



University of  
Zurich<sup>UZH</sup>



University of Bern | University of Zurich  
vetsuisse-faculty

Veterinary Ophthalmology

# Clinical results II

Simon A Pot<sup>1</sup>, Frank Famose<sup>2</sup>, Manuela Crasta<sup>3</sup> & Farhad Hafezi<sup>4,5</sup>

*Vetsuisse Faculty, University of Zurich, Switzerland<sup>1</sup>*

*Clinique des Acacias, Toulouse, France<sup>2</sup>*

*VisionVet, San Giovanni in Persiceto, Italy<sup>3</sup>*

*The ELZA Institute, Zurich, Switzerland<sup>4</sup>*

*Center for Applied Biotechnology and Molecular Medicine, University of Zurich, Switzerland<sup>5</sup>*



# PACK-CXL in human patients: meta-analysis

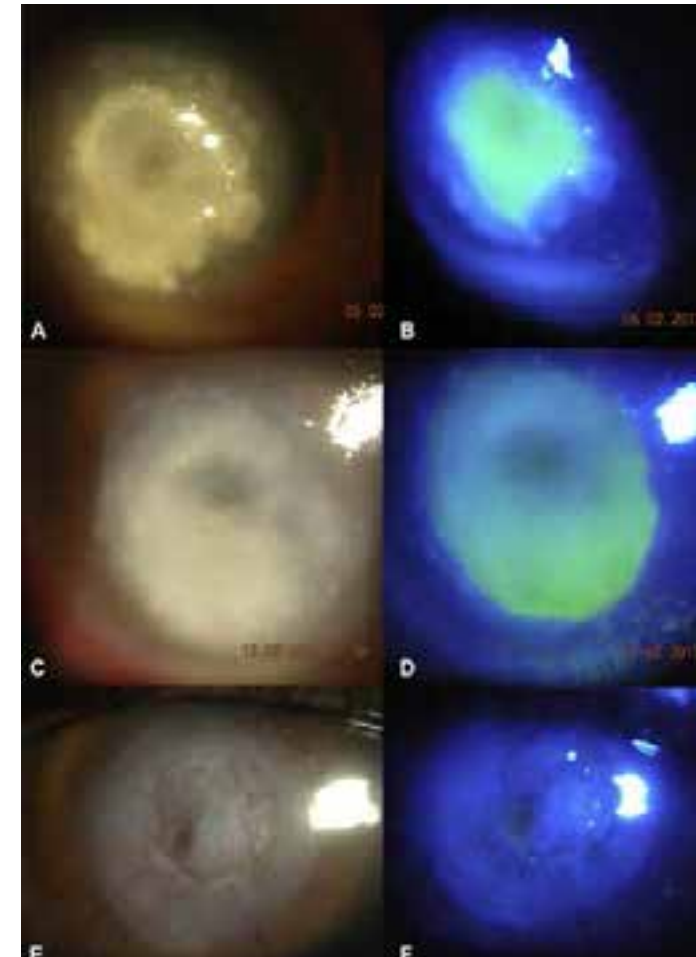
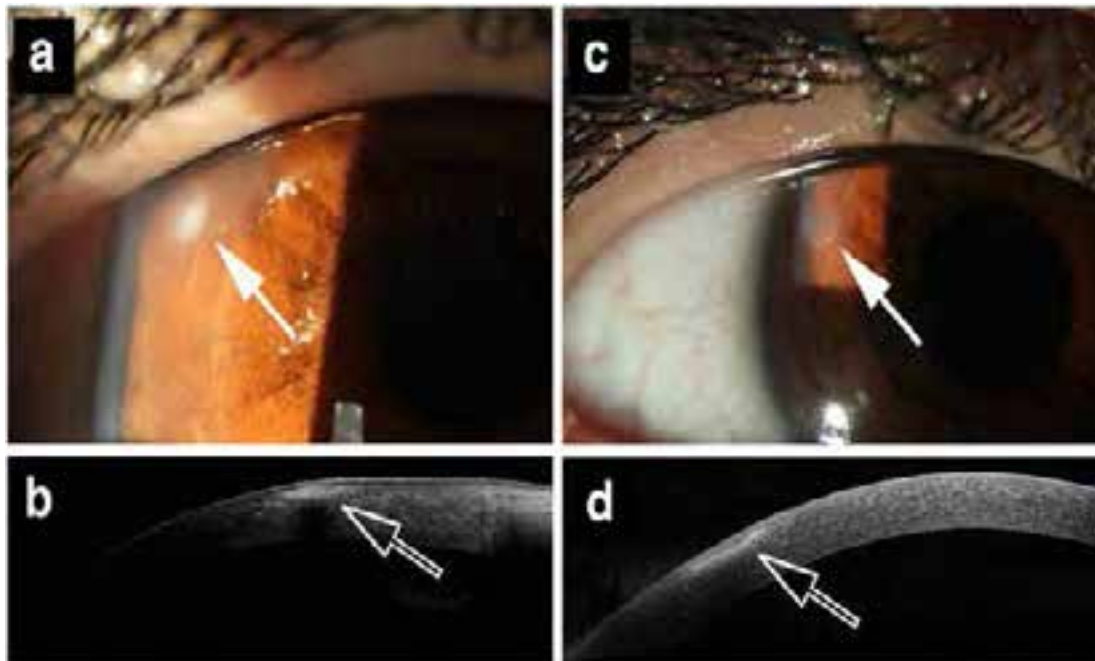
	Total	Bacterial	Fungal
# eyes (25 studies)	175	96	32
2 trials, 13 case series, 10 case reports			
Treatment failure	22/175 (13%)	14/96 (15%)	7/32 (22%)

- Ulcer size variable
  - Smaller ulcer size: higher success rate
  - Hypopion: reduced success rate
- Treatment → reepithelization: 4 <-> 99 days (pathogen dependent)
- Culture positive: all (inclusion criterium)

• Papaioannou, L., M. Miligkos, and M. Papathanassiou, Corneal Collagen Cross-Linking for Infectious Keratitis: A Systematic Review and Meta-Analysis. Cornea, 2016. 35(1): p. 62-71.



