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Timeline for corneal crosslinking procedures for keratoconus: A review

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Background: In 1998, corneal crosslinking (CXL) was introduced in animals to halt the progression of keratoconus (KC) and other corneal ectatic disorders by strengthening the cornea.

Aim: The article presents a review of CXL and its evolution over the last 27 years. The article reviews epithelium-on (*epi-on*) and epithelium-off (*epi-off*) methods of CXL.

Method: A literature search was conducted in bibliographic databases, including PubMed, ScienceDirect, Scopus, ResearchGate and Google Scholar, to identify peer-reviewed publications relevant to CXL. The search incorporated key terms including 'keratoconus', 'corneal crosslinking', and 'cornea'.

Results: A total of 142 records were initially identified across Google Scholar, PubMed, ScienceDirect, Scopus and ResearchGate. After removal of 46 duplicates, 96 titles and abstracts remained for screening. Of these, 37 papers were excluded because they were unrelated to CXL, not available in English or contained incomplete methodological data. Ultimately, 57 publications met the inclusion criteria and were analysed qualitatively in this review.

Conclusion: In the management of KC and corneal ectasia, CXL has emerged as a transformative advancement, shifting care from predominantly rehabilitative strategies to proactive biomechanical stabilisation. Accelerated, transepithelial, thin cornea and combination approaches evolved over time- yet the Dresden protocol remains the benchmark for efficacy and long term stability.

Contribution: This review synthesises published evidence on the development of crosslinking over the past 27 years and describes the evolution of major treatment protocols, including *epi-off*, *epi-on*, iontophoresis-assisted, accelerated and thin-cornea techniques. By summarising reported efficacy, safety profiles and clinical considerations, the review provides an overview of how crosslinking approaches have developed and their role in the management of KC and related corneal ectatic disorders.

Keywords: crosslinking; keratoconus; collagen; ectatic disorders; riboflavin; ultraviolet radiation.

Introduction

Keratoconus (KC) is a degenerative, bilateral and asymmetrical condition characterised by mild-to-severe visual impairment (VI).[1,2] The reported prevalence of KC varies widely, ranging from approximately 0.17 per 1000 in the United States to as high as 40 per 1000 in Iran, with an overall estimated prevalence of 1.38 per 1000 in the general population.[1,3] This variability likely reflects differences in study design, genetic and environmental factors, geographic location and diagnostic criteria. Keratoconus usually starts during adolescence and progresses over the next 10–20 years, reaching a plateau in the late 30s or early 40s, with a few exceptions.[4] Keratoconus affects men and women equally.[1]

Although KC has an unknown pathogenesis, there is a strong association with vernal keratoconjunctivitis, reduced ocular rigidity, connective tissue abnormalities, protein inhibitors, genetics, atopy and eye rubbing.[5,6,7,8] Lysyl oxidase is a corneal crosslinking (CXL) enzyme that is found in very low concentration in KC corneas.[2] In 2015, KC ceased to be regarded as a non-inflammatory disease to more correctly considered an inflammatory-related or quasi-inflammatory disease.[5,6] Keratoconus is found not to be associated with systemic inflammation, but rather disruption of the homeostasis of the cornea due to variance between inflammatory and anti-inflammatory molecules.[6] Genetic susceptibility, atopy, family history (autosomal dominant and

sporadic pattern), ethnic differences and eye-rubbing are key factors that play a role in causing KC.[1,6,8] The diagnosis of KC relies on clinical examination and corneal imaging modalities such as slit-lamp biomicroscopy and corneal tomography, together with quantitative indices including maximum keratometry (Kmax) and simulated keratometry (SimK) values that characterise corneal curvature changes.[5,9] Keratoconus progression is typically defined by changes in multiple tomographic parameters rather than a single index. These include increases in maximum keratometry (Kmax), progressive corneal thinning and changes in anterior or posterior corneal curvature or elevation. Although an increase in Kmax of ≥ 1 dioptre (D) within 12 months is commonly used as a clinical indicator of progression, current consensus guidelines recommend evaluating several parameters simultaneously to confirm true disease progression.[9,10] In KC eyes, there is a decline in thickness and volume of the cornea, together with asymmetrical displacement of the anterior and posterior apex of the cornea. The posterior cornea exhibits KC changes first, underscoring the importance of early imaging.

