

# Accelerated PACK-CXL as adjuvant treatment in infectious keratitis

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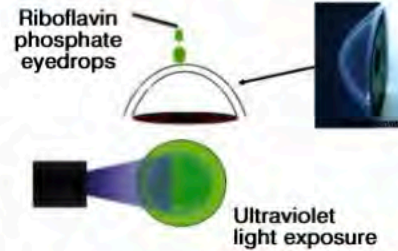


- Disclosure:

**NO FINANCIAL INTEREST**

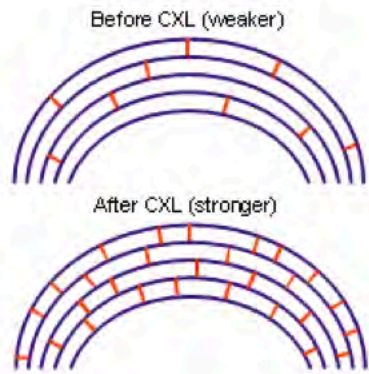
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# Effects of PAKK-CXL in infective keratitis



## Cornea

## Microorganism



**PAKK-CXL**

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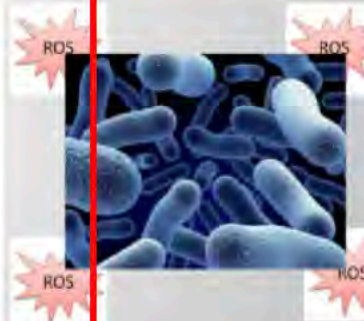
**2.** Stabilize and increase response of cornea to digestive enzymes of pathogens.

**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.



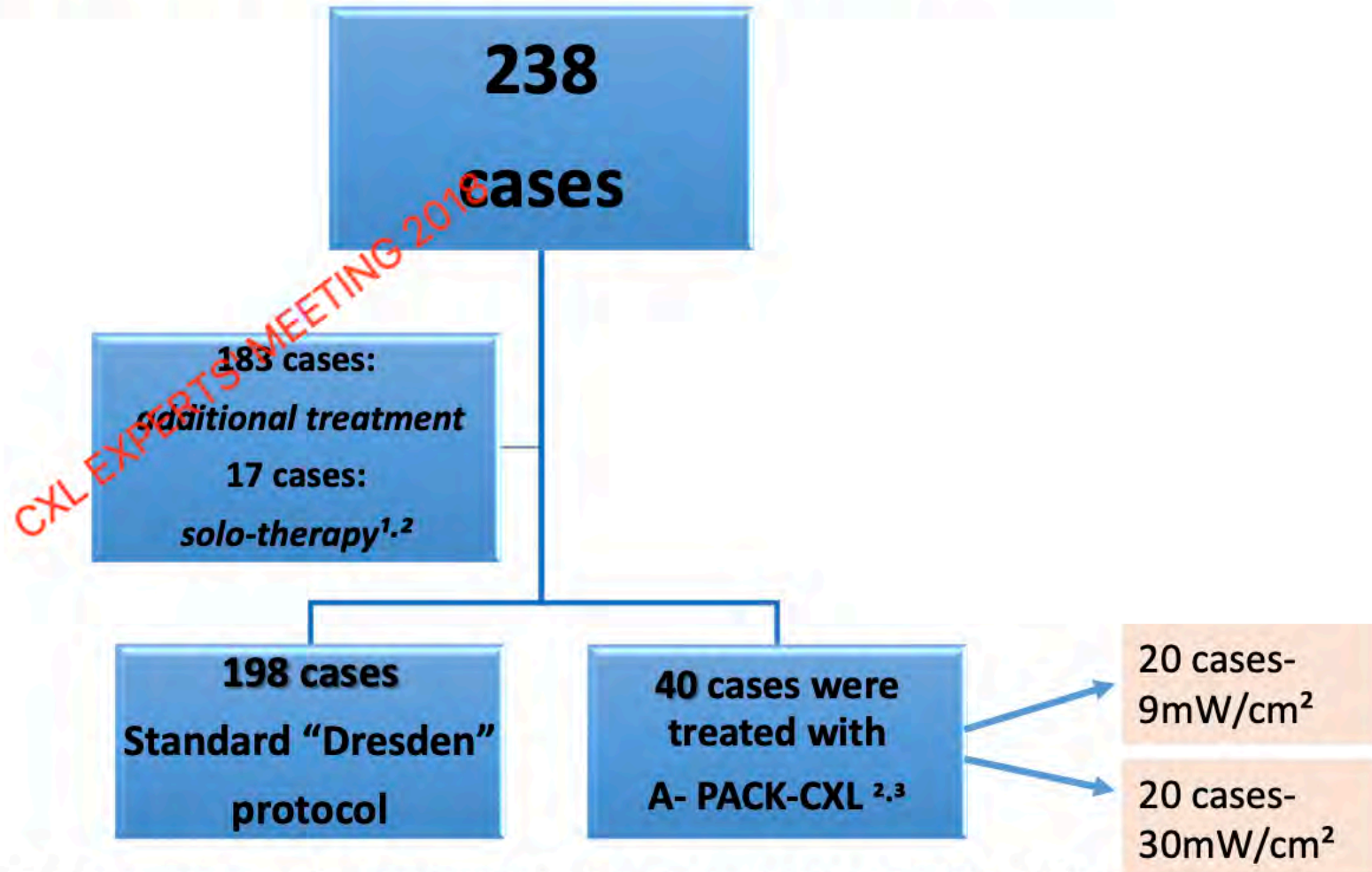
Intercalation with DNA = stops replication