## PACK-CXL in human patients



- Said, D.G., et al., Collagen cross-linking with photoactivated riboflavin (PACK-CXL) for the treatment of advanced infectious keratitis with corneal melting. *Ophthalmology*, 2014. 121(7): p. 1377-82
- Tabibian, D., C. Mazzotta, and F. Hafezi, PACK-CXL: Corneal cross-linking in infectious keratitis. *Eye Vis (Lond)*, 2016. 3: p. 11.



## PACK-CXL in human patients: masked trial

	Total	PACK-CXL	Control	
# eyes	30	15	15	
Stromal infiltrate size (mm <sup>2</sup> )		5.0	10.6	p = 0.66
Epithelial defect size (mm <sup>2</sup> )		0.7	4.6	P = 0.41

- Moderate to severe infectious keratitis
- Culture positive: all (bacterial < fungal)
- No difference in outcome between groups
- Most infiltrates in posterior corneal stroma
- Complication rates and BPVA: similar across groups

• Kasetsuwan, N., U. Reinprayoon, and V. Satitpitakul, Photoactivated Chromophore for Moderate to Severe Infectious Keratitis as an Adjunct Therapy: A Randomized Controlled Trial. Am J Ophthalmol, 2016. 165: p. 94-9.



## PACK-CXL in human patients: deep fungal keratitis

	Total	PACK-CXL	Control	
<b># eyes</b>	13	6	7	
<b>Treatment failure</b>		5	4	p = 0.56
- Perforation		4	0	p = 0.02
- Increased infiltrate size		1	4	P = 0.27

- Trial stopped prior to full enrollment
- 50% Aspergillus and Fusarium spp., rest unidentified

• Uddaraju, M., et al., Corneal Cross-linking as an Adjuvant Therapy in the Management of Recalcitrant Deep Stromal Fungal Keratitis: A Randomized Trial. Am J Ophthalmol, 2015. 160(1): p. 131-4 e5



## PACK-CXL in dogs and cats: literature

	Total	Dogs	Cats
# eyes (5 studies)	49	23	26
Brachycephalic/total		17/23	10/26
Treatment failure	5/49 (10%)	5/23	0/26

- Ulcer depth (%): 50% (15-80)
- Ulcer size variable
- Treatment → stabilization: < 14 days
- Treatment → defect closure: 14<->30 days
- **Dogs potentially do worse**

- Spiess BM, Pot SA, Florin M, et al. Corneal collagen cross-linking (CXL) for the treatment of melting keratitis in cats and dogs: a pilot study. *Vet Ophthalmol.* 2013.
- Famose F. Evaluation of accelerated collagen cross-linking for the treatment of melting keratitis in eight dogs. *Vet Ophthalmol.* 2013.
- Pot SA, Gallhofer NS, Matheis FL, et al. Corneal collagen cross-linking as treatment for infectious and noninfectious corneal melting in cats and dogs: results of a prospective, nonrandomized, controlled trial. *Vet Ophthalmol.* 2013.
- Famose F. Evaluation of accelerated collagen cross-linking for the treatment of melting keratitis in ten cats. *Vet Ophthalmol.* 2013.
- Famose F, Roy P. Evaluation of accelerated corneal collagen cross-linking (CXL) after impregnation of riboflavin by iontophoresis for the treatment of melting keratitis in 6 cats, Proceedings ECVO conference London 2014.



## PACK-CXL in dogs and cats: compilation

	Total	Dogs	Cats
# eyes (5 studies, unpublished data)	209	137	72
Brachycephalic/total		95/137	29/72
Treatment failure	28/209 (13%)	20/137	8/72

- Ulcer depth variable: 50% (0-80)
- Ulcer size variable: 0 – 15x16mm
- Treatment → stabilization: 2 <-> 45 days (mostly < 14 days)
- Treatment → defect closure: 0 <-> 90 days (mostly < 30 days)
- **Failure rate institution dependent: patient selection?**
  - Infiltrate density?
  - **Most treatment failures: deep ulcers (22/28 > 50% stromal loss)**



## PACK-CXL in dogs and cats: controlled study

- Non-inferiority PACK-CXL compared to medical Tx
- Stabilization of all corneas receiving PACK-CXL rescue treatment
- **No CXL-related complications observed**

