Complications of Corneal Collagen Cross-Linking

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Core Messages

- Corneal CXL procedures allow the treatment of corneal ectasias but are responsible for some side effects.
- Early and late postoperative assessment of the cross-linked patient is important to detect postoperative complications and to manage them properly.
- Corneal CXL has been proposed for different corneal pathologies other than ectasias, such as some infections, and edema due to pseudophakic bullous keratopathy, corneal transplant rejection, and Fuchs' endothelial dystrophy.
- All the modifications to the CXL standard protocol aim to minimize side effects, maintaining an adequate therapeutic effect and extending the indication of the treatment.

40.1 Introduction

Corneal cross-linking (CXL) represents a fundamental evolution in the treatment of corneal ectasia pathologies improving corneal biomechanical properties [1]. Although it is a relatively safe procedure, some side effects and complications can occur; thus, it is very important to diagnose them early. CXL effect involves the interaction of ultraviolet rays with riboflavin producing free radicals and photo-oxidation that photopolymerize the corneal stroma, increasing collagen fibril interconnections [2]. For its mechanism of action, CXL can be useful in the treatment of many infective keratitis, in stabilizing corneal procedures, and as a therapeutic option for conditions involving corneal edema [3]. The first and most validated technique, proposed in 1996 by a research group at the Dresden Technical University, is "epi-off" CXL which removes the corneal epithelium before starting UVA irradiation [4]. Although this procedure allows the best penetration of riboflavin inside the corneal stroma, epithelium removal is linked to most of CXL complications. Other CXL strategies have been proposed to reduce the duration of the treatment and its complications [5]. The aim of recent researches is thus, to find the best irradiation technique combined the best imbibition strategy improving CXL efficacy and safety.

40.2 Effect of CXL on Cornea

From a biomechanical point of view, it has been widely demonstrated that human corneal rigidity increases immediately after CXL with a 328.9% increase of Young's modulus [6]. A study using rabbit eye proved that the effect of stiffness persisted 8 months posttreatment [7].

From a histological point of view, the whole corneal cell population has been largely studied [44–47].

The epithelium is fully regenerated by peripheral epithelial cells within 3–4 days after the "epi-off" procedure but remains very thin in the apex of the keratoconus (10–20 μm) 1 month after CXL, resembling to preoperative data between 3 and 6 months after the treatment. Limbal stem cell damage is avoided, thanks to the protective effect of the overlying epithelial cells [8].

Keratocyte loss is observed immediately after CXL. In spaces left by keratocytes, apoptosis leads to lacunar edema that persists for 4–6 weeks and then resolves with keratocyte repopulation. Nuclear keratocyte activation leads to an increase in the density of the extracellular matrix with more new collagen fibers 3–6 months after the treatment [9]. After

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CXL, keratocyte have been observed as a stromal demarcation line that could represent the transition zone between corneal cross-linked tissue and corneal non-cross-linked tissue. Refractive surgeons observed that a deeper demarcation line was associated with a larger decrease in central corneal thickness (CCT). They hypothesized that this line represents the activation of keratocytes, which is followed by the repopulation of keratocytes and new collagen synthesis [10].

Nerve fibers disappear after the procedure. In the first month, the subepithelial plexus regenerates, and during second and third postoperative months, there is a restoration of anterior-midstromal fibers with a normal corneal sensitivity in the sixth month after the CXL [11].

Endothelial damage threshold was determined by animal experimental studies that showed significant necrosis for high energy dose (4 mW/cm^2 radiation on epithelium and 0.5 mW/cm^2 on endothelium) [6]. However, few cases of endothelial damage post-CXL have been reported [12]. In corneas with a thickness of 400 μm, the radiation to avoid cytotoxicity of this layer should be 0.18 mW/cm^2 [13].