Oxydative stress



# PACK-CXL: published data

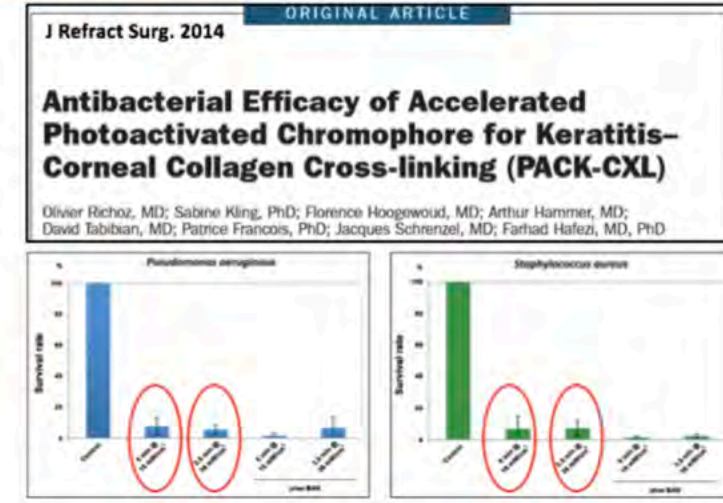


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2. Tabibian D. Accelerated PACK-CXL as a First-line and Sole Treatment in Early Fungal Keratitis. *J Refract Surg.* 2014; 30:855-857
3. Knyazer B. Accelerated PACK-CXL for Moderate Therapy-Resistant Infectious Keratitis. *Cornea.* 2018;37:528-531.

# Why to accelerate PACK-CXL?

- Evidence based- ✓
- Save time of the patients and medical staff- ✓
- Save money for the health system- ✓
- Efficacy and Safety- ✓
- More bactericidal features- ?

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TECHNIQUES

### Accelerated Corneal Cross-Linking With Photoactivated Chromophore for Moderate Therapy-Resistant Infectious Keratitis

Boris Knyazer, MD,\* Yonit Krakauer, MD,\* Yael Baumfeld, MD,† Tova Lifshitz, MD,\* Sabine Kling, PhD,‡ and Farhad Hafezi, MD, PhD,§¶||

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

**Methods:** In this interventional cohort study, 20 patients (11 men and 9 women), aged 65.5 (interquartile range = 21.5–78.5) years, who were hospitalized for moderate-sized therapy-resistant bacterial corneal ulcers (11/20 microbiologically confirmed) were treated with hypotomolar 0.1% riboflavin solution and Ultraviolet A (UVA) irradiation for 3 minutes at 30 mW/cm<sup>2</sup> (5.4 J/cm<sup>2</sup>) as additional therapy to standard antimicrobial treatment.

**Results:** We did not observe any adverse effects of accelerated PACK-CXL on the corneal stroma or limbus. The median ulcer size was 3.00 (2.63–4.50) mm, the median time to reepithelialization was 6.50 (5.00–18.0) days, and the mean hospitalization period was 8.5 ± 4.5 days. Tectonic keratoplasty became necessary in 1 patient (5%).

**Conclusions:** Our results suggest that accelerated PACK-CXL may provide an antimicrobial effect similar to the low-intensity, slow setting (30 minutes at 3 mW/cm<sup>2</sup>) and may be used as additional treatment in moderate-sized therapy-resistant infectious keratitis.

**Key Words:** PACK-CXL, corneal cross-linking, infectious keratitis, antimicrobial resistance

(Cornea 2018;37:1–4)

Infectious keratitis is a potentially sight-threatening condition. It can be of various origins—bacterial, fungal, viral, protozoal, and parasitical.<sup>1</sup> Several risk factors are known including ocular trauma, contact lens wear, ocular surgery, and ocular surface disease.<sup>2,3</sup> The World Health Organization classifies infectious keratitis as a “silent epidemic,” with an estimated 800,000 new cases every year in India alone.<sup>4</sup>

The standard bacterial keratitis treatment according to the guidelines of the American Academy of Ophthalmology includes the use of broad-spectrum topical antibiotics. However, antimicrobial resistance (AMR) is rising at an alarming speed, and the World Health Organization has published an urgent call to identify alternatives to antibiotics in its global report on AMR.<sup>5</sup>

Corneal cross-linking (CXL) with riboflavin and UVA might represent such a method. Originally introduced for the treatment of keratoconus by improving the biomechanical features of the cornea,<sup>6,7</sup> CXL was used in 2008 in a pilot study in therapy-resistant infectious keratitis by Iseli et al.<sup>8</sup> They successfully treated 5 eyes using the linking settings of 3 mW/cm<sup>2</sup> for 30 m protocol.<sup>8</sup> In the same year, Martins et al demonstrated the and riboflavin against a variety of pathogenic infectious keratitis.



