PACK-CXL: Corneal Collagen Crosslinking for Infectious Keratitis

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Thought to involve both direct antimicrobial and corneal tissue-stabilizing action, there is evidence to support the use of corneal collagen crosslinking (CXL) in the treatment of infectious keratitis. Currently, however, available research points to CXL as a salvage therapy, best employed to stabilize cases of severe, refractory keratitis and avoid emergency keratoplasty.

A procedure with established efficacy in treating keratoconus and post-LASIK ectasia, CXL received its long-awaited approval from the US FDA for these indications in 2016. Its ability to enhance the biomechanical strength of the cornea has led researchers to investigate CXL for other conditions where corneal tissue integrity is at risk, such as bullous keratopathy. The fact that photoactivated riboflavin can also be used to inactivate pathogens (e.g., in donated blood products) has suggested a possible role for CXL in treating corneal infection.

CXL for infection (which some researchers differentiate by the name “photo-activated chromophore for keratitis” or “PACK-CXL”) is thought to work both by direct antimicrobial action and by strengthening the cornea against melting and perforation. Photoactivated riboflavin inhibits microbial replication and may also damage cell walls by the release of reactive oxygen species (See Box: In Vitro Antimicrobial Efficacy of CXL). In addition, crosslinks created within the corneal stroma enhance tissue resistance to enzymatic degradation, the result of either bacterial proteases or collagenases released as part of the immune response.

The greatest fear with a corneal ulcer is perforation, a potentially devastating complication that may require an urgent transplant. The likelihood of graft failure is higher when keratoplasty is performed on an actively infected and inflamed eye, so a treatment that may forestall such an emergency is worth considering in these cases.

While relatively time-consuming, the CXL procedure is technically simple. Some practitioners advocate...
variations on the original technique, developed by researchers at the University of Dresden, but most studies of PACK-CXL have used something very close to the Dresden protocol. After applying topical anesthesia and removing the corneal epithelium, a solution of 0.1% riboflavin and 20% dextran is applied every few minutes for 30 minutes, or until its penetration into the anterior chamber is visible at the slit lamp; then, the eye is exposed to ultraviolet A (UVA) light (370 nm) for 30 minutes at an irradiance of 3 mW/cm², with continued riboflavin application every few minutes. It should be noted that, regardless

IN VITRO ANTIMICROBIAL EFFICACY OF CXL

In vitro research shows that combined UVA and riboflavin can inhibit the growth of:

- Staphylococcus aureus
- Methicillin-resistant S. aureus
- Staphylococcus epidermidis
- Pseudomonas aeruginosa
- Multidrug-resistant P. aeruginosa
- Drug-resistant Streptococcus pneumoniae

But there is mixed evidence for UVA and riboflavin in eradicating:

- Fungi (such as Candida albicans, Fusarium solani, Aspergillus fumigatus)
- Acanthamoeba cysts and trophozoites

Reports of adjunctive PACK-CXL in cases of infectious keratitis points to in vivo efficacy against a wide range of pathogens, including fungi, protozoa, and viruses.1,2,5-9
of technique, PACK-CXL remains investigative and off-label.

**Challenges with Corneal Ulcers**

In developed countries, most cases of infectious keratitis are associated with contact lens wear and most are responsive to treatment with topical antimicrobial drugs.9,10 Though pathogens vary seasonally and geographically even within the US, the majority of corneal infections are bacterial.11,12 And even though these infections are painful, disruptive, and may leave visually significant scars, most of the time, available treatments are effective.13

Among the challenges in managing infectious keratitis are pathogen characteristics, including antimicrobial resistance. Though fortunately rare, bacterial keratitis resistant to commercially available agents may require treatment with a fortified antibiotic such as vancomycin.13 Even herpes simplex virus (HSV) infections—again, very rarely—can prove resistant to antivirals like acyclovir.14 Corneal infection with atypical pathogens like fungi or Acanthamoeba are often difficult to treat, both because of resistance to antimicrobials and because these infections often penetrate into deeper stromal layers (Figure 1).15,16

Identifying the pathogen(s) responsible for a severe corneal ulcer in order to provide targeted treatment is not always straightforward. Corneal tissue samples are necessarily small relative to other anatomical sites, and often, culture results come back negative or unreliable. Even when culture results are definitive, they are not immediate, and most clinicians will initiate empirical treatment of a presumed bacterial keratitis with a broad-spectrum antibiotic while awaiting results from the laboratory. In some cases, this may mean that a patient is paying for two agents (eg, to cover for Gram-positive and -negative pathogens) and being exposed to added epithelial toxicity and irritation, when only one of the drops is actually necessary to treat the infection.

