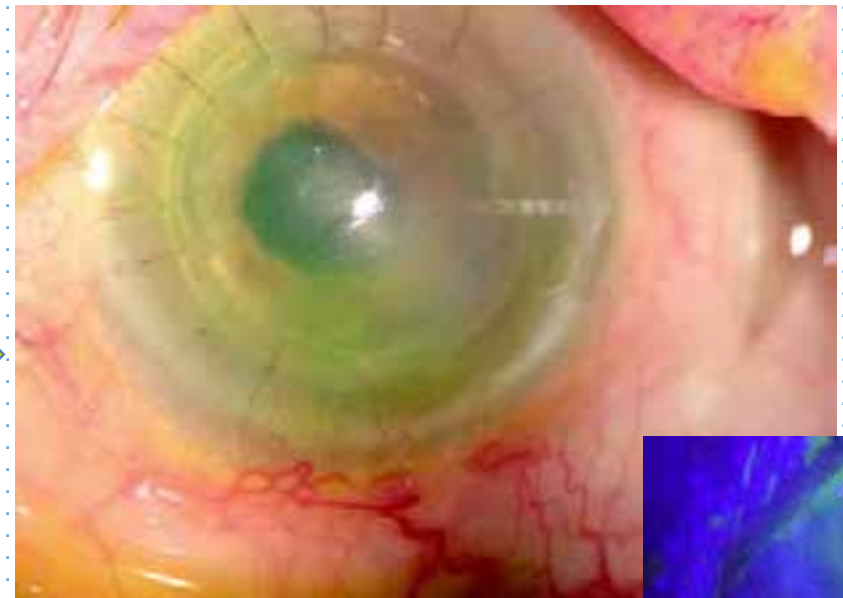
Before PACK



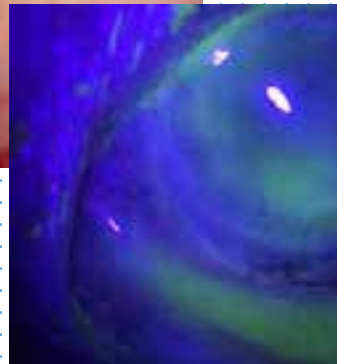
Initial UCVA=HM



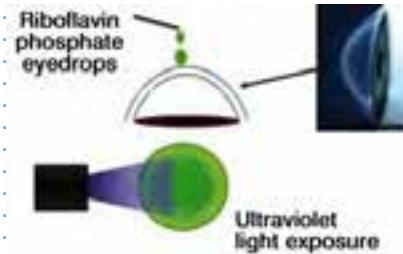
S/P 3 weeks



Final
=6

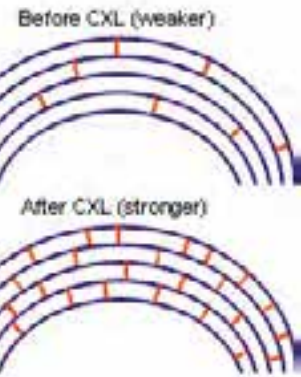


Effects of PAKK-CXL in infective keratitis



Cornea

1. Increase the biomechanical strength of cornea
2. Stabilize and increase response of cornea to digestive enzymes of pathogens.



Microorganism

3. Intercalation of the chromophore (riboflavin) with the nucleic acids of the pathogen and inhibition of replication.
4. Damage to the pathogen's cell walls caused by massive amounts of ROS



Conclusion.

- *This is the first study that shows the promising results of therapy with accelerated PAK-CXL protocol.*
- Our results suggest that accelerated PAK-CXL may provide an antimicrobial effect similar to the low intensity slow settings (30 min @ 3 mW/cm²), and may be used as an additional treatment in moderate-sized therapy-resistant infectious keratitis.
- Further research is needed to show the beneficial effect of this accelerated treatment for infective keratitis.

Thank you