# Purpose

**To evaluate the therapeutic effect of PACK-CXL with riboflavin on therapy-refractory infectious keratitis and compare it to the effect of the standard antibiotic therapy.**

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# Patients and Methods

- A retrospective, single central, interventional, comparative study (may 2013-may 2018).

## Inclusion criteria:

Only patients with moderate corneal ulcers with diameters of **up to 7 mm**

## Antimicrobial therapy

- Antimicrobial therapy in both groups consisted of fortified **Vancomycin** and **Ceftazidime** eye drops, artificial tears and cycloplegia.
- In both groups, a therapeutic 14-mm diameter **soft contact lens** (PureVision, Baush&Lomb, USA) was placed **after 50% reepithelization was achieved.**

## Exclusion criteria:

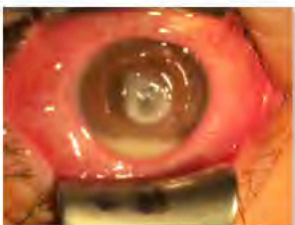
- suspicion of non-bacterial keratitis, (viral, fungal, Acanthamoeba keratitis)
- descemetocele,
- corneal perforation,
- pregnancy or breast feeding,
- immunosuppressed/immune-compromised patients,
- -corneal ulcers that were **less than 2.0 mm.**

## Treatment endpoints:

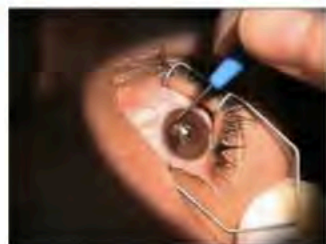
- Day of re-epithelization
- Final UDCVA
- Rate of emergency PKP
- Period of follow up
- # of FU visits

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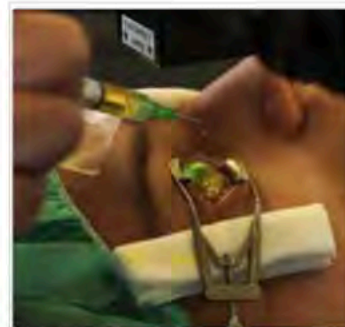
# Accelerated PACK-CXL



Abrasion of epithelium.  
(1mm around the borders)



Corneal scraping for culture



Medio-cross hypo-osmolaric 0.1%, riboflavin (each 2 min for 20 min)



UV-A radiation  
(30mW/cm<sup>2</sup>  
For 3 min,  
Lightmed Ltd.)

Rinsing and patching with Ab. ointment



LightLink-CXL lamp, LIGHTMED Ltd.

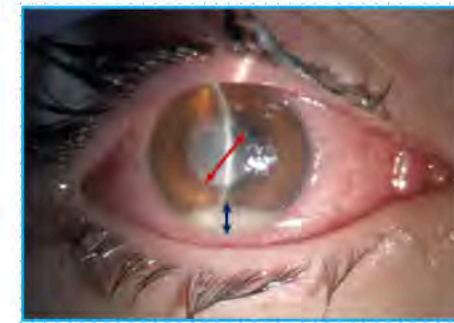
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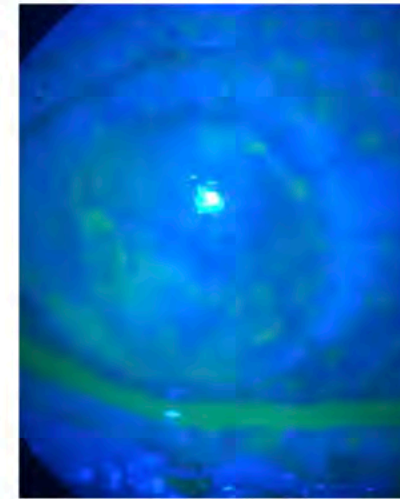
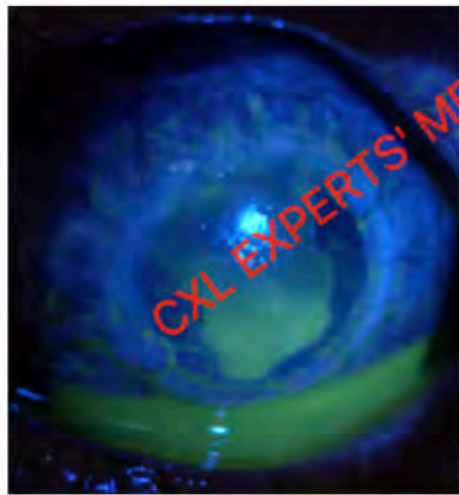
# Results