Indeed, tolerability and adherence issues also complicate the management of infectious keratitis, especially severe cases. In addition to killing pathogens, many ophthalmic antimicrobials are toxic to normal epithelial cells.13 Dosing may be as frequent as every hour, and compounded agents often require refrigeration. For all these reasons, something like PACK-CXL would be desirable: a treatment with a lower burden of patient adherence, with the potential to inactivate microbes in a nonspecific way and strengthen the cornea against pathogenic and immune-related degradation.

### Research on CXL for Infection

Most of the literature on PACK-CXL consists of small case series, with only a few prospective, randomized studies. In 2008, Iseli and colleagues published a series of five cases of severe infectious keratitis with corneal melting, treated with PACK-CXL after progression of infection on topical and systemic antimicrobial therapy.17 Four of these were post-LASIK interface infections (with Mycobacterium and filamentous fungus Acremonium) and one was related to contact lens wear (with Fusarium).17 The combination of maximal medical therapy and PACK-CXL stabilized each case so that keratoplasty (full- or partial-thickness) could be performed successfully.17

The findings of subsequent case series have been largely similar, with a trend toward a possible benefit of adjunctive PACK-CXL.4,7 A pilot study carried out by Makdoumi and colleagues in 2012 used PACK-CXL as the sole treatment modality in 16 patients.18 All cases achieved reepithelialization, though antibiotic therapy was initiated in two patients due to suspected progression of infection, and one patient underwent amniotic membrane transplantation.18 Notably, the corneal ulcers in this study were relatively small (0.1 mm to 2.5 mm in diameter).7 Another single case report of early fungal keratitis showed complete healing within days of PACK-CXL, without adjunctive antifungal agents.19

One prospective, randomized trial was undertaken by Said and colleagues in 2014. Forty patients with infectious keratitis of bacterial, fungal, Acanthamoeba, or mixed origin with corneal melting were randomized to CXL and antimicrobial therapy (21 eyes) or antimicrobials alone (19 eyes).20 Neither average time to healing nor final visual acuity were significantly different between the two groups.20 In the antimicrobial therapy–only group, there were more (but not significantly more) cases of serious complications: three patients experienced corneal perforation and one had a recurrence of infection.7,20

Another study, published by Kasetsuan and colleagues in 2016, randomized 30 eyes with moderate to severe corneal infection; 15 eyes were treated with standard antiinfective treatment alone (for bacterial ulcers: fortified cefazolin 50 mg/mL and amikacin...
Indeed, several researchers agree that CXL seems ill-suited to treating infectious ulcers with deeper corneal involvement, which often includes fungal or *Acanthamoeba* infections.4,7 Interestingly, while the totality of the evidence suggests that CXL should be reserved for severe, refractory cases, to forestall emergency keratoplasty, it might truly be most effective in early, relatively superficial bacterial or fungal keratitis.7 However, such a scenario—in which patients would have to pay out of pocket for an unproven treatment, in cases that might just as well be managed by antifungal drops—is not supported by the literature or the current payment model.

**Risks and Considerations**

Many of the short-term risks of PACK-CXL are the same as those that apply when the procedure is used for ectasia. A transient ocular surface and anterior chamber inflammatory response can be expected, as can possible haze and scarring.8,20,21 Some of the other risks of removing the epithelium (pain, secondary infection) can be par for the course with a corneal ulcer. PACK-CXL may also diminish the ability of topical medications to penetrate the cornea post-procedure.4

Corneal thickness is always a concern with CXL: the standard Dresden protocol is expected to treat to a depth of 250 μm to 300 μm, with a minimum corneal thickness of 400 μm considered to be a safe cutoff.4 So although PACK-CXL may be appropriately positioned as a rescue therapy to stabilize corneal melting, it should not be used on corneas in imminent danger of perforation, or those which are so thin in spots that they risk UVA-mediated damage to the endothelium or anterior chamber.22

It is generally agreed that CXL should be avoided in patients with a known or suspected history of HSV keratitis, due to the risk of triggering latent infection with UVA exposure.4 However, a recent case series did report on the use of PACK-CXL in two patients with stromal HSV keratitis refractory to medical therapy.23 One patient had a recent history of keratoplasty and a necrotizing, PCR-positive HSV ulcer near the graft-host junction; stromal infiltration was decreased within 5 days of PACK-CXL and complete resolution and reepithelialization was evident at 25 days post-procedure, with no recurrence after 7 months of follow up.23 The other patient, who also had a PCR-positive central HSV ulcer showed initial resolution in the first few weeks after PACK-CXL; but the infection recurred. It was resolved with medical therapy and had not recurred after 4 months of follow up.23

Finally, while essential for examining a corneal ulcer, fluorescein dye should not be used immediately before PACK-CXL, since it competes for UVA absorption and may diminish the effect of photoactivated riboflavin.4,7