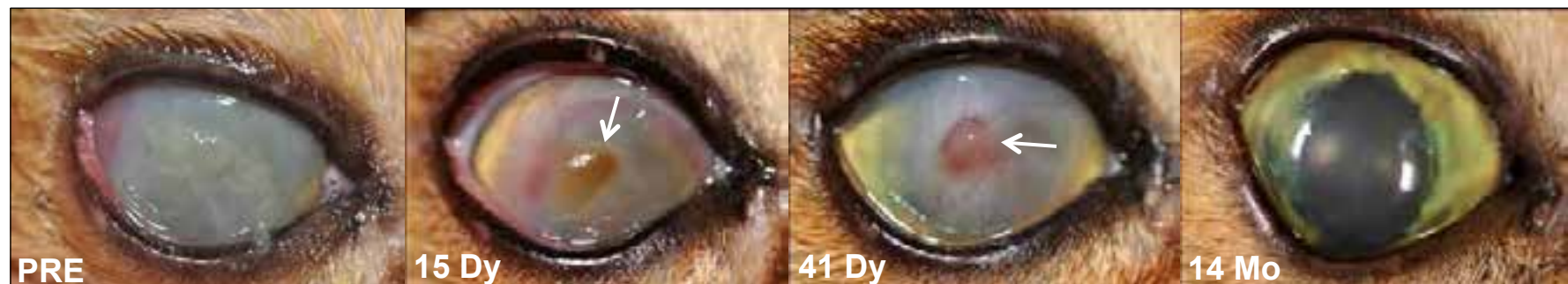


- Pot SA, Gallhofer NS, Matheis FL, et al. Corneal collagen cross-linking as treatment for infectious and noninfectious corneal melting in cats and dogs: results of a prospective, nonrandomized, controlled trial. *Vet Ophthalmol.* 2013. Epub 2013/08/15.



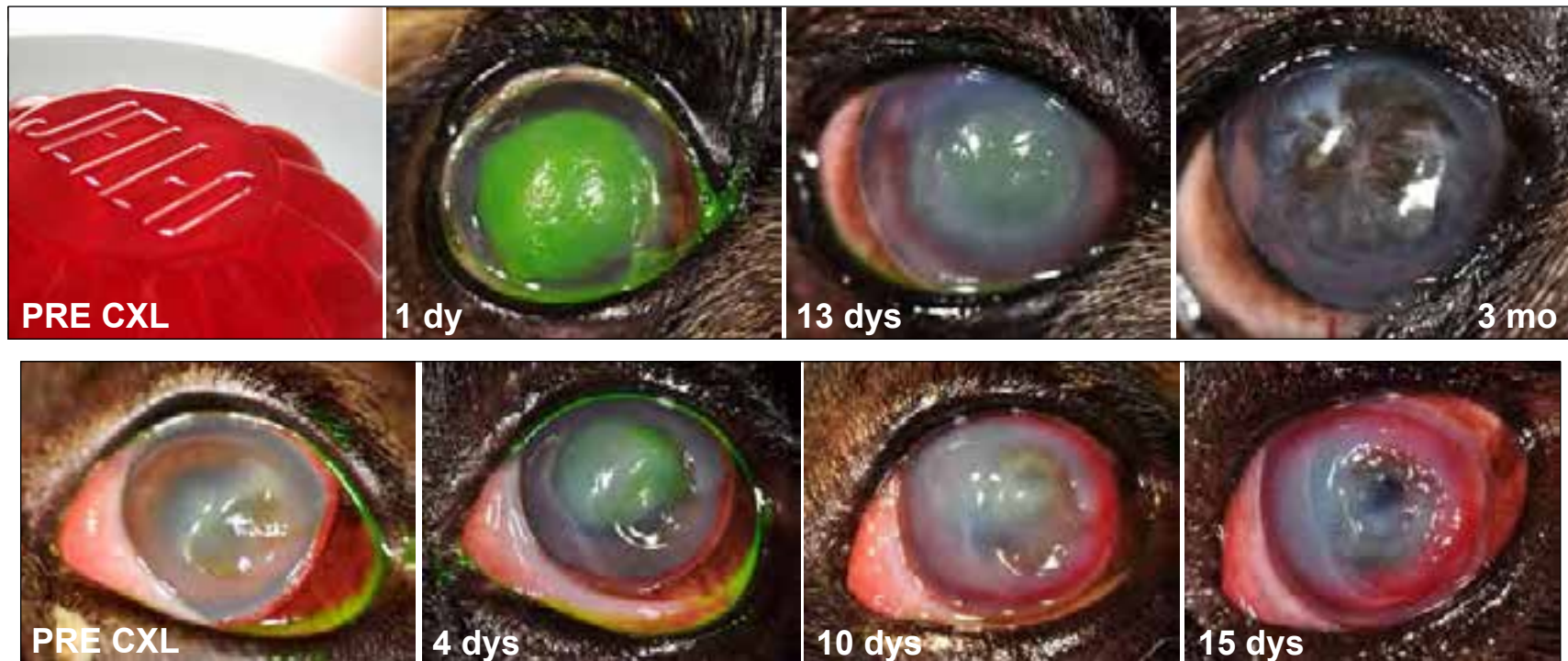


# PACK-CXL in cats: examples



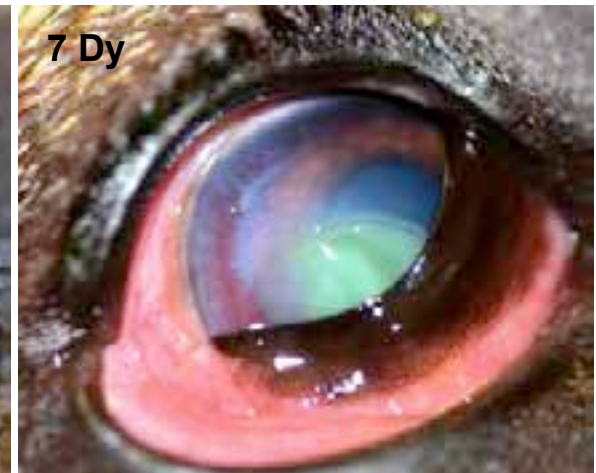
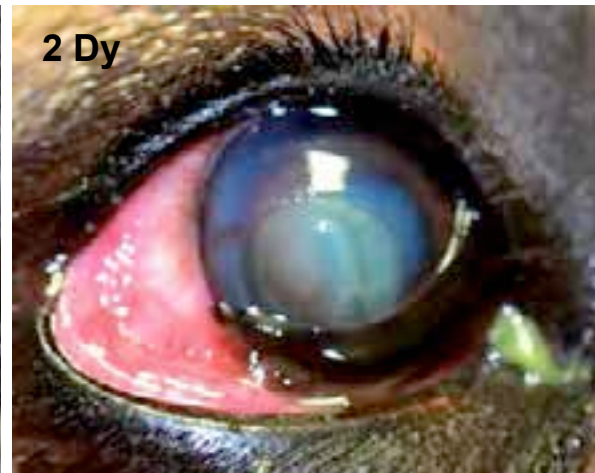