Variables	<u>PACK+Ab group</u> (n=40 pt.)	<u>Antibiotic group</u> (n=30 pt.)	P-Value
Age (years)	48.9±26.89	68.29±23.59	0.001
Gender (Male)	24 (60%)	18 (60%)	0.7
Origin (Jewish/Bedouin)	28/12 (70/30%)	24/6 (80 /20%)	0.42
Diabetes Mellitus	9 (23%)	10 (33.3%)	0.7
Hypopion	10 (25%)	5 (17%)	1.0
Initial UCVA (LogMAR)	1.7	1.7	0.8
Size of corneal ulcer (mm)	3.2± 1.3	3.1±1.2	0.7

# Results

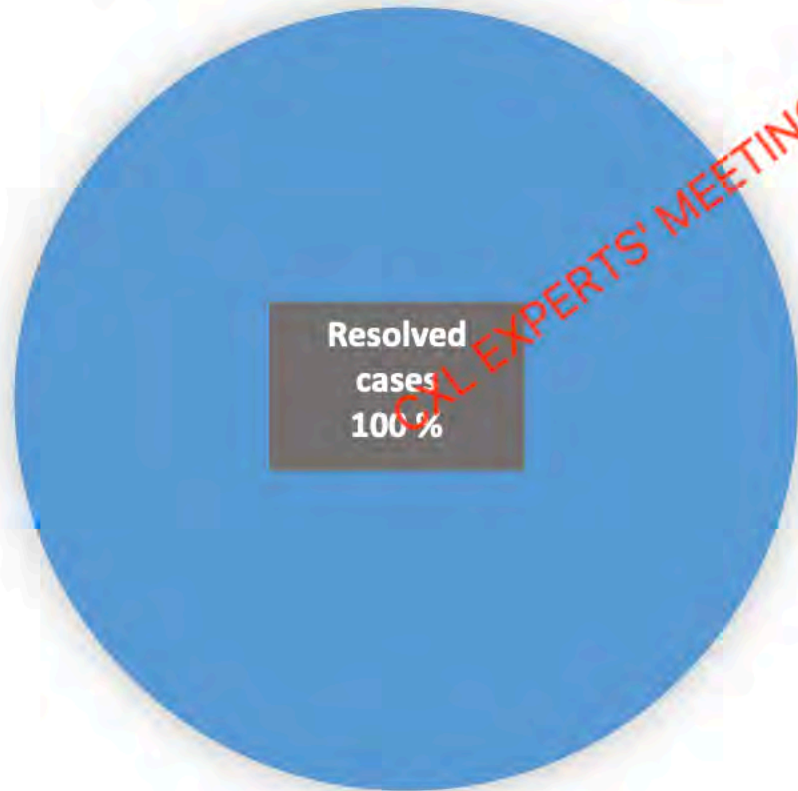
- The mean duration to **complete re-epithelization** in days



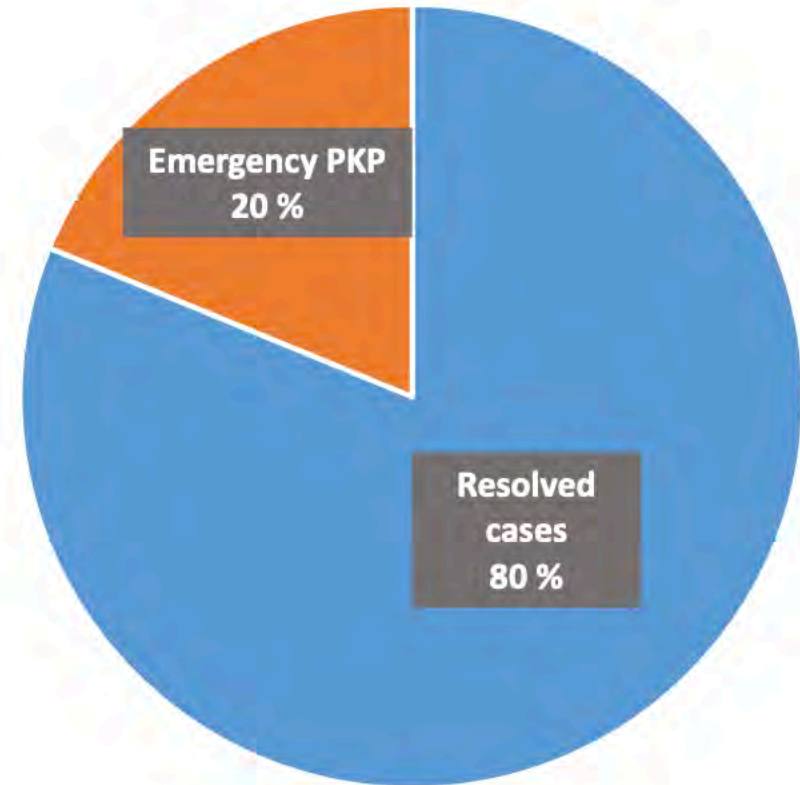
<b>AB group</b>	<b>12.0 ± 4.5 days</b>	<b>P &lt; 0.001</b>
<b>PACK+Ab group</b>	<b>7.0 ± 2.5 days</b>	