**Present and Future of PACK-CXL**

At present, PACK-CXL is very seldom performed, especially in the US. Most patients with presumed infectious keratitis who present to a general ophthalmologist respond well to empirical antibiotic therapy, and those severe, high-risk, refractory cases that would be suitable for intervention with PACK-CXL may be rarely seen, even by cornea specialists.24

Further study in this area may help refine patient and ulcer characteristics (eg, pathogen involved, size and depth of infiltrate) that are associated with the best response to this treatment. In addition to variations on the Dresden protocol, future developments in PACK-CXL may include the use of anterior-segment optical coherence tomography (AS-OCT) or confocal microscopy to assess infiltrate depth; a more portable CXL device that could be used in-office; or the exploration of chromophores other than riboflavin.4 For now, it benefits US ophthalmologists and cornea specialists to be aware of the PACK-CXL application, know to whom they can refer appropriate patients if they do not have direct access to a CXL device, and continue following this area of research.

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20 mg/mL, instilled hourly, and for fungal: amphotericin B 1.0 mg/mL and natamycin 50 mg/mL, also instilled hourly), and 15 received PACK-CXL in addition to medical therapy.21 Notably, these authors did not debride the epithelium prior to the CXL procedure, reasoning that the existing epithelial defect was enough to permit riboflavin penetration.21 Thirty days after treatment, they found no significant differences between the study groups in the size of the stromal infiltrate or epithelial defect, the complication rate, or the best pinhole-corrected visual acuity. They noted that the underwhelming efficacy of adjunctive CXL in these cases could have been related to the relatively deep stromal location of many of the infiltrates.22

Making comparisons between these studies is challenging, due to differences in protocol and endpoints, but together, they suggest that while PACK-CXL is not superior to standard medical therapy, it could be a valuable adjuvant in managing severe, refractory infectious keratitis associated with corneal melting.20,21

**Penetration**

Targeting infection in the deeper layers of the stroma is a challenge with PACK-CXL, as it is with topical antifungal drops. While “Epi-on” CXL techniques remain under debate for managing ectasia, in the context of infection, most authors remove the epithelium beyond the observable margins of the infiltrate to enhance penetration.4 As mentioned, CXL has shown some efficacy in treating infections at the LASIK flap interface, but deeper infiltrates—particularly fungal—are problematic.7,17 Experimenting with different PACK-CXL protocols, Price and colleagues reported a case of a shallow fungal infiltrate that cleared within 3 days of the procedure, with no conventional antifungal treatment; on the other hand, deeper penetration of fungal elements (observed on confocal microscopy) resulted in poorer outcomes: clearing in the anterior stroma but exacerbation of the deeper infection.4

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months, she has not had a financial relationship with any commercial organization that produces, markets, resells, or distributes healthcare goods or services consumed by or used on patients relevant to this manuscript. Medical writer Jennifer Zweibel of Condus Clinical/Science Communications, LLC, assisted in the preparation of this manuscript.

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Common Infections in the Presence of Chronic Ophthalmic Disease

Melissa B. Daluvoy, MD

A pre-existing chronic ocular disease can confound the diagnosis and management of common ocular infections in various ways.

Microbial infection is one of the most common ocular surface disorders encountered by eye care providers. Depending upon the causative organism and the infected tissue, the infection may differ markedly in clinical presentation. Acute conjunctivitis in most cases is mild and self-limiting, for example, whereas infectious keratitis is frequently progressive and sight-threatening (Figure 1). The management approaches to common ocular infections vary widely as well, ranging from supportive and palliative care to aggressive antimicrobial and antiinflammatory therapy.

Regardless of the type of infection, clinicians should be mindful that certain patients require extra precautions during management and counseling, because of a potentially higher risk for more serious outcomes. In this article, we discuss how an underlying chronic ocular disease, such as glaucoma, uveitis, or age-related macular degeneration (AMD), may influence the result of common ocular surface infections and what general management strategies can help improve the diagnosis and treatment of ocular infections in such patient populations.

The Risk of Infection

Contact lens wear continues to be the single most common predisposing factor for corneal infection.1 Regional epidemiological data from the US has indicated that contact lens wearers have a nearly 10 times higher risk for ulcerative keratitis compared with non-contact lens wearers.2 At present, no clinical evidence exists that infectious conjunctivitis or keratitis occurs more frequently in patients who have a chronic disease such as glaucoma or uveitis. The ocular surface of these patients, however, could be predisposed to infection or to potentially more serious complications of infections as a side effect of treatment measures.