Corneal thinning most commonly occurs in the inferior-temporal and central quadrants of the cornea, but it can also occur in the superior corneal quadrant.[4] As KC progresses, the patient notices distorted vision. Clinical signs include steepening of the cornea, changing corneal curvature and an increase in coma-like aberrations.[5,6] Thinning of the cornea in the central and paracentral quadrants can result in nipple or oval cones. The most important clinical signs are the changes in the anterior and posterior curvatures of the cornea, as well as corneal thinning via pachymetry.

Pellucid marginal degeneration (PMD) is characterised by a marked steepening in the inferior corneal periphery along the vertical axis.[11] Not much is known about the aetiology of PMD and its incidence, but PMD is characterised by severe against-the-rule astigmatism, hydrops and the 'lobster-claw pattern' or 'kissing doves' sign, which is observed with corneal topography.[11] Pellucid marginal degeneration and post-refractive-surgery ectasia share overlapping features with KC but remain distinct in morphology and progression patterns.[8] Collectively, ectatic disorders impose substantial visual, psychological and economic burdens, particularly in settings where access to speciality lenses and keratoplasty is limited.

In the early stages, patients with KC are asymptomatic, thus making it difficult to diagnose the condition. Initially, only spectacles or soft or rigid gas permeable (RGP) corneal lenses may be required for adequate vision; however, the gradual progression of KC cannot be prevented by spectacles or contact lenses.[12,13,14] Reduced corneal thickness results in myopia, irregular astigmatism and visual disturbances such as ghosting and glare.[9] As the disease progresses, spectacle or soft contact lenses do not improve vision adequately. Once the better eye is significantly affected, patients will start to notice diminishing visual acuity (VA). Keratoconus in the more severely affected eye would then be at a more advanced stage by the time the patient presents to the optometrist or ophthalmologist. At that point, patients with KC who are not already wearing corneal RGP lenses are typically fitted with them to improve vision. Such RGP corneal lenses create a new uniform optical surface, thereby improving vision more than soft contact lenses while allowing good tear exchange.[7] In progressive KC, corneal opacities or hydrops due to previous rupture of the Descemet membrane may reduce VA with contact lenses.[9,15] Eventually, some patients will be unable to see with either eye, and RGP corneal lenses may not be well tolerated.[16,17] In advanced cases of KC, where RGP corneal lenses or scleral lenses cannot be fitted, medical procedures such as intracorneal ring segments (ICRS), deep anterior lamellar keratoplasty (DALK), phakic intraocular lenses, photorefractive keratectomy (PRK) or penetrating keratoplasty (PK) become the primary options for patients.[6,10] Such medical treatment options can be expensive and rely on the surgeon's skill for success.[18] These techniques can present with graft failure and rejection or surgically induced high postoperative astigmatism.[18] In some patients, KC eventually stabilises, and invasive surgery (such as DALK or PK) may not be required.

Keratoconus and other corneal ectatic disorders are progressive conditions that distort corneal architecture, degrade visual quality, and, when advanced, often necessitate keratoplasty.[1,2,3] For decades, management has been centred on optical rehabilitation, spectacles, RGP corneal lenses or scleral lenses, and, in severe cases, surgical intervention. These approaches, however, did little to arrest biomechanical weakening of the cornea. The advent of riboflavin/ultraviolet A (UVA)–mediated CXL fundamentally changed this paradigm by biologically strengthening stromal collagen and thereby slowing or halting ectatic progression.[9,19,20,21]

Crosslinking was originally described as the formation of covalent bonds between long-chain polymers in industrial and biomedical applications.[22] Its ophthalmic translation, photochemically induced corneal collagen crosslinking, relies on riboflavin as a photosensitiser and UVA light to generate reactive oxygen species that form additional intrafibrillar and interfibrillar bonds within the corneal stroma.[4,19] Early laboratory work established safety thresholds, tissue penetration characteristics and the pivotal role of oxygen, laying the groundwork for human application. The seminal 'Dresden protocol', introduced in the early 2000s, standardised the parameters for an epithelium-off procedure and rapidly became the clinical gold standard.[23,24]

Since its introduction, CXL has diversified. Variants include accelerated protocols applying Bunsen–Roscoe reciprocity to shorten treatment time, transepithelial ('*epi-on*') techniques aimed at reducing discomfort and infection risk, iontophoresis-assisted delivery to enhance riboflavin penetration and customised or 'CXL Plus' approaches that combine CXL with refractive procedures to optimise visual

outcomes.[5,6,7,8] Parallel innovations address the perennial challenge of thin corneas, traditionally excluded because of endothelial safety thresholds, through hypo-osmolar riboflavin swelling, contact lens-assisted corneal crosslinking (CACXL) and spatially modulated irradiation.[4,11,12] Collectively, these developments reflect a shift from a single, lengthy protocol to a spectrum of tailored interventions balancing efficacy, safety and patient comfort.