40.3 Early Postoperative Assessment of the Cross-Linked Patient

All patients should be instructed on how to follow postoperative regimen. It is important to inform them that they will experience some pain, photophobia, tearing, and red eye after the procedure. To prevent discomfort during the procedure and pain straight after the surgery, it is recommended to perform local anesthesia. Early assessment starts at the surgery room and should be performed during the healing process, to reduce pain and avoid infections. All patients after CXL are applied with a therapeutic contact lens that supports reepithelialization and reduces pain. After this procedure, patients should instill antibiotic, cycloplegic, and steroid drops. The most commonly used topical antibiotics are the broad-spectrum ones. Cycloplegic paralyzes the ciliary muscle relieving pain due to ciliary spasm secondary to ocular inflammation. The Contact lens is removed after full epithelialization. Some surgeons give steroid after removing the contact lens and others straight after the procedure, continuing the instillation for up to 10–20 days [14, 15]. Steroids act as an anti-inflammatory agent that prevents the development of corneal scars. Antibiotic and cycloplegic drops are administered usually for 7 days after the treatment until the achievement of full reepithelialization and improvement of acute inflammation. All surgeons give hyaluronate sodium drops six times daily, for approximately 5 weeks postoperatively. It is important to use preservative-free eye drops as preservatives can interfere with reepithelialization. Some doctors give oral amino acid supplements for 7 days [15].

Postoperative pain could be intense. It is associated with epithelium debridement. It may need oral analgesics [3]. Some authors give oral ibuprofen 400 mg (three times a day) and codeine phosphate 30–60 mg (four times a day) [7]. Some surgeons give three vials of benoxinate 0.4% with instructions to be administered if the postoperative pain is severe and with maximum dosage of one drop every 2 h for a maximum of 48 h. Treatment of postoperative pain should be individualized due to the different pain thresholds among patients [7].

As mentioned, another issue of early postoperative assessment is controlling the healing process up to full epithelialization. It is important to restore the epithelium as quickly as possible. It helps to improve patient's comfort and visual acuity and also reduces the risk of infection acting as a protective barrier. To prevent haze, some surgeons recommend vitamin C. It is based on researches made on PRK patients. But some surgeons found no additional effect on prevention of haze after refractive surgeries compared to the effect of topical mitomycin-C alone [16]. Control visits are set up 1–2 days after the procedure, 5–7 days, 2 weeks, 4 weeks, 3 months, 6 months, 1 year, and then every year. Authors of different publications about CXL, perform different examinations on control visits. But everyone should check visual acuity, intraocular pressure (IOP), refraction, keratometry, full slit-lamp examination, pachymetry, and topography. Additionally, some authors compare endothelial cell count and biomechanical properties of the cornea before and after CXL [2].

40.4 Early Postoperative Complications and Their Management

Several case reports describe the *melting process* after collagen CXL for keratoconus [17]. One case presented severe corneal haze, endothelial precipitates, and inflammatory cells in the anterior chamber the first postoperative day. This evolves with very slow reepithelialization and progressive thinning resulting in a descemetocele, with perforation in the second postoperative month [18]. This case suggests paying particular attention to patients with delayed epithelialization conducting very close follow-up, promoting epithelialization and preventing corneal perforation using, e.g., PRP, topical application of matrix regeneration therapy, or amniotic membrane transplant. Another case of acute corneal melt with perforation was reported 1 week after CXL associated with uncontrolled use of topical diclofenac and proparacaine eyedrops [18]. Bilateral corneal melt with *perforation* was observed in a patient with Down syndrome and stable keratoconus with thin corneas who underwent simultaneous bilateral CXL. The described complication occurred in one eye 1 week postoperatively and in the second eye 4 weeks

postoperatively and required emergency corneal grafts [18]. This case highlights how important is the right preoperative selection of patient: corneas were very thin and with a lack of evidence of disease progression. Another example of Par patient selection is a 45-year-old patient with severe atopic disease and keratoconus who developed corneal melting after CXL and deep anterior lamellar keratoplasty due to subclinical infection with herpes simplex virus. He required penetrating keratoplasty and intensive antiviral and immunosuppressive systemic treatment [18]. Patients with atopic disease have high risk of postoperative healing delay and prolonged epithelialization, being more susceptible to infection and at a higher risk of procedure failure (Fig. 40.1).

