

OCULAR SURGERY NEWS[®]

Cover Story on PACK-Cross-Linking

Increasing evidence shows efficacy of PACK-CXL as potential first-line treatment for infectious keratitis

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PACK cross-linking has the potential to become an effective, simple, fast and cost-saving alternative treatment for infectious keratitis, according to several experts.

“The beauty of PACK-CXL is that it is an unspecific weapon that works with bacteria, antibiotic resistant bacteria, even multi-resistant *Staphylococcus aureus*, and at the same time it works with fungi. It might change the paradigm in the future of how we treat the infection on the surface of the eye,” **Farhad Hafezi, MD, PhD**, OSN Europe Edition Board Member and principal investigator of a large study on this technique, said.

PACK-CXL — short for photoactivated chromophore for infectious keratitis corneal cross-linking — works by at least two mechanisms, he explained. On one hand, the stabilizing effect of cross-linking on the corneal stroma increases its resistance to enzymatic bacteria degradation, avoiding progression to corneal melting. On the other hand, photoactivated riboflavin has bactericidal properties against some common pathogens, as shown by in vitro experiments.

Hafezi was part of the team that performed the initial pilot study of cross-linking for infectious keratitis.

“We were inspired by the solar water disinfection (SODIS) method established here in Zurich at the Swiss Federal Institute of Technology (ETH Zurich). They found that the addition of riboflavin and other vitamin B compounds resulted in accelerated disinfection. In 2008, we published in *Cornea* our pilot study,” he said.



Farhad Hafezi, MD, PhD, pioneer and principal investigator of a large multicenter study on PACK-CXL, foresees that this technique will become first-line treatment for infectious keratitis, allowing for earlier treatment, cutting costs and overcoming compliance issues.

Image: Hafezi F

Currently, a large prospective, randomized multicenter trial on PACK-CXL is ongoing. The study involves nine centers, with four more centers awaiting approval, and is comparing PACK-CXL as first-line therapy against the current standard of care with antibiotics.

“We aim at 250 eyes to be statistically relevant, which will make this the largest PACK-CXL study to date,” Hafezi said.

Since it was demonstrated that PACK-CXL can be accelerated to 30 mW/cm² for 3 minutes without losing the efficacy of the killing effect, all centers have been asked to use the same fluence of 5.4 J/cm² with either 9 mW/cm² for 10 minutes or 18 mW/cm² for 5 minutes.

Causes and pathogens

Infectious keratitis has a global incidence that ranges between 6.3 and 710 cases per 100,000 persons per year. It is induced by a variety of bacteria, fungi, protozoa and viruses, which, if not treated adequately, may lead to corneal ulceration, melting and perforation.

Most cases in developed countries are bacterial, and incidence has been increasing due to higher rates of contact lens use. A study of the Hong Kong Microbial Keratitis Study Group found an annual incidence of 0.63 per 10,000 in non-contact lens wearers and 3.4 per 10,000 in contact lens wearers.



Jes Mortensen

In a series of 50 patients treated with PACK-CXL at Örebro University Hospital, Sweden, the group of **Jes Mortensen, MD**, found that almost half were contact lens users and the most common bacteria were coagulase-negative *Staphylococcus* and *Staphylococcus aureus*.

“My first patient was also a lens user who did not respond to extensive treatment with antibiotic, antiprotozoal, as well as antifungal drugs. Intense symptoms persisted, and corneal melting progressed. We decided to do CXL, and the ulcer healed within a few weeks. This first success increased our interest in the method, and we started using PACK-CXL first with severe keratitis with melting,” Mortensen said.

Healing occurred in almost every case, but when results were presented, they were met by great skepticism.

“Very few really believed us,” he said.

PACK-CXL is the now standard treatment in his clinic, which receives patients from an area with 328,000 inhabitants. Since 2007, more than 100 cases have been treated.

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"Today we use PACK-CXL in almost every case but always do culturing to look for the bacteria," Mortensen said.

Shihao Chen, MD, MSc, OD, professor at Wenzhou Medical University, China, said that in his area bacterial infections are the most common type of infection. Fungal infections tend to be seen with a seasonal change, while mixed-type infections are relatively rare.



Shihao Chen

He noted that while bacterial infections are easily controlled in most cases, there is a shortage of effective medical treatments, topical or oral, for fungi.