# PACK-CXL in dogs: examples





Veterinary Ophthalmology





## PACK-CXL in horses: conflicting results

Two studies from Sweden (21 eyes, standard protocol):

Treatment effect of stand-alone PACK-CXL inconsistent

- 13/21 culture positive (many G+, 2 fungal)
- 2013: 1/9 failed
- 2014: rescue with antibiotics needed



- Hellander-Edman A, Makdoui K, Mortensen J, et al. Corneal cross-linking in 9 horses with ulcerative keratitis. *BMC Vet Res.* 2013;9:128. Epub 2013/06/28.
- Hellander-Edman A, Strom L, Ekestén B. Corneal cross-linking (CXL) in comparison to medical treatment in horses with ulcerative keratitis, Proceedings ECVO conference London 2014.



University of  
Zurich <sup>UZH</sup>



University of Bern | University of Zurich

vetsuisse-faculty

Veterinary Ophthalmology

## Why do some cases do well and others not ??

Variation in response to treatment

- Days to weeks
- No response/treatment failure



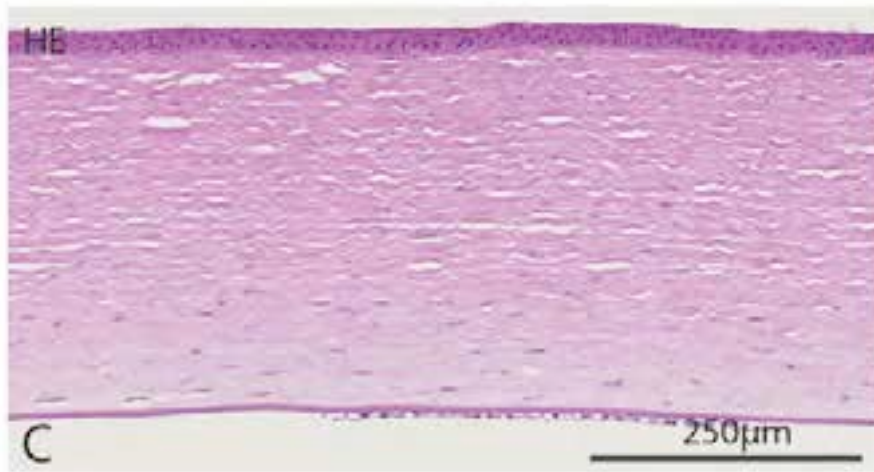
University of  
Zurich<sup>UZH</sup>



University of Bern | University of Zurich  
vetsuisse-faculty

Veterinary Ophthalmology

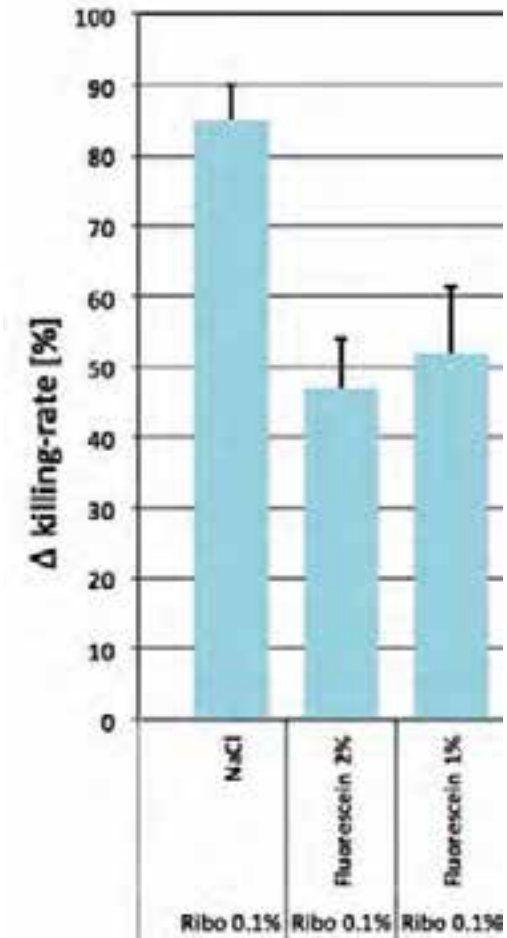
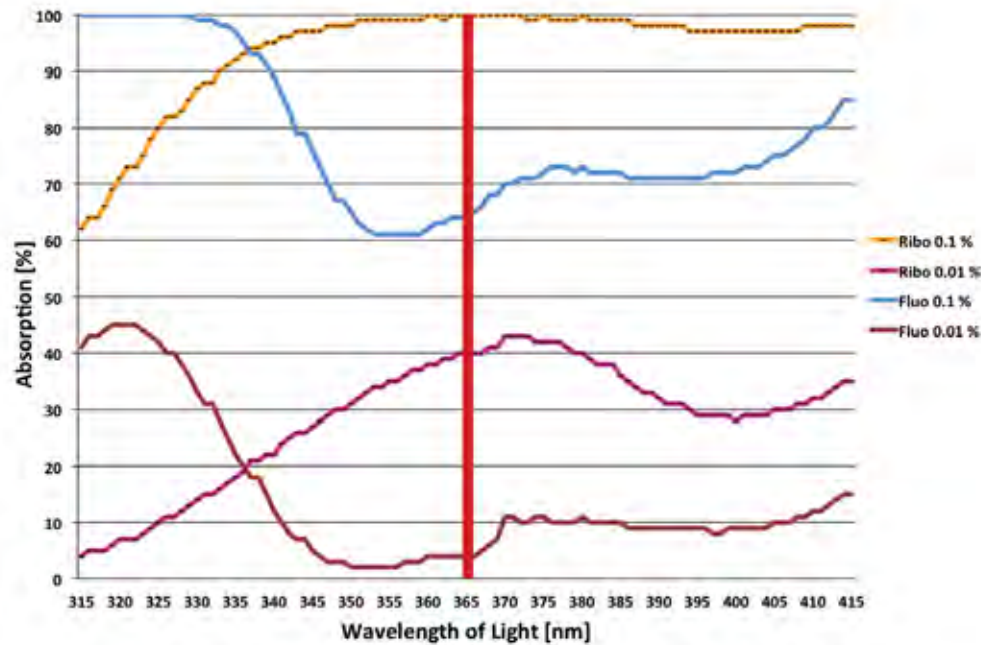
## PACK-CXL effect: epithelium