Another group of early postoperative complications includes *infective keratitis* (Fig. 40.2). Several causal agents have been reported. Acanthamoeba has been related to eye washing under the tap water [19]. A patient who underwent CXL for keratoconus presented 1 day postoperatively with a painful red eye due to polymicrobial keratitis caused by *Streptococcus salivarius*, *Streptococcus oralis*, and coagulase-negative *Staphylococcus* sp. This patient removed and "cleaned" his therapeutic contact lens in his mouth before reapplying it in his eye [18]. Thus it is very important to instruct patients before surgery about the postoperative treatment regimen and behavior necessary to minimize postoperative complications. Other cases of bacterial keratitis were caused by *E. coli*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* [20–22]. It is crucial to prevent contamination of the surgical field during removal of the epithelium as well as to avoid contamination of riboflavin drops. Excimer laser corneal episcrape no-touch technique could be a useful tool to reduce the possibility of transferring pathogens, and single-use packaging for the riboflavin solution is essential in order to avoid contamination.

One patient with no previous history of herpetic keratitis developed geographical ulcer related to herpes simplex virus [23]. *Reactivated herpetic keratitis* and neurodermitis have also been reported after CXL. It seems that UVA light can be a potent trigger of reactivation of latent HSV infection [18]. Potential risk factors for that are topical corticosteroids instillation and mechanical trauma caused by epithelial debridement, which can lead to actual damage of the corneal nerves. Surgeons should treat patients with a medical history of corneal herpetic disease only in selected cases providing a systemic and topical antiviral treatment. Patients should be informed about the possible complications. Diffuse lamellar keratitis (DLK, stage III) during the first posttreatment days after CXL for iatrogenic keratectasia was reported. The microbiology culture was negative, and the DLK resolved in 2 weeks after intensive treatment with topical steroids [18].

Surgeons should be aware of these complications and be able to discover them quickly and treat them properly. In such cases, it is very important to closely monitor the patients until complete reepithelialization.