# Emergency PKP

PACK+Ab group



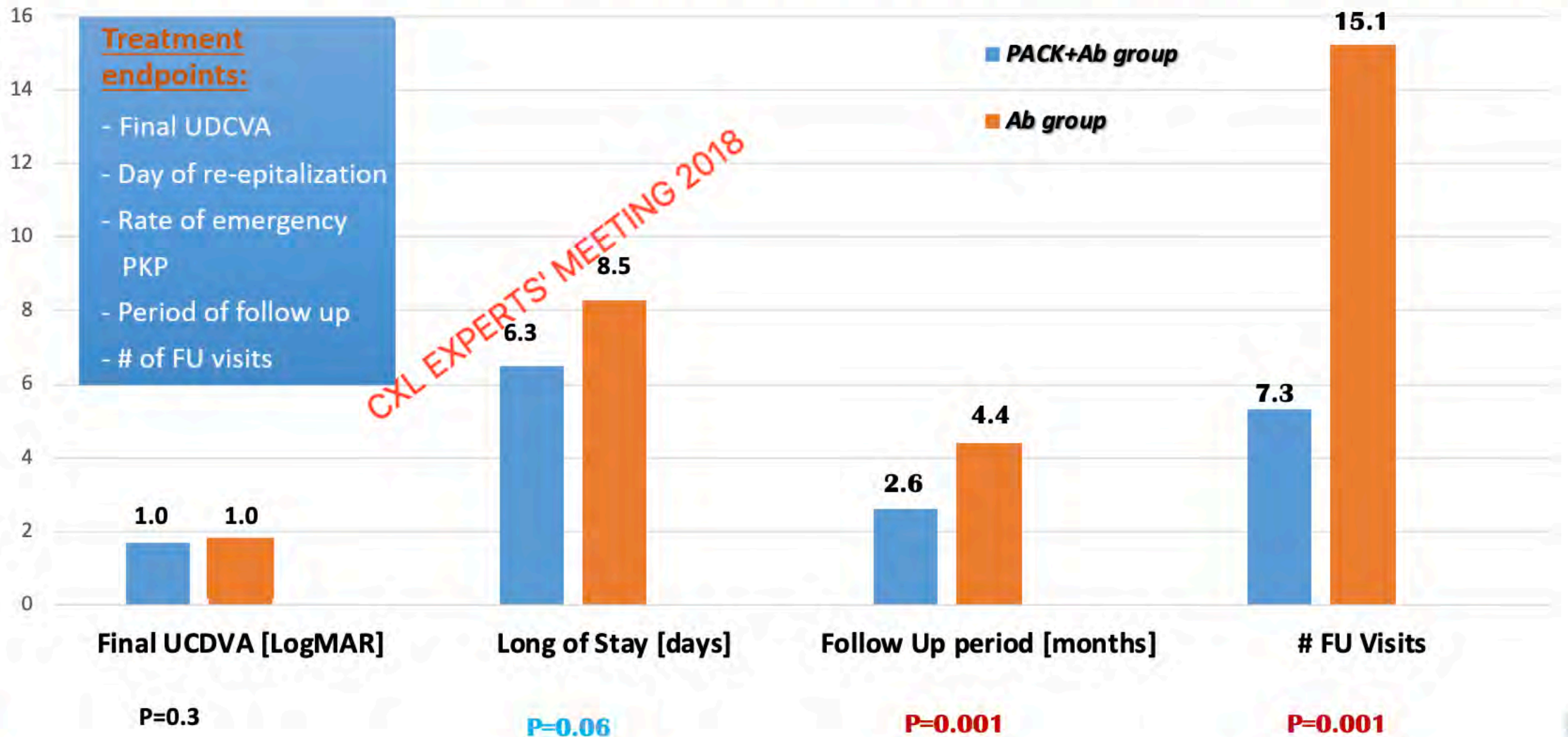
Antibiotic group



**P < 0.001**

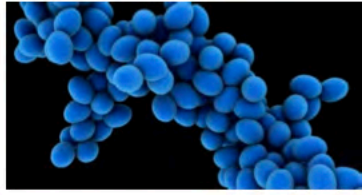
■ Resolved cases ■ Emergency PKP

# Outcome results in the study populations



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