The incidence of KC, its often-early onset and its potential to impose lifelong visual disability underscore the importance of timely detection and intervention.[5,6] With accumulating long-term data demonstrating sustained corneal stability and reduced need for keratoplasty, CXL has emerged as a cornerstone in modern ectasia management.[14,15] Nevertheless, questions remain regarding optimal energy dosing, depth of effect, paediatric applications and long-term outcomes of newer protocols.

The aim of this paper is to critically synthesise three decades of evidence on CXL, from the original Dresden protocol to contemporary accelerated, transepithelial, thin-cornea and 'CXL Plus' variants, highlighting the relative advantages, limitations and clinical outcomes of *epi-off* versus *epi-on* techniques in order to guide current practice and future research in the management of KC and other ectatic corneal disorders.

Methods

Design

This article is a structured narrative review that involves a systematic search and organisation of relevant literature using predefined search terms and databases, followed by a qualitative synthesis of the evidence. This approach was chosen to examine the chronological development of CXL procedures for KC and other corneal ectatic disorders across different study designs and time periods.

Data sources and search period

Literature searches were conducted in PubMed, Scopus, ScienceDirect, Google Scholar and ResearchGate for publications between 01 January 1998 and 31 December 2023. Searches were limited to studies involving humans and/or clinically relevant laboratory work underpinning clinical CXL protocols.

Search strategy and Boolean operators

The primary search used combinations of keywords and Boolean operators, including:

> ('corneal crosslinking' OR 'corneal cross-linking' OR CXL OR 'riboflavin UVA' OR 'riboflavin ultraviolet A') AND ('keratoconus' OR 'corneal ectasia' OR 'ectatic disorder*' OR 'post-LASIK ectasia' OR 'pellucid marginal degeneration' OR PMD OR keratoglobus) AND ('Dresden' OR 'standard protocol' OR 'accelerated' OR 'transepithelial' OR 'epi-on' OR 'epi-off' OR 'iontophoresis' OR 'thin cornea' OR 'hypo-osmolar' OR 'contact lens-assisted' OR 'CXL Plus' OR 'Athens Protocol' OR 'topography-guided').

Reference lists of key articles were also hand-searched to identify additional relevant studies not captured in the database searches.

Eligibility criteria

Studies were included if they: (1) Reported development, technique, protocol parameters or outcomes of CXL relevant to KC or other ectatic corneal disorders; and/or (2) Provided clinically relevant experimental and laboratory evidence supporting protocol evolution (e.g. safety thresholds, oxygen dependence, treatment depth and/or demarcation line).

Studies were excluded if they:

- Were not related to CXL (e.g. contact lens-only management without CXL).
- Were not available in full text or had insufficient methodological detail for protocol description.
- Were not in English.
- Were duplicate reports of the same dataset (in such cases, the most complete or most recent report was retained).
- Were opinion pieces without technical or procedural information relevant to the evolution of CXL protocols.

Study selection and reasons for exclusion

Titles and abstracts were screened for relevance to CXL protocol evolution. Full-text screening was then undertaken for potentially eligible articles. Exclusions at the full-text stage were documented under the following categories: duplicate and/or overlapping data; incomplete methods or outcomes; non-ectasia indications only (if not relevant to protocol evolution); or not addressing CXL protocols. The final set of included publications was then used for qualitative synthesis and chronological mapping.

Data extraction and synthesis

From included studies, the following were extracted: protocol type (*epi-off*, *epi-on*, iontophoresis, accelerated, thin-cornea, CXL Plus or customised), riboflavin formulation and soak time, UVA wavelength or irradiance or duration or fluence (where reported), sample characteristics (age group, disease severity), and key outcomes (e.g. Kmax change, VA, pachymetry or thickness safety, complications, demarcation line depth when available). Findings were synthesised narratively and organised chronologically to demonstrate changes in techniques and indications over time.

Ethical considerations

Ethical clearance to conduct this study was obtained from the Faculty of Health Sciences, University of Johannesburg research ethics committee (No. REC 1538-2022).