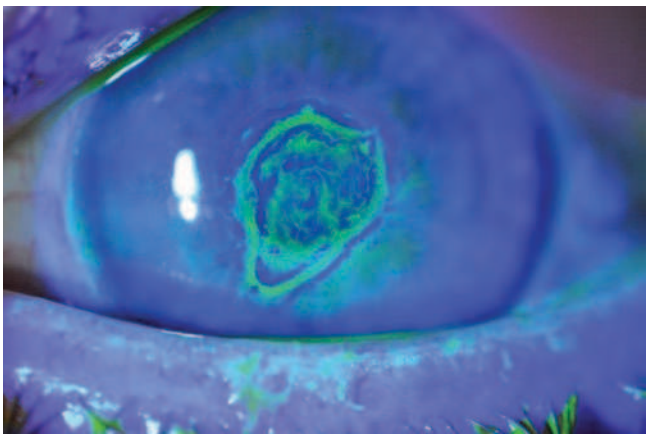


Fig. 40.1 Delayed epithelialization after CXL

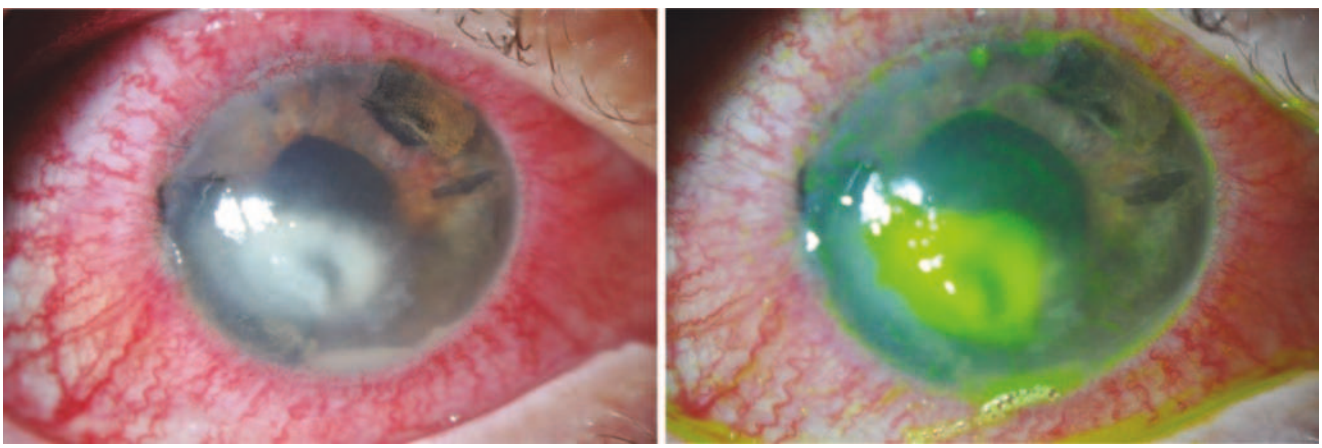


Fig. 40.2 Bacterial keratitis with corneal ulcer and stromal melting after CXL

40.5 Late Postoperative Assessment of the Cross-Linked Patient

At the first month visit, the most important factors that should be checked are visual acuity, full slit-lamp examination, monitoring healing process, and IOP. In the late postoperative, penon, doctors should focus on examinations that will assess the effect of CXL in stopping the progression of keratoconus. IOP measurements following CXL show overestimation caused by change in corneal biomechanics, leading to increased corneal rigidity. The difference in IOP measures following CXL ranged from 1.2 to 3.1 mmHg depending on the tonometer used [24, 25].

Reliable topography and refraction could be obtained minimum after 1 month postoperatively. Remodeling of the stroma and epithelium affects refraction and topographical readings during at least the first month after the procedure. According to Kanellopoulos, it takes even 1 year before the thickness maps are reliable [8]. Topography obtained 1 month after CXL paradoxically shows an increase in the steepness of the cone. Those findings are visible until the epithelium is fully restored. The effect of flattening of the cornea is evident after 6 months from the procedure [14]. Optical coherence tomography and very high frequency digital ultrasound arc-scanning technology show that the epithelium acts as a smoothing agent that reduces corneal power, astigmatism, and irregularity of keratoconic corneas [26]. Elevated cornea readings in the short time after the procedure are due to epithelium debridement.

Corneal thickness reduces shortly after CXL. It usually improves after the first 6 months and at 1 year returns to baseline values [27].

In the late postoperative period after CXL, we can investigate histological and biomechanical corneal changes. As previously mentioned, there is a significant decrease in the mean anterior keratocyte density at 1, 3, and 6 months postoperatively, while the posterior keratocyte density doesn't change after CXL [10]. Late changes in corneal stroma after CXL include collagen fiber diameter increases and reorganization of collagen fibrils in a parallel, lamellar structure similar to a non-keratoconic cornea [3]. Macroscopically the cornea shows significant flattening with reduction of *K* values [28].

Greenstein et al. measured biomechanical changes after corneal collagen cross-linking with the Ocular Response Analyzer (ORA). To describe the biomechanical properties of the cornea, two core metrics are used: corneal hysteresis (CH) and corneal resistance factor (CRF). Initially there was a significant increase in CRF between baseline and 1 month. This is concomitant with the corneal thinning that is seen 1 month after CXL [27, 29]. Thinner corneas seem to be correlated with lower CRF values. This suggests that the increase in CRF is an indication of corneal strengthening at 1 month. In this study, the ORA metrics of CH and CRF did not significantly change over time or 1 year after CXL [29]. Further clinical studies are needed to elucidate the in vivo biomechanical changes consequent to the CXL procedure.

40.6 Late Postoperative Complications and Their Management

A common complication of CXL is *corneal haze* (Fig. 40.3). Studies show that the depth of the CXL can be observed by following the demarcation line seen in the corneal stroma or by grading the corneal haze with the slit lamp. Several authors reported transient stromal haze resistant to topical steroids appearing 2–3 months after CXL and associated with an increased extracellular fibrillar matrix density, which was greater in patients with more advanced keratoconus [30–32, 40–43]. In these patients, dark Vogt microstriae are also present, a non-detectable finding in patients with early-stage disease. Management with topical preservative-free steroids promotes the resolution of the opacities in 30–40 days. Preoperative confocal analysis in those patients older than 20 years showed strong Vogt striae and dark, reticular-patterned microstriae in the anterior stroma to a depth of 80 μm, while preoperative confocal analysis in patients