"Therefore, we need complex and aggressive treatment strategies for fungal, eg, intrastromal injection, conjunctival flap covering and eventually corneal transplant in some cases," he said.

Minor trauma is the main cause of infection in his area, followed by contact lens wear and immune system-related infection.

Immune deficiency, trachoma and trauma are related to the high prevalence of infectious keratitis in the African continent.

"We see all types of viral, bacterial, fungal and mixed infection, and quite often, in at least 50% of the cases, the causative agent is not found," **Abdelouahed Amraoui, MD**, of Casablanca University in Morocco, said.

A broad-spectrum, early treatment option

One of the advantages of PACK-CXL is that it is unselectively effective against a wide range of bacteria and fungi. If large studies are able to provide evidence for this, the treatment could become first-line, together with antibiotics or even as a standalone procedure to perform immediately when patients present with symptoms and signs of infection. This would avoid treatment delays and progression to advanced stages.

"In Switzerland and in most European countries, people present early but rarely present directly to specialized tertiary centers. They are treated by the family doctor or by the general ophthalmologist, and in case they do not respond to the treatment, they are referred to us. Therefore, quite a lot of the cases we see are fairly advanced cases," Hafezi said.

Treatment is often delayed because infectious keratitis poses a diagnostic and therapeutic dilemma.

"When the patient comes in, the doctor can only make decisions based on clinical signs and gut feelings. We prescribe antibiotics in most cases and in the meantime do swaps and scrapes and send them in for testing. Results may take days to come back, and over that time span we treat the patient without having a documented origin of the infection," Hafezi said.

"Personally I like to think that PACK-CXL will be used as a very first treatment option in a few years. We could still use antibiotics at the same time, but the cross-linking procedure would be the broad-range weapon we use before we know from the lab what exactly we have to fight against," he said.

A weapon against antimicrobial resistance

With emergence and spread of antimicrobial resistance (AMR) in a more globalized world, the search for new, alternative remedies has become an urgent challenge of modern medicine. The G7 summit in 2015 had three main topics on its agenda: global warming, terrorism and antimicrobial resistance.

"In about 10% of infectious keratitis we experience increasing resistance to treatment, and maybe 2% of them end up with a really bad outcome. AMR is a fast-growing problem. According to the WHO, in 2050 more people will die from AMR than cancer and diabetes together," Hafezi said.

"In China, AMR is increasing due to overuse and inappropriate use of antibiotics. PACK-CXL has the potential to become an interesting alternative treatment modality in the future against resistant organisms," Chen said.

A more affordable treatment

Many cases of corneal melting or corneal ulcers are seen in Morocco, where self-medication is a widespread problem, delaying proper treatment.

"People go to the pharmacist who prescribes corticosteroids that aggravate the condition. When they come to us, they have already progressed to the advanced stages," Amraoui said.

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In these cases, currently he discontinues all medications for at least 48 hours, does a swap and then treats with cross-linking.

“I am very happy with this new opportunity because the current standard treatment with antibiotics is often disappointing and is expensive. In our country only 30% of the population have social security coverage, and the majority of our patients are unable to afford the costs,” he said.



Abdelouahed Amraoui

“A single cross-linking treatment currently costs the equivalent of 150, while a full course of specific, long-term antibiotics amounts to 1,500, which the majority of patients have to pay out of pocket. To this, we have to add the cost of frequent visits and traveling maybe from far. There is very little chance that patients will come again and very little chance that they will buy and take the antibiotics regularly,” he said.

Hospital costs, compliance

PACK-CXL has a huge saving potential also in terms of reducing the costs of hospitalization, Mortensen said.

“Since we moved from standard of treatment to PACK-CXL, very few patients are hospitalized. We have only one hospital bed in a population of 328,000 inhabitants for the eye clinic. Severe keratitis with melting would occupy that hospital bed for weeks,” he said.

According to an Australian study, the cost of a corneal ulcer, including hospitalization, is US\$5,000.

“During my time as chairman of ophthalmology at the University of Geneva, I almost always had at least one patient hospitalized for non-healing corneal ulcer, and the usual time was 3 or 4 weeks. This amounts to hundreds of thousands francs for hospitalization in Switzerland,” Hafezi said.

In addition, compliance with long-term antibiotics is a challenge in developed areas.