# PACK-CXL effect: pretreatment

- Fluorescein
- (Fluoroquinolones?)

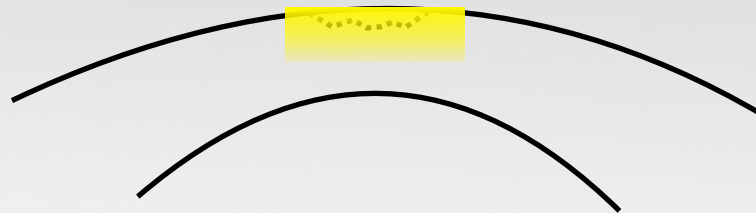


- Richo, O., et al., Impact of fluorescein on the antimicrobial efficacy of photoactivated riboflavin in corneal collagen cross-linking. J Refract Surg, 2013. 29(12): p. 842-5.



# PACK-CXL effect: lesion depth

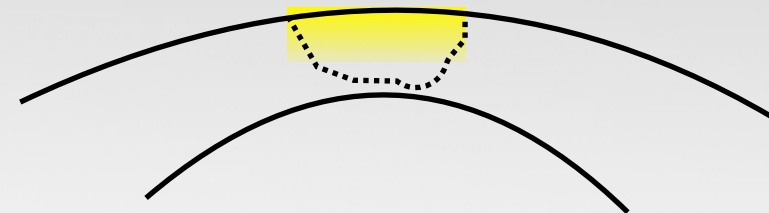
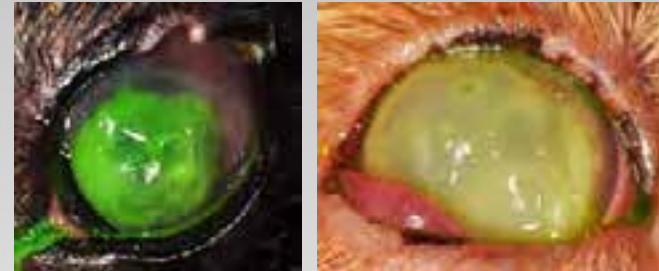
## Infiltrate / early ulcer ?



PACK-CXL: prospective, randomised multicenter trial 2017 – xxxx

PACK-CXL Study Group  
(Prospective, randomised multicenter trial, 16 sites)

## Advanced ulcer ?



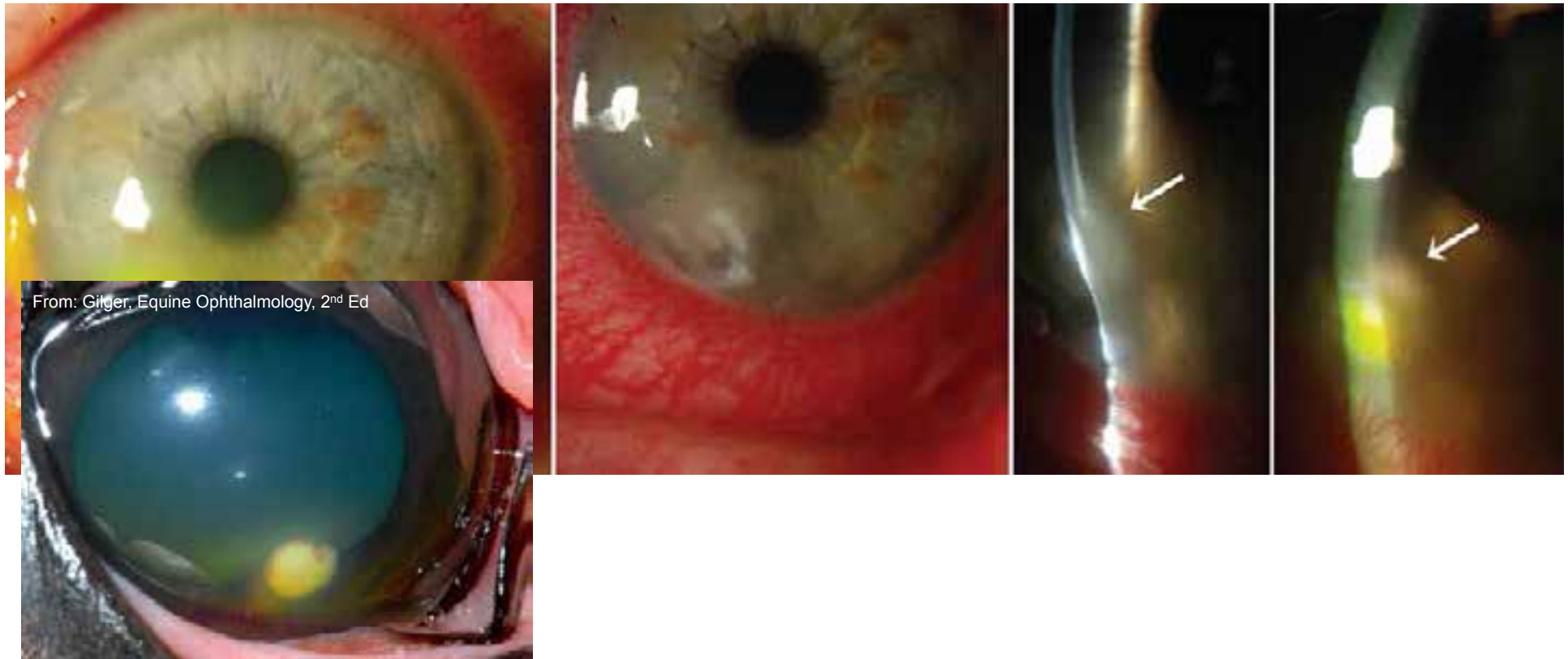
Pot et al. CXL in cats and dogs: prospective, nonrandomized, controlled trial. *Vet Ophthalmol.* 2013.