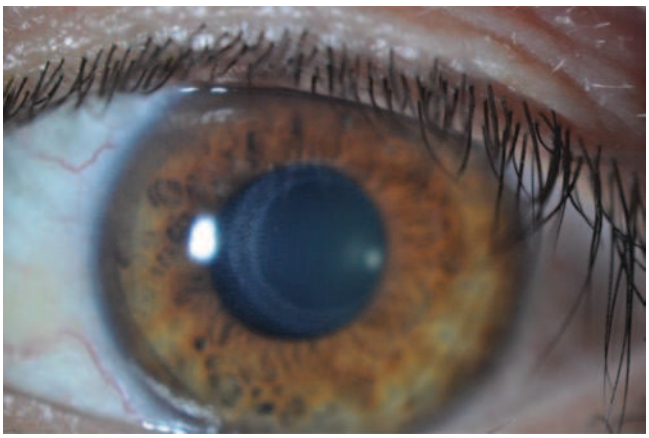


Fig. 40.3 Corneal haze after CXL

younger than 20 years old revealed hyperactivated keratocyte nuclei [31]. These could be risk factors for corneal opacity after CXL. The natural history of corneal haze after CXL was objectively quantified: it was greatest at 1 month, plateaued at 3 months, and significantly decreased between 3 and 12 months [39]. Changes in haze did not influence postoperative clinical outcomes [30]. Other factors connected with post-CXL corneal haze are stromal swelling, pressure changes, proteoglycan-collagen interactions, and glycosaminoglycan hydration. Those patients developing significant corneal haze after CXL had lower preoperative corneal thickness, and mean keratometry significantly increased. Using Scheimpflug image densitometry, some authors found corneal haze in 90% of cross-linked patients. Greenstein et al. compared two groups after CXL: at 1 year, haze remained significantly elevated compared with baseline values in keratoconus, unlike the ectasia group where the slit-lamp haze returned to baseline levels. From 3 to 6 months, the mean CXL-associated corneal haze measured by densitometry decreased more in the ectasia subgroup than in the keratoconus subgroup. Authors of the research observed that CXL-associated haze measured by densitometry was significantly correlated with several clinical parameters like corrected distance visual acuity, maximum *K* value, mean *K* value, and thinnest pachymetry.

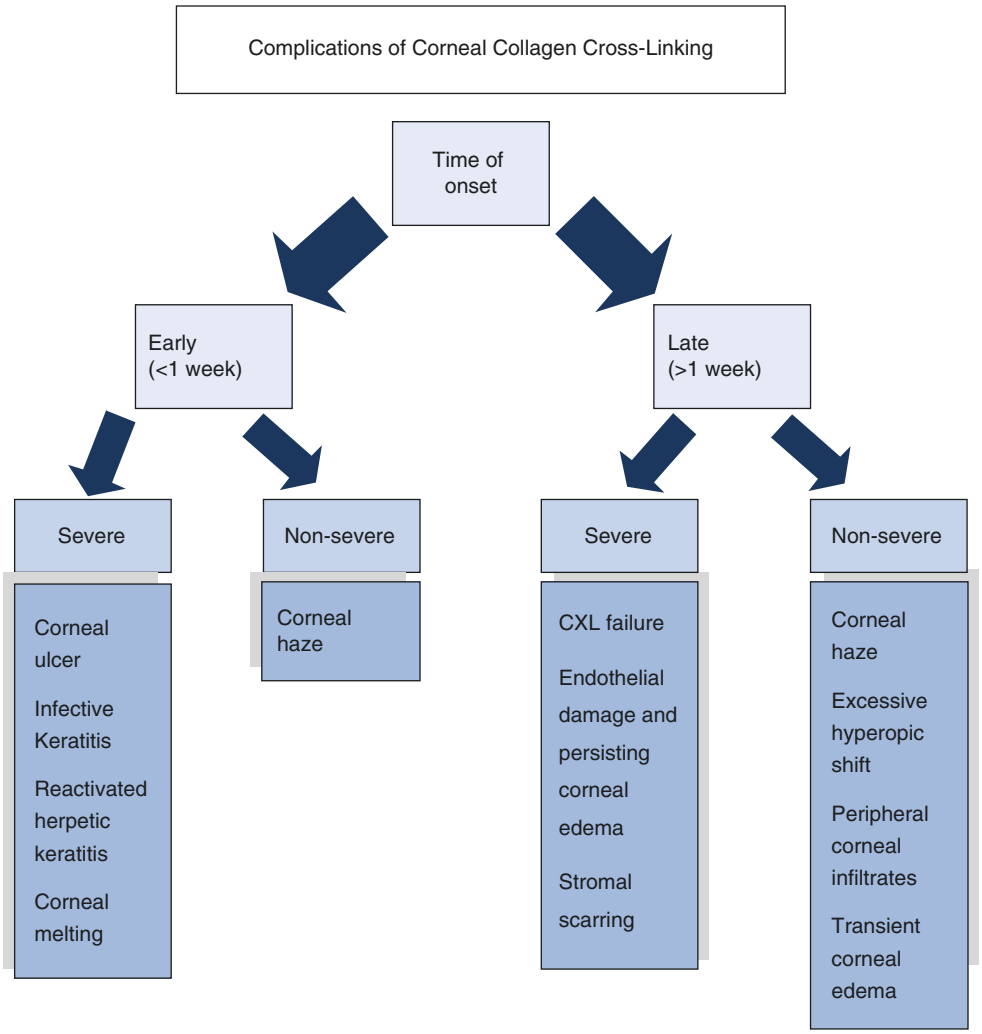
Another complication to take into account is *stromal scarring*. It has been associated with high K_{max} values (mean 71.1 D) at the apices and thin corneas (mean 420 μm) [32].