Review findings

The 57 included publications collectively describe the progressive evolution of CXL from a single standardised protocol to a spectrum of individualised treatment approaches. Across the reviewed studies, the evidence synthesised can be grouped into five major themes: (1) biomechanical efficacy and safety of the standard epithelium-off Dresden protocol; (2) development of accelerated protocols to reduce treatment time and postoperative morbidity; (3) emergence of transepithelial and iontophoresis-assisted techniques to improve patient comfort and epithelial safety; (4) modified strategies to enable treatment of thin corneas previously considered unsuitable for CXL; and (5) combined or 'CXL Plus' procedures aimed at simultaneous biomechanical stabilisation and visual rehabilitation.

Corneal crosslinking pioneers, Wollensak et al.[19] found an increase in the rigidity of the cornea by 328.9% and in Young's modulus by a factor of 4.5 after CXL. Corneal crosslinking has been approved by the Food and Drug Administration (FDA) to modify the corneal stroma in the management of KC and other corneal disorders.[3] Riboflavin or vitamin B2 is important for maintaining health in humans and animals and is a readily absorbed micronutrient. Topical iso-osmolar riboflavin interacts with UVA of wavelength 370 nm to induce CXL of the cornea. The riboflavin molecule, upon exposure to UV light, becomes excited to higher energy states and acts as a photosensitiser, producing singlet oxygen. These free radicals activate the natural lysyl oxidase pathway. In this excited state, riboflavin can induce covalent bonds, thus causing collagen fibres in the collagen stroma to crosslink with each other. Corneal crosslinking with UV makes the cornea more rigid and stable by linking collagen and non-collagen molecules.[2] For this reason, the term 'corneal collagen' crosslinking is not entirely accurate.[19]

While keratocyte aptosis in the corneal stroma occurs during CXL, it does not affect corneal transparency and thickness.[19,20] Corneal crosslinking appears to be effective for KC as well as infectious and non-infectious keratitis and keratectasia, while its use in the treatment of bullous keratopathy is indefinite.[9,21] Previous studies have shown that stabilisation and flattening (an increase in keratometry readings) of the cornea in both paediatric and adult populations take place after CXL.[21] Corneal crosslinking occurs naturally with age due to natural lysyl oxidase pathways.[23]

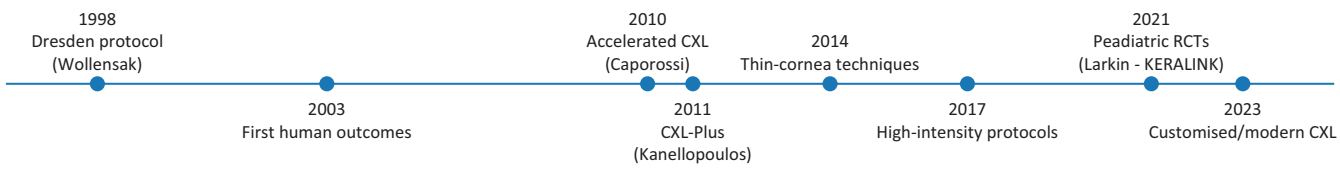
Corneal crosslinking treatment is a minimally invasive option in the treatment to halt the progression of keratectasia.[15] It has also been used to manage other conditions such as ulcerative keratitis, infectious ulcers and bullous keratopathy. Laser-assisted in situ keratomileusis (LASIK), PRK and radial keratotomy (RK) have all been shown to produce keratectasia. Keratectasia secondary to refractive surgery is seen in only 0.04% – 0.6% of post-LASIK cases but is visually devastating.[21] Risk factors such as thin corneas, high myopic and/or astigmatic corrections, pre-existing KC, PMD and young age should be ruled out during pre-operative screening for refractive surgery to reduce the risk of corneal ectasia. Post-LASIK ectasia exhibits abnormal, asymmetric topographic findings with progression that is unpredictable. Corneal crosslinking has also been administered prophylactically before PRK to prevent complications.[15,25] Once again, management of keratectasia with CXL depends on the severity of the condition. Current CXL protocols have been shown to be safe and effective in halting keratectasia.[13,26,27,28]

The Dresden protocol

Developed in Dresden, Germany, in 1998, this protocol is the original treatment invented by Wollensak.[23,29] Initial tests were carried out on porcine corneas to assess the cytotoxicity of riboflavin, with and without UVA exposure.[28] The treatment has been extensively studied and is reported to be safe with only a few complications (Figure 1).