Said et al. PACK-CXL treatment of advanced infectious keratitis with corneal melting. *Ophthalmology.* 2014.





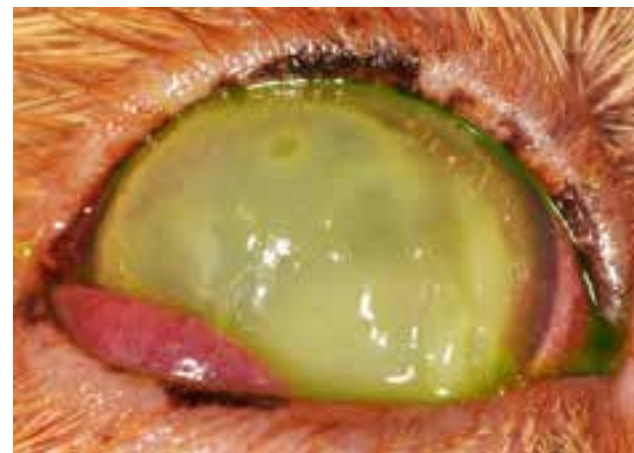
## PACK-CXL effect: lesion location



- Price, M.O. and F.W. Price, Jr., Corneal cross-linking in the treatment of corneal ulcers. Curr Opin Ophthalmol, 2016. 27(3): p. 250-5

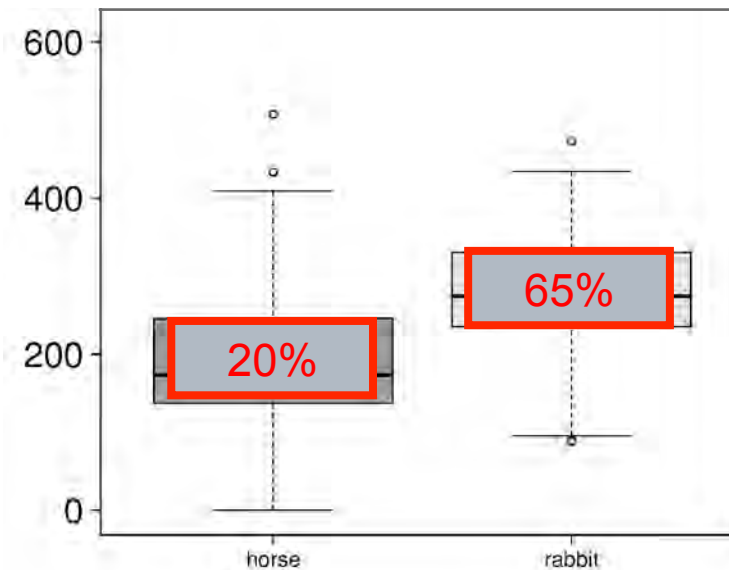
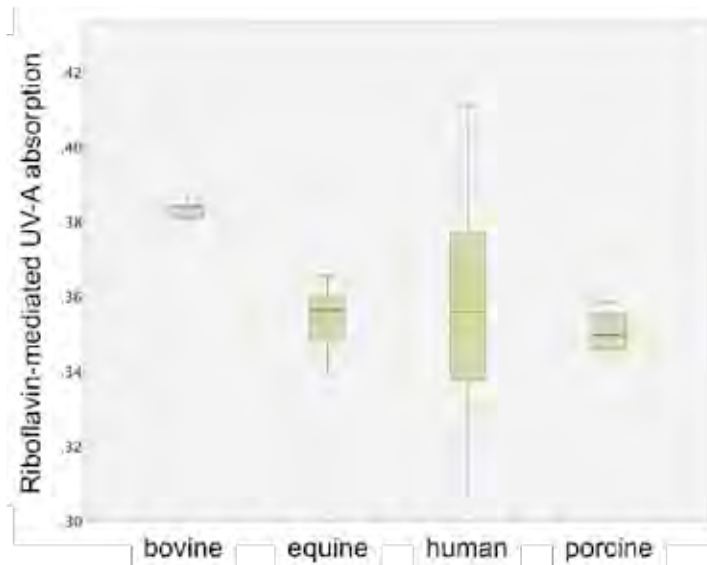


