PACK-CXL
for infectious keratitis

Farhad Hafezi, MD PhD
Financial disclosures

• Named co-inventor on PCT applications CH2012/0000090 and PCT2014/CH000075

• Chief Scientific Officer EMAGine SA
AMR (Antimicrobial resistance), a global problem
1. Background

WHO's first global report on antimicrobial resistance, with a focus on antibiotic resistance, reveals that it is no longer a prediction for the future. Antibiotic resistance—when bacteria change and antibiotics fail—is happening right now, across the world.

What you need to know

ANTIMICROBIAL RESISTANCE
Global Report on surveillance 2014

Over the last 30 years, no major new types of antibiotics have been developed.

How can infections be prevented in the first place to reduce the need for antibiotics?

What you can do

- Use antibiotics only when prescribed by a health professional
- Complete the full prescription, even if you feel better
- Never share antibiotics with others or use leftover prescriptions

What does this mean?

Without urgent action we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill.

What can countries be prepared to do first to reduce the need for antibiotics?

- Better hygiene
- Access to clean water and sanitation
- Infection control in healthcare facilities
- Vaccination

WHO report 2014
1. Background

The report is the most comprehensive picture to date, with data provided by 114 countries. Looking at 7 common bacteria that cause serious diseases from bloodstream infections to gonorrhoea, high levels of resistance found in all regions of the world. Significant gaps exist in tracking of antibiotic resistance.

Over the last 30 years, no major new types of antibiotics have been discovered.

Discovery void

Penicillin  Cephalosporin  Carbapenem  Fluoroquinolones

What does this mean?
Without urgent action we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill.

What you can do

- Use antibiotics only when prescribed
- Complete the full prescription
- Never share antibiotics with others
1. Background

AMR, a global problem

How does AMR compare?

Major causes of death (annual figures)

- Tetanus: 60,000
- Cholera: 100,000 - 120,000
- Measles: 130,000
- AMR in 2050: 10,000,000
- Road traffic accidents: 1,200,000
- Diarrhoeal disease: 1,400,000
- Diabetes: 1,500,000
- Cancer: 8,200,000

Source: The Review on Antimicrobial Resistance
1. Background

Diagnostic dilemma, therapeutic dilemma
1. Background

Infectious keratitis - “Silent epidemic” (WHO)

- Antibiotic resistance
- Mixed infections
- High costs
- 6-8 Million new cases / year
- 205'000 ophthalmologists

Developed countries

Developing countries
1. Background

2. Need gap: AMR

3. Need gap: Corneal infection


- Kills both bacteria and fungi
- Reduce diagnostic and therapeutic dilemma
- Alternative to antibiotics
Zurich, Switzerland: 2004

1. Background

IROC
(Seiler, Mrochen, Hafezi, Iseli)

ETH
Swiss Federal Institute of Technology
1. Background

Cross-Linking effects

1. Biomechanical stiffening

2. Steric hindrance

3. DNA/RNA intercalation

4. Oxidative stress

1. Background

2. First Results

Post-LASIK keratitis

Ten days after PACK-CXL

Iseli et al, 2008, Cornea
Laboratory

• Staph aureus growth inhibition by 97% in 30 minutes (Dresden keratoconus protocol)

Figure 1. Percent of growth inhibition of organisms with exposure to riboflavin, ultraviolet (UV) light, or combined riboflavin and UV light.

Schrier et al., IOVS, 2008
Martins et al., IOVS, 2008
1. Background

2. First Results

Pot and Hafezi, *Vet Ophthalmol, 2013*

Mortensen et al., *Vet Ophthalmol, 2013*
2011 Phase 2 Clinical Trial

No antibiotics

Before PACK-CXL

Two weeks after PACK-CXL

Makdoumi et al., Curr Eye Res, 2011
1. Background

2. Results

3. Optimize

Kill bacteria and fungi simultaneously

**BACTERIA**
- Up to 98% *in vitro*
- With fluence currently used in clinical setting

**FUNGI**
- 60-70% *in vitro*
- With high fluence currently used in clinical setting (7.2 J/cm²)

<table>
<thead>
<tr>
<th></th>
<th>MSSA</th>
<th>MRSA</th>
<th>P. aeruginosa</th>
<th>S. epidermidis</th>
<th>C. albicans</th>
<th>Fusarium</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4 J/cm²</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>(✓)</td>
<td>(✓)</td>
</tr>
<tr>
<td>98%</td>
<td>99%</td>
<td>98%</td>
<td>97%</td>
<td>60-70%</td>
<td>60-70%</td>
<td></td>
</tr>
</tbody>
</table>

Schrier et al., IOVS, 2008
Martins et al., IOVS, 2008
Richoz et al., JRS, 2014
Richoz et al., unpublished data
Future treatment needs

• Simplify
• Accelerate
• Access to all
1. Background

2. Results

3. Optimize
2010-2013: Advanced ulcers

Collagen Cross-Linking with Photoactivated Riboflavin (PACK-CXL) for the Treatment of Advanced Infectious Keratitis with Corneal Melting

Dalia G. Said, MD, FRCS,1,*, Mohamed S. Elaify, MSc,1,*, Zisis Gatzionas, MD, PhD,2
Ehab S. El-Zakzonek, PhD,1 Mansour A. Hassan, MD,3 Mohamed Y. Saif, MD,4 Ahmed A. Zaki, MD,1
Harminder S. Dua, MD, PhD,4 Forhad Hafezi, MD, PhD2,4

Ophthalmology, 2014
Treat Early

Infiltrate / Early ulcer ?

Advanced ulcer ?

Price et al., JRS, 2012

Said et al., Ophthalmology, 2014
Accelerate: bactericidal effect

Richoz et al, JRS, 2014
Accelerate: enzymatic digestion

Cross-Linking Biomechanical Effect in Human Corneas by Same Energy, Different UV-A Fluence: An Enzymatic Digestion Comparative Evaluation

Anastasios J. Kanellopoulos, MD,* † Yannis L. Loukas, PhD, † and George Asimellis, PhD*

Kanellopoulos et al, Cornea, 2016
Phase 2 trial: accelerated PACK-CXL

• 180 seconds @ 30 mW/cm²
• Adjuvant to antibiotics

Knyazer et al., in preparation
Phase 2 trial: accelerated PACK-CXL

• 180 seconds @ 30 mW/cm²
• Adjuvant to antibiotics

Knyazer et al., in preparation
Swiss PACK-CXL multicenter trial

• Phase 3 prospective, randomized, multicenter trial
• Non-inferiority study
• Infiltrates and small ulcers < 2 mm, < 300 µm depth
• n = 252

11 sites
10 countries
Introduction at ESCRIS 2016 Copenhagen

C-Eye© device

5. CXL at the slit lamp
Conclusions PACK-CXL

- Accelerated to 3 minutes
- Highly efficient in bacteria and fungi
- CXL at the slit lamp: access to all
Conclusions

MedLine 1997 - 2016

- Papers on CXL for keratoconus
- Papers on PACK-CXL for infectious keratitis

• PACK-CXL is a new technology, do not use as a routine procedure (yet)