Corneal crosslinking is performed in a sterile environment by an ophthalmologist on an outpatient basis.[29] The lids are separated by a speculum. The superficial corneal epithelial layers are removed; thereafter, the corneal stroma is saturated with riboflavin and irradiated with UVA at 370 nm of light for 30 min to provide a fluence of 5.4 J/cm^2 to cause corneal stromal covalent crosslinking.[19] Riboflavin, UVA light and singlet oxygen (oxygen in its most reactive form) are all equally important for the photochemical reaction that leads to CXL.[29]

Experimental evidence has demonstrated that oxygen is a critical factor in CXL. In studies conducted under oxygen-depleted conditions (helium environment), no biomechanical strengthening effect was observed, confirming that oxygen, particularly in the form of reactive singlet oxygen, is essential for the photochemical CXL reaction.[30] These findings also help explain the reduced efficacy of transepithelial and accelerated



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CXL, corneal crosslinking; RCT, randomised controlled trial.

FIGURE 1: Chronological evolution of corneal collagen crosslinking protocols (1998–2023).

CXL protocols. The intact epithelium acts as a barrier to oxygen diffusion and consumes available oxygen, limiting its availability within the stroma. Similarly, accelerated protocols may deplete oxygen too rapidly, preventing adequate crosslink formation, whereas the standard Dresden protocol allows sufficient time for oxygen replenishment during treatment.[30] The optimal riboflavin concentration with the combination of ideal UVA light intensity was established *in vitro* in various animal models.[20,28,31] Hafezi and Hafezi performed CXL on porcine eyes in a helium-filled chamber and found that CXL did not take place, confirming the importance of the presence of oxygen in CXL.[30]

The eye is then treated with antibiotics and a soft bandage contact lens until re-epithelialisation has occurred.[2,12,32] *Epithelium-off* CXL is the preferred method, as riboflavin's ability to penetrate the cornea through intact epithelium is inadequate, as riboflavin is a macromolecule with a molecular weight of 376 Da.[30]

The first method used to crosslink the cornea employed a wavelength of 365 nm and was found to successfully stabilise the cornea and prevent ectasia progression by creating additional bonds within the structure of the cornea, without negatively impacting other structures of the eye.[30,33,34] This is because only the anterior 200 µm – 300 µm of the stroma is affected by the biochemical nature of the CXL, and UVA absorption is at its maximum there.[21,35] Corneal crosslinking parameters are effective only in the anterior 300 µm of the cornea.[20] The formation of crosslinks is primarily influenced by the riboflavin concentration, as well as the wavelength, duration and energy dose of the light source.[27] Riboflavin is safe to use systemically and can absorb light across an extended range of wavelengths. Kymionis et al.[31] state that the stroma absorbs about 95% of the UV radiation during CXL. Two important considerations were to avoid endothelial damage by remaining below the damage threshold of 0.35 mW/cm^2 and to induce anterior, mid and deep stromal effects.[21] Keratocyte apoptosis can be caused by the cytotoxicity of

TABLE 1: *Epi-off*, accelerated and other corneal crosslinking procedures that halted the progression of keratoconus.