Endothelial cell loss should also be considered as a possible complication. It is very important for appropriate selection of patients. The main risk factor for endothelium damage is thin cornea, less than 400 μm [13]. Endothelial cells are safe in eyes with sufficient corneal thickness. However, we should take into account that after riboflavin and dextran solution imbibitions, corneal thickness decreases. This can be related either to evaporation through the denuded corneal surface or to the oncotic effect of 20% dextran used to form iso-osmolar riboflavin solution. This effect can increase the risk of endothelial damage leading to persisting corneal edema requiring corneal transplant. In other cases, transient anterior stromal edema could be related to lacunar spaces secondary to keratocyte loss assuming spongy or honeycomb aspect [9]. A miscalibration of the fluence or of the distance of UV light sources could expose patients to potential toxic levels of UV light that could create significant corneal opacities and severe damage of the anterior segment. These changes include corneal neovascularization, pigment clumps on the back of the cornea, and iris atrophy with intraoperative floppy iris syndrome or persistent epithelial defect extended beyond the limbus, suggesting limbal stem cell damage. Endothelial damage after CXL is a very rare complication, but it may happen. To prevent this complication, the surgeon should be sure that the corneal thickness is more than 400 μm, and should remove the lid speculum during the instillation of riboflavin drops to prevent excessive thinning secondary to evaporation. The equipment should be calibrated often.

In some cases after cross-linking, peripheral *sterile infiltrates* are observed. They occur as a result of enhanced cell-mediated immunity to staphyloccocal antigens deposited at high concentrations in areas of static tear pooling beneath the contact lens. In observations of Koller et al., sterile infiltrates occurred in 7.6% of the eyes (out of 105 in total). They resolved within 4 weeks with treatment of dexamethasone four times a day [33].

Another late complication of CXL is an atypical *big hyperopic refractive shift* that has to be taken into account in hyperopic patients. O'Brart demonstrated continued statistically significant flattening of corneal topographic parameters with a mean hyperopic shift of almost 0.8 D 7 years after CXL in 36 eyes, hyperopic shift over +2 D in 8 eyes (22%), and over +3 D in 4 eyes (11%) [34]. Very excessive hyperopic shift has been described in a 28-year-old woman with flattening greater than 14 D and in a 14-year-old boy with flattening of 7 D after 12 months. Another report of 11 D corneal flattening associated with over 220 μm corneal thinning has been described in a 23-year-old woman at 5-year follow-up [28]. The pathophysiology of excessive hyperopic shift is yet unclear. It may be due to a central cone location and a more advanced disease resulting in a greater CXL and wound healing effect.

Failure of CXL is defined as keratoconic progression after treatment. In one study of 117 eyes from 99 patients who underwent CXL, the failure rate was 7.6% [33]. Preoperative risk factors for worsening after CXL are age older than 35 years, cornea thickness less than 400 μm, maximum *K* reading greater than 58 D, female sex, and VA better than 20/25. To avoid keratoconus progression, appropriate qualification of patients is necessary. Surgery of the second eye should be performed straight after healing of the first eye. Due to relevant safety of the procedure, it could be even performed bilaterally on the same day.