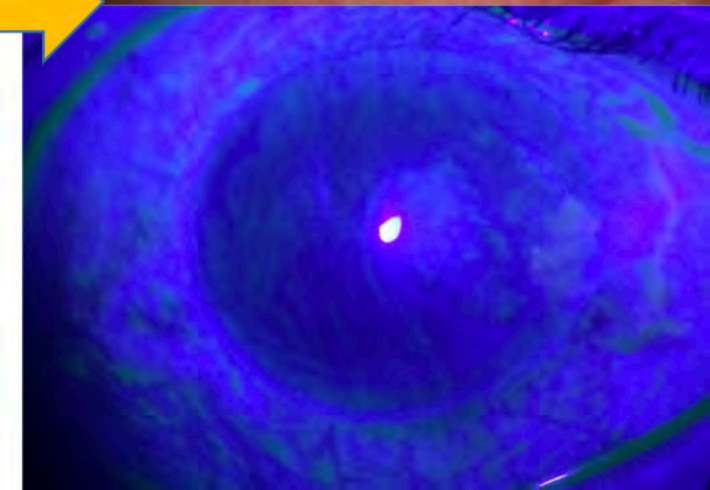
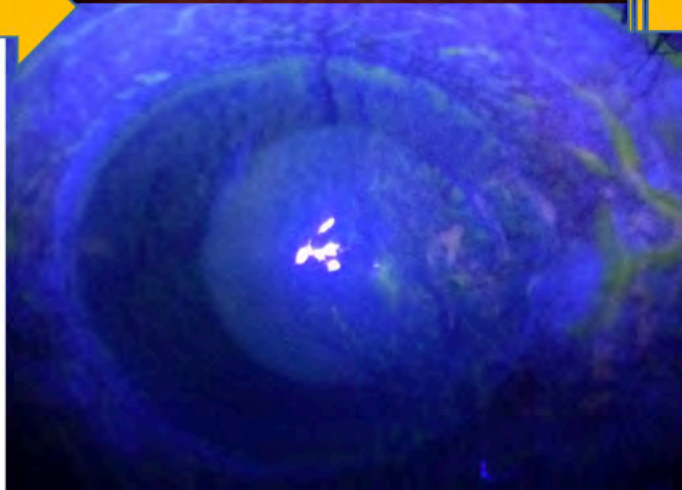
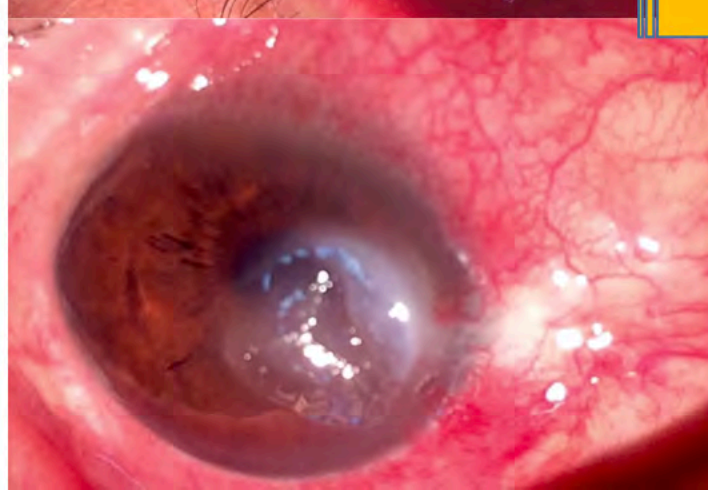
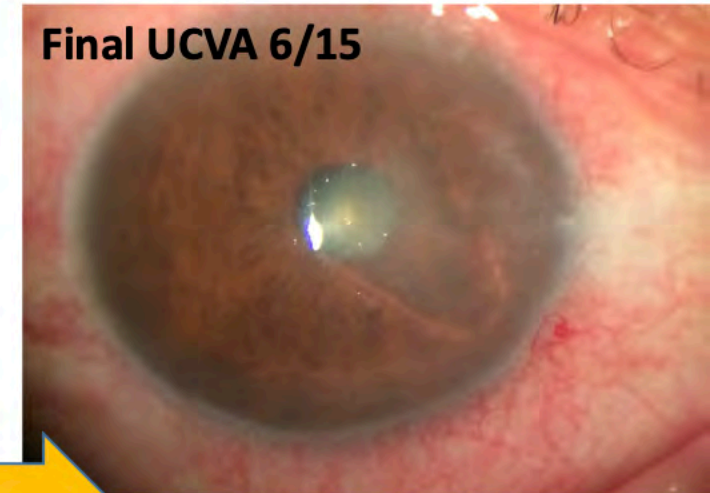
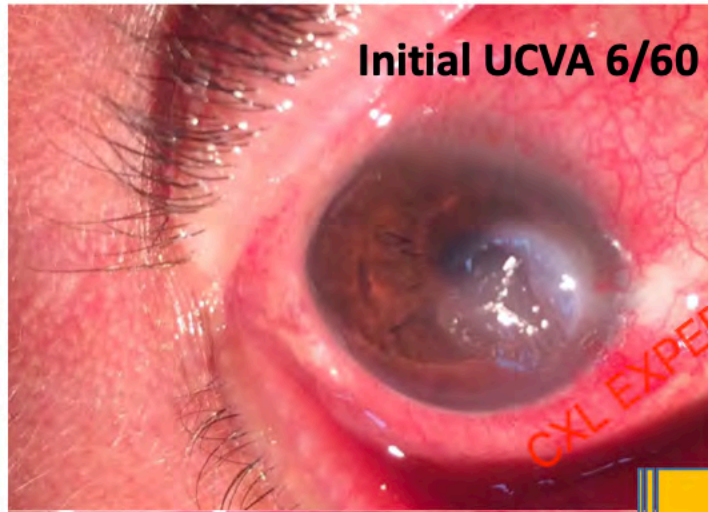
- Staphylococcus epidermidis.