In the case of glaucoma, long-term exposure to preserved glaucoma medications can lead to cumulative tissue damage and development of ocular surface disorders such as dry eye.3 Benzalkonium chloride (BAK), the most common preservative found in ophthalmic formulations, has been found to destabilize the tear film, reduce the density of goblet cells, and impair the corneal epithelium’s barrier function.4,5 When the epithelial barrier function is disrupted, in theory, the ocular surface’s natural defenses against microbial invasion weakens and the risk for infection increases.

For patients with noninfectious uveitis, locally administered corticosteroids are the mainstay of therapy. With prolonged use, however, these highly effective antiinflammatory agents can cause serious side effects, including increased susceptibility to serious bacterial infections and exacerbation of existing infections.6,7 In addition, corticosteroids are known to suppress host immune responses. Patients with long-term corticosteroid therapy are therefore prone to certain opportunistic infections that are otherwise rare, such as fungal or atypical mycobacterial infections.8,9

Inflammation vs. Infection

Corneal infection and anterior uveitis, two common causes of red eye, can be very similar in their manifestations: pain, photophobia, injection, discharge, diminished vision, and, in severe cases, hypopyon. When a patient presents with such symptoms and signs, my first step in the diagnostic process is to determine the nature of the underlying etiology: is it inflammatory or infectious?

Even if the patient has had previous episodes of uveitis, one cannot automat-
Atypical mycobacteria should always be considered. Unlike common bacterial keratitis, which tends to progress quickly, atypical mycobacterial and fungal infections are more likely to have an indolent course. When questioned, those affected often have a longer history of a red, irritated eye.

**Treatment Considerations**

With an underlying chronic ocular disease, the potential consequences of ocular surface infections may be more serious. For glaucoma patients who have had trabeculectomy surgery or drainage implantation, the risk for blebitis (Figure 2) and endophthalmitis increases with bacterial conjunctivitis or blepharitis.10,11 Similar to patients with AMD, advanced glaucoma patients might not seek eye care until the infection becomes severe; because their vision is often diminished at baseline, these patients might not notice visual signs and symptoms as quickly. The ensuing delays in diagnosis and initiation of therapy could result in a poorer prognosis. Given the relatively high stakes in these situations, it is important to manage diligently and treat aggressively to get any surface infection under control as quickly as possible.

In the uveitis population, long-term use of corticosteroids is commonplace. If patients are undergoing chronic corticosteroid therapy, clinicians will find themselves performing a balancing act—a red eye can arise sometimes from an under control infection when lowering the corticosteroid dose, they need to be careful not to trigger a flare; before ramping the dose back up, they must make sure the infection is well under control.

**Patient Counseling**

Clinicians should emphasize to patients with a chronic ocular disease the need to be evaluated should any symptoms of infection occur. Glaucoma patients with a filtering bleb from trabeculectomy surgery or aqueous shunt, in particular, should be told that a red eye is not something to ignore; seemingly minor symptoms such as redness, irritation, and watery discharge could be signs of an urgent condition that requires care in a timely manner. The same applies to patients with uveitis: they should be made aware of the fact that a painful red eye can arise sometimes from an inflammatory flare-up and other times from an infection, and that the latter could be worsened and prolonged by employment of corticosteroids. I usually tell my patients “If you feel the need to increase or restart a steroid, you should be seen by an ophthalmologist.”

Macular degeneration by itself does not increase a patient’s risk for infection. But those who are getting periodic intravitreal injections with an anti-VEGF agent should be counseled about the (albeit rare) possibility and signs of infection. Each intravitreal injection is associated with about a 0.05% risk of infectious endophthalmitis.12 Though it rarely occurs, such an intraocular infection can have devastating visual consequences.

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1. Randomized studies of PACK-CXL and conventional antimicrobials have found:
   A. Significantly better visual acuity with PACK-CXL
   B. No significant difference in final visual acuity with PACK-CXL
   C. Significantly higher complication rate with PACK-CXL
   D. Significantly faster time to healing with antimicrobials

4. According to Dr. Daluvoy, which of the following changes may exist as a potential risk factor for microbial infection in patients receiving long-term glaucoma medications?
   A. Tear film instability
   B. Corneal epithelial barrier disruption
   C. Corneal endothelial dysfunction
   D. Lower IOP

8. Infectious keratitis is most frequently associated with:
   A. Long-term use of glaucoma medications
   B. Intravitreal injections
   C. Corticosteroid therapy
   D. Contact lens wear

9. PACK-CXL should not generally be performed in:
   A. Patients with reduced corneal thickness
   B. Patients with a history of HSV keratitis
   C. Patients already on topical antimicrobial therapy
   D. A and B

10. Limitations of PACK-CXL include:
    A. Treatment depth of roughly 250 μm to 300 μm
    B. High risk of retinal damage by UVB light
    C. Likely to cause corneal melting
    D. May be inactivated by topical antimicrobials