**PACK-CXL effect: infiltrates**





## PACK-CXL effect: patient species



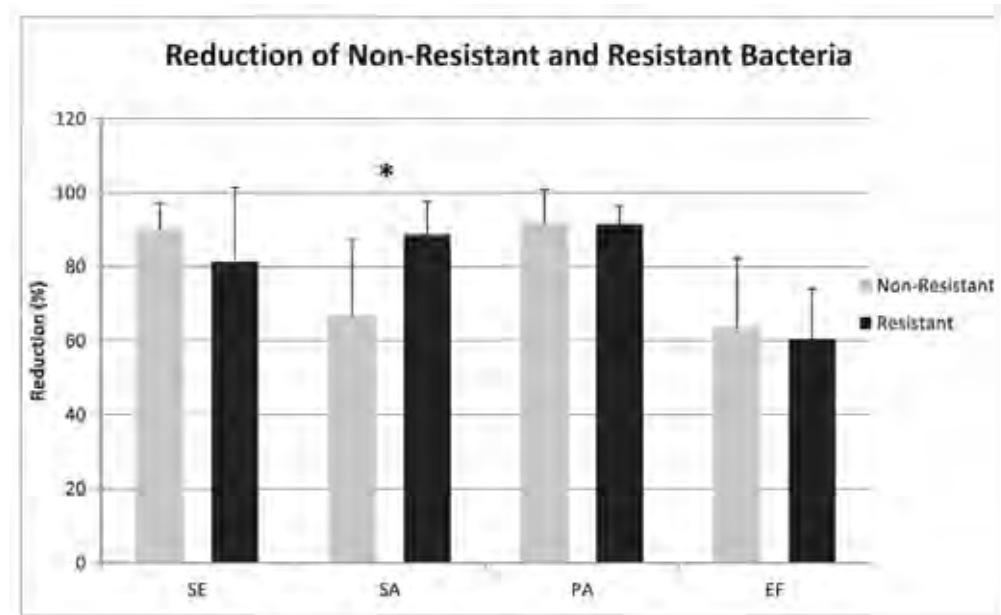
**Corneal thickness →  
customized treatment**

- Gallhoefer, N.S., et al., Penetration depth of corneal cross-linking with riboflavin and UV-A (CXL) in horses and rabbits. *Vet Ophthalmol*, 2016. 19(4): p. 275-84.
- Wuarin R, Richo O, Kling S, Pot SA, Tabibian D, Salmon B, Hafezi F. Riboflavin-mediated UV-A absorption in corneal cross-linking is species-dependent. *JRS*



## PACK-CXL effect: target microorganisms

- Avoid viral
- Bacterial vs fungal
- Variability in bacterial isolate susceptibility?



- Papaioannou, L., M. Miligkos, and M. Papathanassiou, Corneal Collagen Cross-Linking for Infectious Keratitis: A Systematic Review and Meta-Analysis. *Cornea*, 2016. 35(1): p. 62-71.
- Makdoui, K. and A. Backman, *Photodynamic UVA-riboflavin bacterial elimination in antibiotic-resistant bacteria*. *Clin Exp Ophthalmol*, 2016. 44(7): p. 582-586.
- 'In vitro bactericidal effect of PACK-CXL on bacterial isolates from veterinary patients with septic keratitis', Dissertation Anja Suter cand med vet, Vetsuisse Faculty, Equine Clinic, University of Zürich. (April 2014 – present)

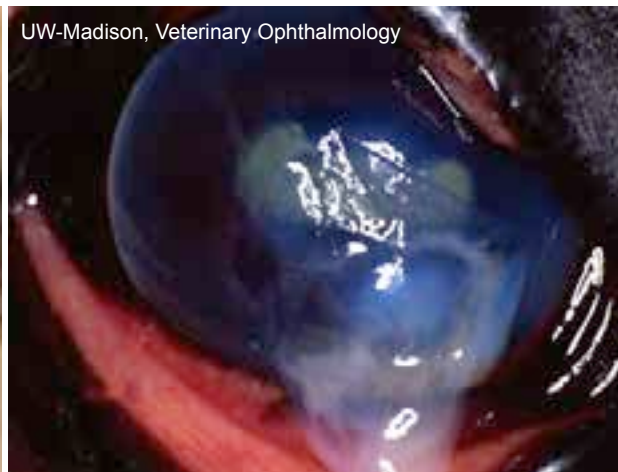


## CXL effect: indication

Bullous keratopathy



Septic keratitis



Deep stromal abscess





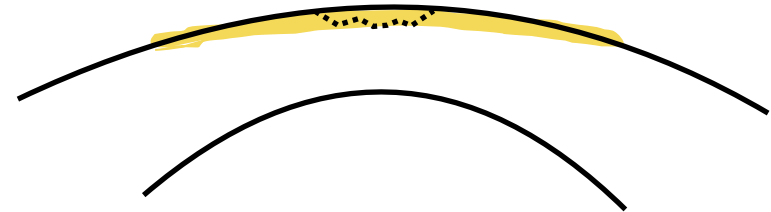
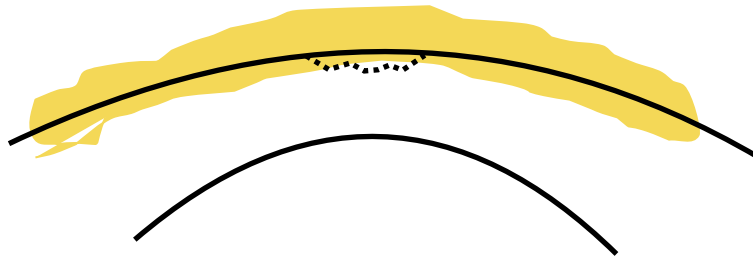
University of  
Zurich <sup>UZH</sup>