“Young people are usually good, but older people are often poorly compliant,” Chen said.

Conversely, Hafezi said he has the greatest problems with teenagers who were careless with contact lens hygiene in the first place and tend to be equally careless with treatment because they do not understand the severity of the condition.

Work in progress

PACK-CXL is not yet an established method. It should not be used routinely but only in well-designed studies to test the limits of the method, Hafezi said.

“If we use it too rapidly and uncontrolled, or in studies with poor study design, we may end up with poor results, as it happened in some cases. The protocol for PACK-CXL is not yet standardized. It is a work in progress, and a lot has yet to be defined,” he said.

His research group is experimenting with different fluence intensities to improve the efficacy on fungi and maybe find the key to fight viruses and *Acanthamoeba*. Another research focus is photosensitizers, aiming to find a compound that is more specific than riboflavin. The best UVA irradiation time for efficacy is also under investigation.

“Eventually we should be able to customize the treatment, setting the best UV dose, intensity and time combination for individual patients, as well as modulating riboflavin concentration and soaking time according to the stage of the disease and perhaps corneal thickness,” Chen said.

Presently, riboflavin is not approved in China, where the only available device is the standard Avedro CXL platform, and the cost of the treatment is much higher than antibiotics.

“We need a technology that is accessible to all clinicians, and we need to lower the costs,” Chen said.

Amraoui said that the technology available at his clinic only allows for the standard protocol with long exposure time and advocates a better compound than standard riboflavin.

“This is the reason why we joined Prof. Hafezi’s study and look forward to being able to adopt the new protocol,” he said.

The Geneva University spinoff company EMAGine has developed the C-Eye device, a mobile cross-linking technology that will allow for slit lamp CXL and PACK-CXL treatments.

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“What I dream of and reasonably foresee within 5 years is PACK-CXL in the hands of general ophthalmologists, performed at the slit lamp. It makes a lot of sense, and it will be a giant step forward in the management of the disease,” Hafezi said. – *by Michela Cimberle*

[Click here to see the Point/Counter to this article.](#)

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Should PACK-CXL be used as a first-line procedure for or in addition to antimicrobial treatment?

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POINT

PACK-CXL would bypass problems of antibiotic resistance

In 2014 we published in the *British Journal of Ophthalmology* one of the first papers on PACK-CXL. We reported on a series of patients who did not respond to full medical therapy. After CXL, bacterial infections resolved very well. What we were dealing with and could effectively defeat with CXL were most likely antibiotic-resistant bacteria.

Despite growing alarm, antibiotics are overprescribed worldwide. Overuse and misuse are leading to increasing resistance, and many of the common bacteria have become hard to fight with the antibiotics we have today. Not many new antibiotics are in the market nowadays. The last big thing was moxifloxacin. Whatever the reason, financial or scientific, behind this halt of research, we are now disarmed against bacteria



Rohit Shetty

Cross-linking has shown to help in patients who are resistant to antimicrobial therapy. It is a safe method that causes no collateral damage, and I would recommend it as first-line treatment. There are not many published papers supporting this yet, but I am part of an ongoing trial that might prove that PACK-CXL is safe and effective and can be used straight away, together with if not before medications.

PACK-CXL might be a true sight saver, particularly in areas where access to therapy is not very good and due to logistic, economic and cultural reasons it is very difficult to have patients take antibiotic drops regularly and visit the doctor every day.

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Rohit Shetty, MD, PhD, is vice chairman and chief of cornea and refractive surgery, Narayana Nethralaya Eye Hospital, Bangalore, India. Disclosure: Shetty reports no relevant financial disclosures.

COUNTER

There is not enough evidence, and complications should be a concern

PACK-CXL is a promising technique, but not enough data have yet been produced to support its use as a first-line procedure. I would still suggest to use antibiotics as first-line, and maybe consider cross-linking in selected, special cases.



Martin Dirisamer

Although cross-linking seems to be a safe procedure, we should not forget that there are potential complications involved. Cases of severe corneal melting after cross-linking have been reported, and concerns about this possibility should be even greater when dealing with corneas that are weakened by an infection.

All in all, I think antibiotics are still the method of choice. However, antibiotic resistance is a fast-growing problem, and this might lead cross-linking to become the standard procedure in a not too distant future. Where I see a role for PACK-CXL even now is in underdeveloped countries where there is no access to antibiotics.