40.7 Extending Indication of CXL

As discussed, the most common use of CXL is to manage ectatic corneal disorders. The top indication is keratoconus, where CXL halts the progression. The best candidates to CXL are patients with progressive keratoconus who still have good corrected visual acuity (RETICS classification grades II and III) [35]. Nevertheless, recent investigations propose new applications of CXL with promising results.

Among ectatic disorders other than keratoconus, CXL showed encouraging results in pellucid marginal degeneration with a safe profile despite the decentered treatment toward the limbus [18].

In post-LASIK ectasia patients treated with the CXL procedure, *K*-values progression was documented in patients with additional risk factors for ectasia progression, such as neurodermitis, allergy treated with systemic steroids, preexisting keratoconus or subsequent pregnancy [18]. In this group of patients, frequent follow-up is important, and eventual retreatment may be necessary. Most controversial is the use of CXL at the same time of LASIK, as a prophylaxis against myopic or hyperopic regression or to reduce the incidence of postoperative ectasia. Although intriguing, there is limited evidence that prophylactic CXL will be efficacious.

Few data are available about CXL in post-RK ectasia: A case report showed no significant improvement after the treatment; thus, a large cohort with long follow-up time is necessary to determine the real potential efficacy in this case. However, it has been suggested that patients with prior incisional refractive surgery should not be considered for CXL because the contraction of the collagen lamellae can cause the rupture of keratotomy incisions [18].

Therapy-resistant infectious keratitis associated with corneal melting presented positive outcomes after CXL. The progression of the melting process was halted avoiding emergency keratoplasty in several cases. Bacterial cases show a better time to reepithelialization compared to fungal, *Acanthamoeba*, and culture-negative cases, with a higher risk of requiring corneal transplantation in fungal and *Acanthamoeba* cases [36]. When using CXL for this indication, it would be advisable to discontinue all topical

antibiotics and avoid fluorescein instillation for at least 24 h prior to the treatment, because these substances are stronger absorbers of UVA irradiation at the 365 nm wavelength than riboflavin.

Some case series suggest an anti-edematous effect of CXL when used in pseudophakic bullous keratopathy, corneal transplant rejection, and Fuchs' endothelial dystrophy with improvement in corneal transparency, corneal thickness, and ocular pain 1 month postoperatively [18]. However, a regression to preoperative values is observed 6 months after the procedure.

Appropriate patient selection for standard CXL	
Indications	Contraindications
• Clinical evidence of progressive keratectasia • Age < 35 years • Visual acuity <20/25 • Pachymetry >400 μm • Keratometry readings <58 D	• Pregnancy and breastfeeding • Patients with prior incisional refractive surgery • Age can be a risk factor associated to visual loss, but no limit has been established • Best corrected visual acuity ≥20/25 • Pachymetry <400 μm • Keratometry readings >58 D • Cornea with central opacity • Serious dry eye syndrome

40.8 Standard Technique and Other CXL Protocols

A critical issue in order to obtain an effective CXL is stromal riboflavin concentration. Tight junctions between epithelial cells constitute a major barrier to the penetration of riboflavin. Because of this, the epithelium is removed to maintain an adequate stromal riboflavin concentration, in the standard technique, but this removal causes most of the CXL complications. All the modifications to the standard protocol listed in this paragraph are currently under investigation and aim to minimize its side effects maintaining an adequate stromal riboflavin concentration and extending the indication of the treatment.

40.8.1 Standard Protocol

Standard "epithelium-off" protocol, also known as Dresden protocol, is used in a standardized way from 2007, 11 years after its description. It is the most studied among CXL procedures and has to date the best demonstrated efficacy in halting corneal ectatic disorder progression. It consists of corneal de-epithelialization of 8–9 mm diameter after the application of topical anesthetic. Then the instillation of one drop of an isotonic 0.1% riboflavin and 20% dextran solution every 2 min for 30 min saturating the corneal stroma. After checking complete stromal saturation using the slit-lamp, UVA radiation at 5.4 J/cm^2 (3 mW/cm^2) is applied for 30 min. Finally, after this treatment, a therapeutic contact lens with topical corticosteroids, antibiotics, and nonsteroidal anti-inflammatory agents is fitted until regeneration of the epithelium [37].