University of Bern | University of Zurich  
vetsuisse-faculty

Veterinary Ophthalmology

## CXL effect: chromophore solution viscosity





## PACK-CXL: influence of

- Patient species
- Corneal thickness/lesion location
- Inflammatory cell infiltrates
- Target microorganism
  - Type: bacterial-fungal
  - Interspecies differences in susceptibility
  - Intraspecies / interisolate differences in susceptibility
- Pretreatment with antibiotic, antifungal, anticollagenolytic agents



## PACK-CXL: protocol optimization

- Shortening of treatment time: 2.5 vs 30 minutes
- Fluence
- Chromophore
  - Concentration
  - Viscosity
  - Type
  - Delivery (intrastromal?)
- Total energy delivered
- Pretreatment
- Wound bed debridement





University of  
Zurich <sup>UZH</sup>

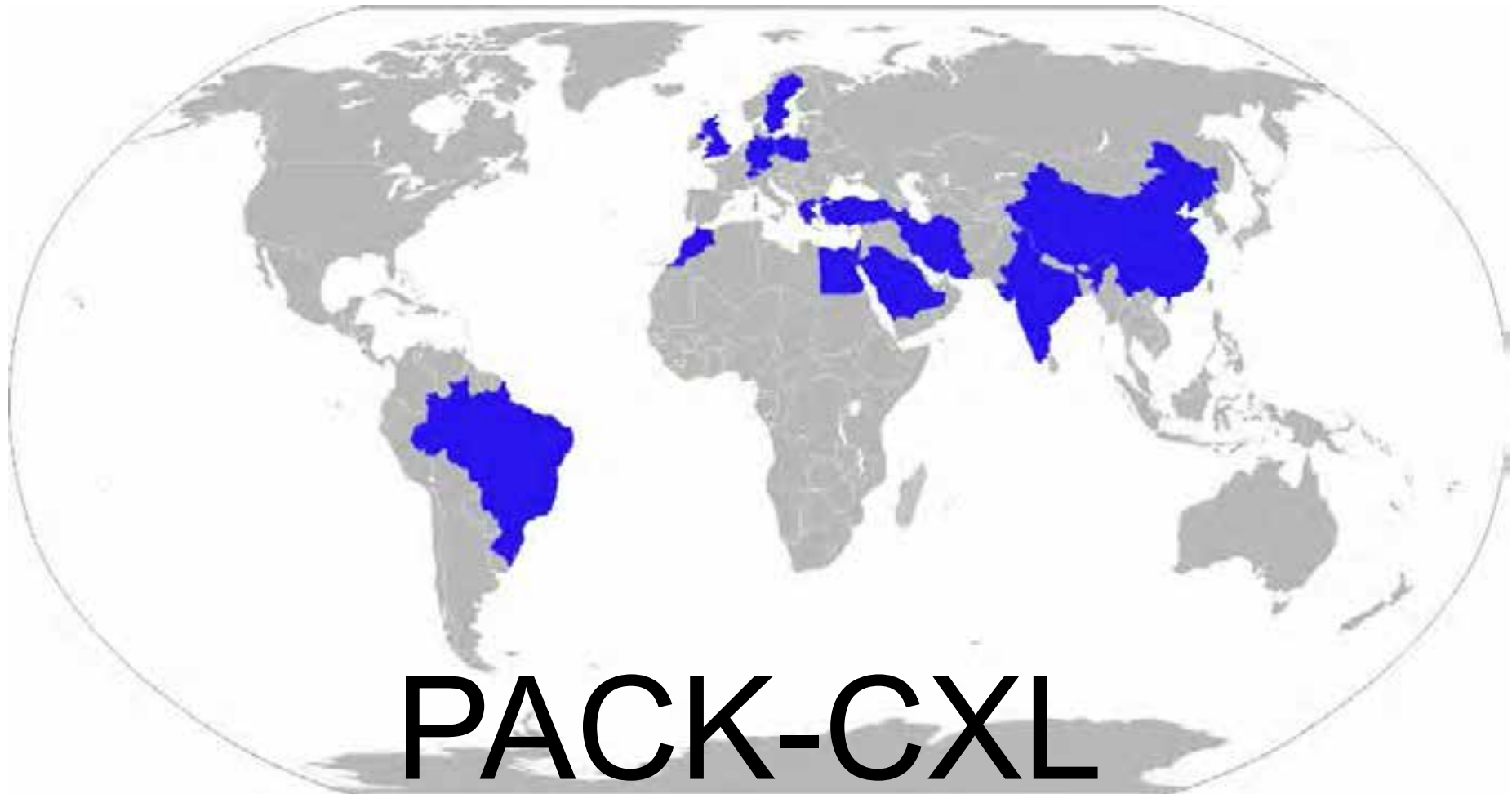
Veterinary Ophthalmology



University of Bern | University of Zurich

vetsuisse-faculty

## PACK-CXL prospective randomized multicenter trial



# PACK-CXL



University of  
Zurich<sup>UZH</sup>

Veterinary Ophthalmology



University of Bern | University of Zurich  
vetsuisse-faculty

## Proposed study

# PACK-CXL for the treatment of melting keratitis in dogs

Conclusive clinical efficacy study:

- Prospective
- Randomized
- Controlled
- Multicenter



## PACK-CXL for melting keratitis in dogs

- PACK-CXL as
  - alternative for
  - adjunct treatment to  
medical management
- Multicenter study: site participation
- Subject participation duration: 1 month
  - Treatment → stabilization: < 14 days
  - Treatment → defect closure: 14<->30 days
- 1° endpoint: rescue therapy



**Questions ?**