before PACK-CXL

S/P 7 Days

S/P 2 weeks

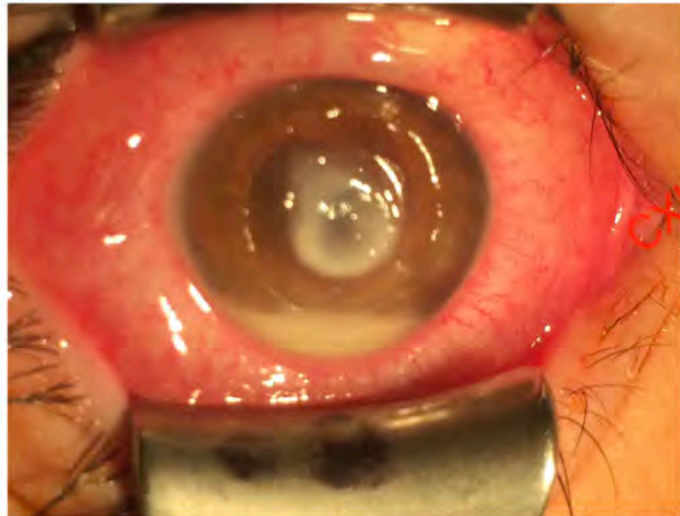


# Pre and Post accelerated PACK-CXL in Gram (-)

- *Klebsiella pneumoniae*, *Pseudomonas Aeruginosa* and *Serratia Morganelle*

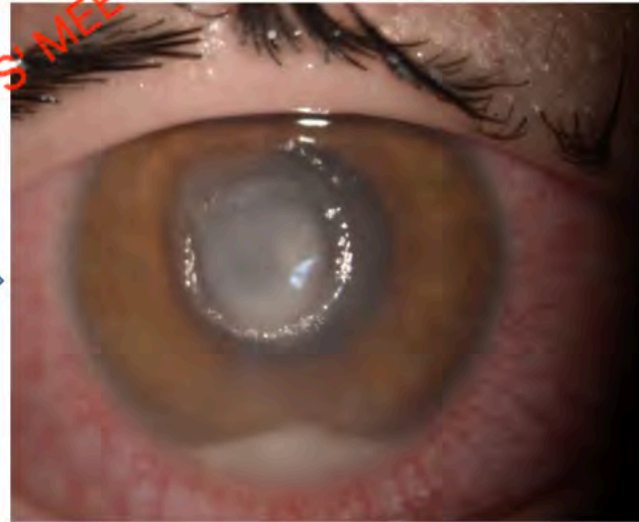


before PACK-CXL

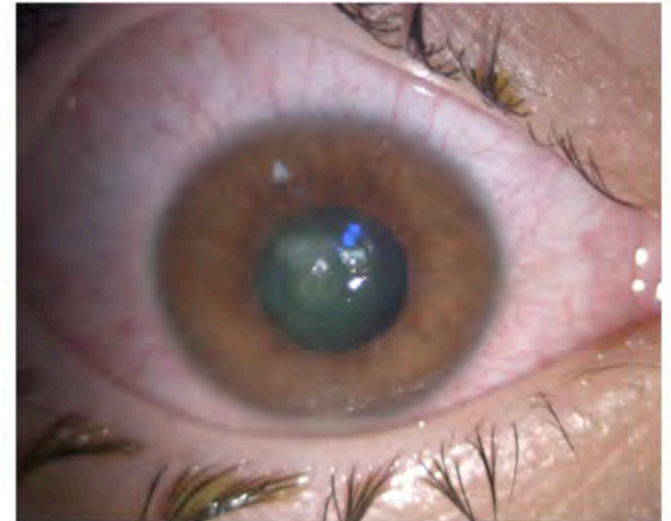


initial UCVA= CF 1 m

S/P 3 Days



S/P 2 weeks



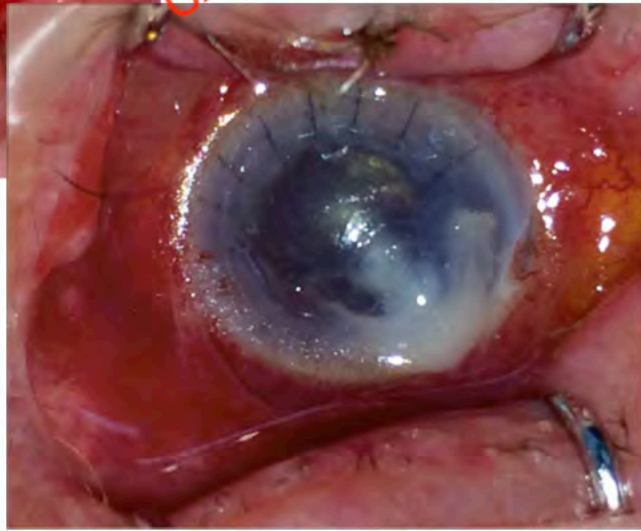
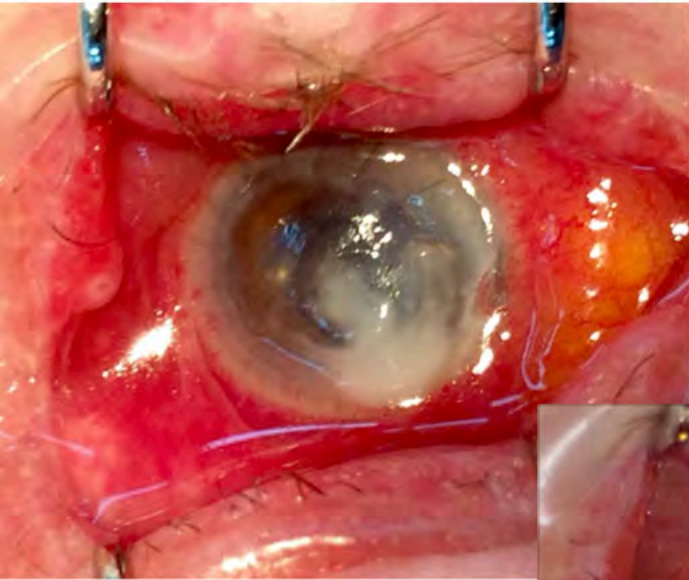
final UCVA= 6/24