Study type and authors	Study name	Country	Participants (mean age)	Riboflavin drop administration	UVA irradiance (Duration of UVA in min) and UVA dose	(Follow-up period) and outcomes
Standard protocol, Wollensak et al., 2003	Dresden	Germany	23 eyes from 22 patients (31.7 ± 11.9)	Every 2 min for 30 min	370 nm, 3 mW/cm^2 (30)	(3–47 months) BCVA improved in 65% of patients by 1.26 lines (p = 0.26). SE improved significantly (p = 0.03). Reduction in K_{max} of 2.01 D in 16 patients. K_{max} remained stable in 5 patients and a minimal increase of 0.28 D in one patient.
CXL in children, Caporossi et al., 2010	Sienna Eye Cross study[42]	Italy	44 eyes (10–40-year-olds)	Every 2 min for 30 min	3 mW/cm^2 (30)	(4 years) Refractive results: SE increased during the first postoperative month, followed by a sustained hyperopic shift throughout the follow-up period. Mean SE values at 1, 2, 3 and 4 years were +1.87 D, +2.12 D, +2.13 D, and +2.15 D. The reduction in SE reached statistical significance after 12 months. Mean UCVA improved by approx. +2.41 Snellen lines at 1 year, increasing to +2.85 lines by 4 years.
CXL in children (accelerated CXL), Larkin et al., 2021	Keralink Trial	United Kingdom	60 eyes (15 ± 1.1)	Every 2 min for 10 min	10 mW/cm^2 (9), 5.4 J/cm^2	(18 months) CXL group vs. standard care group: Statistically significant difference in K2 (mean corneal power in the steepest meridian) (p = 0.002) for the treatment group. Only 43% of patients in the standard care group showed progression of KC.
A-CXL, Yildirim et al., 2017		Turkey	74 eyes from 40 patients (22.8 ± 4.6)	Every 2 min for 20 min	18 mW/cm^2 (5), 5.4 J/cm^2	(12 months) Mean UDVA and CDVA showed improvement at 12 months postoperatively, although the changes were not statistically significant (p = 0.06). Maximum keratometry decreased significantly (p = 0.04). The difference in CCT pre- vs post-operatively – (p = 0.068). The decrease in mean SE was not significant (p = 0.56).
A-CXL, Yildirim et al., 2017		Turkey	72 eyes from 42 patients (22.4 ± 3.8)	Every 2 min for 20 min	30 mW/cm^2 (4), 7.2 J/cm^2	(12 months) Mean UDVA and CDVA showed improvement at 12 months postoperatively, although the changes were not statistically significant (p = 0.08). Maximum keratometry decreased significantly (p = 0.03). The difference in CCT pre- vs post-operatively was not significant (p = 0.72). The decrease in mean SE was not significant (p = 0.56).
Transepithelial CXL, Spadea and Mancucci,2012		Italy	16 eyes from 16 patients (34.4 ± 11.9)	Every 3 min for 15 min	3 mW/cm^2 (30), 5.4 J/cm^2	(12 months for 7 eyes) Stability in CCT (± 10 µm). A small mean reduction in apical ectatic curvature. Kmax values decreased by up to 4.3 D. Both UDVA and CDVA improved slightly (up to three logMAR lines), with a small reduction in mean SE refraction (up to 2.5 D).
Contact lens-assisted CXL, Jacob et al., 2014	CACXL	India	14 eyes from 12 patients (26.6 ± 7.2)	Every 3 min for 30 min	3.0 mW/cm^2 (30)	(6–7 months) No significant change in CDVA (p = 0.276). No progression of keratectasia. No significant difference in the overall mean maximum keratometric value (Wilcoxon test, p = 0.505).

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SE, spherical equivalent; BCVA, best corrected visual acuity; UDVA, uncorrected distance visual acuity; CDVA, corrected distance visual acuity; CCT, central corneal thickness; CACXL, contact lens-assisted corneal crosslinking; UVA, ultraviolet A; CXL, corneal crosslinking; KC, keratoconus.

UVA, and furthermore, permanent injury to the endothelial cells, lens and retina can occur.[21,33]

Between 2 and 4 weeks after crosslinking, a corneal stromal demarcation line can be detected with slit lamp examination, which indicates the shift between the treated anterior stroma and untreated posterior stroma.[20,34] The stromal demarcation line is visible in the first 6 months after treatment and can also be identified through anterior segment Optical Coherence Tomography (OCT) 1 month after CXL.[9,20] The untreated posterior stroma shows normal reflectivity and normal keratocyte numbers, while the treated anterior stroma manifests poor reflectivity and reduced keratocyte nuclei and oedema.[20] By increasing the rigidity of the cornea, further thinning of the cornea is prevented.[16,35] There is an improvement in corneal curvature and VA, especially when KC is treated in its early stages.[19] Keratoconus cannot be cured, but CXL can significantly reduce progression (and cause long-term stabilisation of the cornea) or perhaps prevent progression to advanced stages and give the patient a better quality of life.[16,17,36,37,38]

Long-term follow-up of the original Dresden cohort demonstrates sustained treatment stability for up to 10 years.[35] The Dresden protocol is seen as the gold standard method for treating and strengthening the cornea, maintaining stability for up to 10 years in the original Dresden cohort.[11,16,32,38,39,40,41]