Martin Dirisamer, MD, PhD, is in the Ophthalmology Department, University of Munich, Germany. Disclosure: Dirisamer reports no relevant financial disclosures.

PACK-CXL should be considered an option to treat corneal infections

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Jorge L. Alió, MD, PhD

PACK-CXL is the application of cross-linking for the treatment of corneal infections. Based on extensive experimental data and an important clinical background, we do know that ultraviolet light has teratogenic effects on different germs, which makes it capable of sterilizing superficial infections. Ultraviolet light has been extensively used to disinfect cosmetic and surgical gadgets, aiming to avoid infections. The therapeutic use of ultraviolet light is the background of PACK-CXL. Dr. Hafezi and colleagues have shown preliminary clinical data that has demonstrated that corneal infections, when treated early and not very aggressively, can be sterilized by one or several sessions of ultraviolet light provided at the slit lamp with a special device designed by them. The usefulness of the procedure is demonstrated, and its main advantages are simplicity, cost-effectiveness and ease of application. The treatment performed at the slit lamp is controlled by the surgeon, and it can be repeated according to clinical decisions.

Our research department and I already have more than 6 years of experience in the use of collagen cross-linking for the treatment of corneal infections. Based on the Dresden protocol, we started using it in corneal keratitis resistant to all medical therapies, particularly of fungal origin. Our outcomes have been good and have demonstrated the usefulness of CXL in the treatment of this type of severe, untreatable infection, as a coadjuvant to other therapies. Our experience in *Fusarium keratitis* has been outstanding, and we were able to save cases that were otherwise impossible to solve without a corneal graft, which in acute uncontrollable infections is usually a failed procedure. We have learned that CXL can be repeated twice and even up to four times to sterilize a case. Not only that, CXL decreased from the very beginning pain and inflammation, consolidated the cornea from melting and prevented corneal perforation. We did, based on our results, a meta-analysis review in which it was clear that the evidence in favor of CXL in the treatment of corneal infections was well sustained by evidence.

Our preferred practice at this moment for infectious keratitis is to start with fourth-generation quinolones in case we suspect a bacterial infection, and in cases that we consider that we are dealing with a fungi, microbacteria or *Acanthamoeba*, from the very beginning we use CXL with the Dresden protocol. We eliminate the epithelium around the ulcer, and we treat during the time of the Dresden protocol, the cornea impregnating in the same way as we do in keratoconus. Corneal thickness behaves in a different way than in keratoconus because we are dealing with an opaque area of the cornea, and even in those cases in which there is a thin cornea for cross-linking, we have never suffered a corneal decompensation because the corneal abscess blocks the pass of ultraviolet light. We know that from the beginning the case will improve, but we also know that the treatment should be repeated several times, 1 week apart. At the same time, we are providing topical therapy to the suspected infection.



Jorge L. Alió

So far, PACK-CXL may be applicable and has an indication in early corneal infections, according to recent evidence, particularly when located superficially. Its application should be ideal in bacterial keratitis cases coming from contact lens use, corneal trauma including contamination from the agricultural environment and postoperative corneal graft surgery.

The main pitfalls of PACK-CXL are lack of demonstrated usefulness in well-established bacterial keratitis and doubtful effectiveness in deeply located corneal infiltrates because the superficial layers will prevent the action of the ultraviolet light. It also may not be effective in cases in which the corneal opacity is happening in the environment of the suspected or confirmed corneal infection.

PACK-CXL should be considered an option to treat corneal infections

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Jorge L. Alió, MD, PhD

What are the future perspectives of collagen cross-linking applied to the treatment of corneal infections? A straightforward, cheap device attached to the slit lamp seems to be ideal for medical use. Its ease of use and accessibility will be ideal for those areas of the world in which corneal infections are frequent. Not only that, it may prevent the use of topical medications such as fortified antibiotics, which are toxic for the ocular surface and particularly the corneal epithelium. Based on the evidence published by us and others, and the recent information provided by the work of Hafezi, CXL should be considered as an option for any type of initial corneal infection, particularly, in our opinion, for those in which a resistance to antibiotics is expected or a doubtful bacterial origin is anticipated.

PACK-CXL is a useful technique that deserves further attention by clinical and surgical ophthalmologists.

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