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

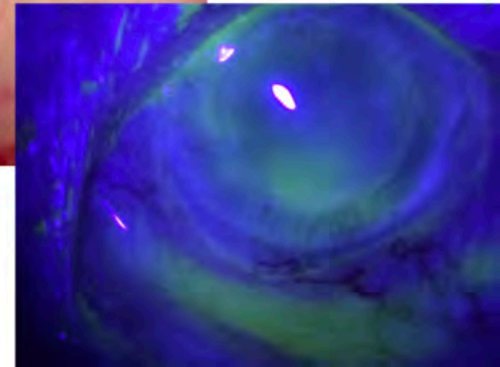
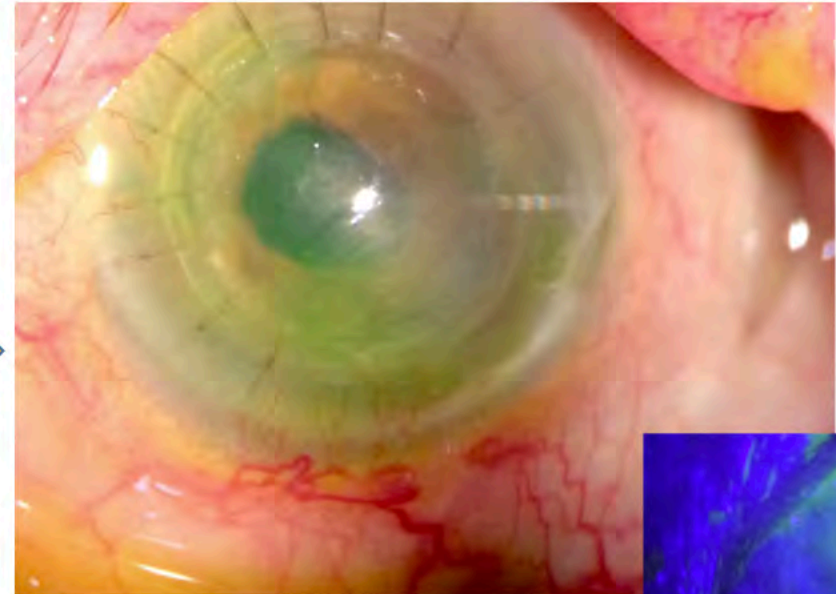


## Klebsiella Pneumonia

Before PACK



S/P 10 days



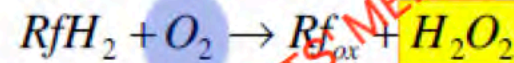
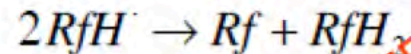
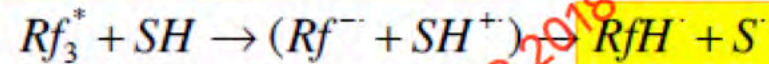
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# Why the A-PACK-CXL may be better than S-CXL?

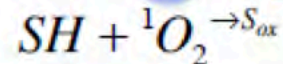
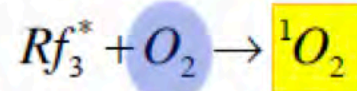
## Reaction mechanisms

### Type I mechanism:



Little oxygen consumption.

### Type II mechanism:



High oxygen consumption.

radicals

reactive oxygen species

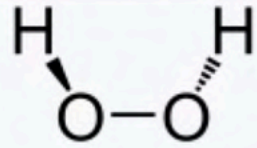






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Hydrogen peroxide



## Conclusion.

✓ *Promising first results using accelerated PACK-CXL with 30 mW/cm<sup>2</sup> intensity .*

✓ Accelerated PACK-CXL beneficial as an additional treatment in moderate-sized infectious keratitis.

✓ Further research is needed for the optimization of treatment parameters to achieve the maximal antibacteriacidal effect in infectious keratitis.

Thank you

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