Accelerated corneal crosslinking and reciprocity-based protocols

The Dresden protocol is fairly time-consuming and uncomfortable; thus, alternative methods have been developed to reduce procedure duration and patient discomfort[19] (Table 1). To accelerate the process of CXL, the application of the law of photochemical reciprocity by Bunsen–Roscoe was implemented.[30] This law states that if the duration of irradiation is shortened while increasing irradiation intensity, the total energy will stay the same.[30] This law, however, is only accurate up to 40 mW/cm^2 – 50 mW/cm^2 of irradiation intensity for more than 2 min. Cummings et al.[26] found that increasing the irradiation intensity while maintaining the illumination dose at 5.4 J/cm^2 halved the CXL treatment time. Accelerated CXL (A-CXL) with greater intensity UV exposure and decreased treatment time has shown variable results. Studies of CXL at 7 mW/cm^2 for 15 min have been shown to stabilise the cornea.[37] Accelerated CXL of 30 mW/cm^2 for 3 min with two differing riboflavin soak times of 10 or 15 min yielded similar results to the standard protocol.[43] Accelerated treatments have been reported to promote faster corneal recovery after CXL and reduce the occurrence of transient postoperative corneal haze in patients undergoing accelerated CXL protocols.[34] Irradiation of the cornea at 9 mW/cm^2 for 10 min has been shown to yield results similar to those of 30-min irradiation, while taking one-third of the time.[32] Several authors have shown shallower demarcation lines in A-CXL.[33,43] There are A-CXL studies that have shown successful halting of KC.[43,44]

Yildirim et al.[43] compared different protocols for A-CXL in progressive KC. Their prospective study compared 74 eyes from 40 patients treated with a fluence of 5.4 J/cm^2 (30 mW/cm^2 of UV-A irradiance for 5 min) to 72 eyes from 42 patients treated with a fluence of 7.2J/cm^2 (30 mW/cm^2 of UV-A irradiance for 4 min). After 12 months, both groups showed a significant decrease in the maximum keratometry (Kmax): group 1 (p = 0.04) and group 2 (p = 0.03). The two groups showed similar differences in central corneal thickness (CCT) pre-operatively versus post-operatively: group 1, p = 0.68; and group 2, p = 0.72. The flat (K1), steep (K2) and mean keratometry readings showed a trend towards flattening at 12 months, but the differences were not significant ($p \geq 0.05$ for each).[40] Between-group comparisons showed no evidence of differences in uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA) or corneal topography before or after surgery. Differences in keratometry and refractive measures were also non-significant.[40]

The Keralink study conducted by Larkin et al.[16] was carried out on 60 children aged between 10 and 16 years. This study showed that accelerated CXL halted the progression of paediatric KC successfully. While the accelerated protocol did stiffen the cornea, the effect was less than that of the Dresden protocol.[30]

Epithelial preservation and patient tolerance

There are certain postoperative disadvantages to removing the corneal epithelium, such as temporary decreased vision, corneal stromal opacification, increased risk of infection, moderate-to-severe pain and extended downtime for the patient.[3,45] The absence of sufficient corneal thickness for absorption of UVA radiation is a critical limitation of CXL.[13] Ultraviolet A radiation alone has a 10 times lower cell damage threshold than UVA irradiation combined with riboflavin.[13,20] With the Dresden protocol, only corneas of 400 µm or more in thickness can be treated to prevent potential endothelial damage from UVA exposure, and thus the method is more useful in early-to moderate-stage KC.[38,44] In an A-CXL study by Cakmak et al.,[46] complications included haze formation (9.1%), loss of two or more Snellen lines in VA (2.4%) and delayed epithelial healing in 1.8% of patients who underwent A-CXL.

Epi-on vs *epi-off* corneal crosslinking

Epithelial-on CXL is carried out without the debridement of epithelium. *Epithelial-on* CXL is said to be less painful and to carry a decreased risk of postoperative infection.[46] The intact epithelium is a barrier to the riboflavin and oxygen molecules.[30] The riboflavin in such instances is modified with ethylenediaminetetraacetic acid (EDTA) and gentamycin to

loosen the tight junctions between the epithelial cells. *Epithelial-on* CXL is more successful with iontophoresis, which uses an electric current to aid intrastromal penetration of riboflavin.[39,45] Riboflavin is a negatively charged, water-soluble molecule with a molecular weight of 376.40 g/mol. So penetration of the riboflavin is enhanced by the iontophoresis.[2,39,47] *Epithelial-on* CXL has a decreased treatment depth but only one-fifth to one-third of the corneal stiffness than with *epi-off* CXL.[2]