40.8.2 Epi-On CXL

The efficacy of epithelium-on (transepithelial) techniques is controversial. Several methods have been studied to increase epithelium permeability to riboflavin including the use of tetracaine, superficial epithelial scraping, benzalkonium chloride, ethylenediaminetetraacetic acid, mechanical epithelial disrupters, incomplete debridement in a crosshatch pattern, stromal channels, and corneal pocket and flap [36]. Iontophoresis is the application of a low electric gradient to enhance molecular transport. Although it allows improved penetration of riboflavin through an intact epithelium over other transepithelial techniques, iontophoresis still does not achieve riboflavin concentrations comparable to the standard cross-linking protocol [10]. Recent studies in rabbits suggest some potential advantages for novel transepithelial approaches, like riboflavin nanoemulsions that could penetrate the corneal epithelium presenting greater stromal concentration compared to standard techniques. Such results need to be proven in human eyes.

40.8.3 Short Time CXL

Another line of investigation studies the reduction of treatment time optimizing CXL parameters, for example, using higher radiation intensities for shorter times to achieve the same level of radiation exposure according to the Bunsen and Roscoe law. Accelerated treatment could have more rapid overall corneal recovery after CXL, which could improve the patient comfort and safety profile. However, the effectiveness is controversial, and only few studies provided encouraging results: using 30 mW/cm^2 for 3 min, 10 mW/cm^2 for 9 min, and 9 mW/cm^2 for 14 min [5].

40.8.4 Thin Corneas CXL

Because standard treatment is contraindicated in corneas with a stromal thickness of less than 400 μm to avoid damaging the endothelial cells with the UV radiation, various methods of CXL have been developed to treat this patient population with varying degrees of success [37]. Corneal thickness can be increased to 400 μm instilling a hypo-osmolar riboflavin solution. The CXL effect is comparable to that in a 400-μm-thick cornea due to a great swell of the posterior stroma [38]. Using this technique, it is possible to treat corneas with a minimum stromal thickness of 320 μm.

Another factor that can be modified is total irradiation dose that can be decreased in accordance with the thickness of the stroma. A shorter irradiation time at 3 mW/cm^2 irradiation intensity avoids reaching endothelium toxicity threshold of 0.63 J/cm^2 in thin corneas when no hypo-osmolar riboflavin solution is available for topical application. Some surgeons suggested the application of UV radiation through contact lens.

Because the toxicity threshold of endothelial cells is much higher without riboflavin, endothelial cells would be protected, even in thin corneas (KXLTM technique), with a brief application of riboflavin to the surface allowing a sufficient concentration in the anterior stroma without riboflavin reaching the endothelium. However, a prerequisite for this procedure is a short irradiation time with a high irradiation intensity (equal dose) to keep the diffusion time short. Unfortunately, no clinical experiences with this technique can currently be cited.

An increase in the concentration of riboflavin to 0.2% leads to a greater absorption of UV light in the anterior stroma and a decrease in UV exposure of the endothelium.

Combinations of various techniques described above may increase safety during the CXL of thin corneas.

40.8.5 The Athens Protocol

The Athens protocol aims to improve the stability and refraction keratoconus patients, minimizing complications by combining CXL with topography-guided trans-PRK. This simultaneous procedure appeared to be superior to sequential treatments in the rehabilitation of keratoconus with minimal haze formation and a reduction in the patient's time away from work [37].

Take-Home Pearls

- Corneal cross-linking (CXL) represents a fundamental evolution in the treatment of corneal ectasia pathologies.
- Epi-off CXL has to date the best demonstrated efficacy in halting the progression of corneal ectatic disorders.
- Epithelium removal is linked to most of CXL complications.
- Proper patient selection allows the reduction of CXL complications.
- Patients' instruction about the postoperative treatment regimen and behavior allows us to minimize postoperative complications.
- In the early postoperative period, it is crucial to closely follow-up patients until complete reepithelialization.

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