A study of 26 eyes over 2 years undergoing *epi-on* CXL concluded that corneal variables improved after the initial 6 months, then regressed after 1 year and worsened after 2 years.[42] *Epithelial-on* CXL is, however, ideal for use on children who are naturally quite sensitive to pain and run an increased risk of side effects such as infection and corneal oedema, in general. *Epithelial-on* is a safer procedure but does not halt KC progression as effectively as the *epi-off* procedure.[2,27] A study conducted comparing *epi-on* and *epi-off* techniques found that a third of the cases that used *epi-on* CXL required re-treatment.[4,41,48] *Epithelial-on* CXL should not be used in dry eye patients due to surface instability.[3]

Expansion to thin corneas and advanced disease

Corneal crosslinking is contraindicated in corneas that are thinner than 400 µm, as endothelial cell damage can occur with an irradiance of 0.37 mW/cm.[2,41,48] Raiskup and Spoerl[41] confirmed that a scar formed with CXL in cases of advanced KC.[41] Assuming a corneal absorption coefficient of 70 cm^{-1} and a surface irradiance of 3.0 mW/cm^2, the transmitted irradiance at a stromal depth of 300 µm is calculated to be approximately 0.37 mW/cm^2. This value represents the ultraviolet energy reaching the corneal endothelium at that depth. For this reason, the 400 µm limit is the clinical standard, as it protects both the endothelium and internal structures of the eye.[33,49] Different methods for thinner corneas have been implemented, such as hypo-osmolar riboflavin, transepithelial CXL with EDTA and trometamol as permeability enhancers, ionophoresis-assisted CXL (I-CXL), customised epithelial debridement technique, CACXL and individualised CXL.[49]

A modified technique, CACXL, was first implemented by Jacob et al.[50] on 14 eyes in 2014. Corneas with pachymetry between 350 µm and 400 µm after epithelial removal were fitted with a 0.9 mm-thick bandage contact lens. The corneal thickness is increased by 100 µm when the contact lens is on the eye.[50,51] In their pilot study, a contact lens (UV barrier-free) was soaked in a riboflavin solution for 30 min, while the cornea was also soaked. The contact lens was placed on the eye, and once the intraoperative pachymetry confirmed a thickness greater than 400 µm, UVA irradiation was applied as per the Dresden protocol. It was found that while the transmission of UVA through the contact lens was reduced, the oxygen availability to the cornea was also diminished, and consequently the effect of the CXL was also a third less efficacious.[19,49,50] More clinical studies are needed with larger cohorts and longer follow-up periods.

In thinner corneas, Hafezi et al.[52] suggested hydrating the cornea to increase stromal thickness to 400 µm. In an iso-oncotic (swollen) environment, the corneal stroma can swell due to its inert swelling pressure.[52] Once the corneal epithelium is removed, the cornea is irrigated with a hypo-osmolar solution, 0.1% dextran-free hypo-osmolar riboflavin, which causes the cornea to double in thickness. Once the thinnest point on the cornea reaches 400 µm, UVA irradiation is initiated.[13,41,49] Raiskup and Spoerl[49] confirmed that thinner corneas with a mean corneal thickness of 382.3 µm ± 41.9 µm stabilised with CXL while maintaining transparency and without any stromal scarring. Customised irradiation based on corneal thickness across different areas was also used. An alternative treatment to halt the progression of KC is oral riboflavin together with direct sunlight exposure; this study was inconclusive.[50]

Combination strategies and refractive combination

Corneal crosslinking can halt KC progression, but patients still require contact lens correction or other treatments to achieve functional vision, even with reasonably regular corneas and optimal preoperative best-corrected visual acuity (BCVA).[52,53] For this reason, 'CXL Plus' was introduced in 2011 to combine CXL with other refractive procedures, providing both corneal stability and vision correction.[31,52,53] Simultaneous combined procedures have presented with a higher risk of postoperative stromal haze, which makes further investigation essential.[54] Photorefractive surgery conducted on the same day as CXL can improve outcomes in vision and refraction, while showing regression in KC parameters such as Kmax.[2]

Kannelopoulos and Binder[55] presented a case of a patient with bilateral KC. One eye underwent CXL and PRK, while the other eye only underwent CXL. Results from this study and others indicate that combining procedures yields greater success than CXL alone; however, more large-scale studies are necessary to confirm that the benefits outweigh the risks.[8,55]

Customised topography-guided corneal crosslinking

Kymionis et al.[54] used customised pachymetry-guided epithelial debridement in two patients with regional corneal thinning. They performed CXL on two patients (one with KC and one with post-LASIK corneal ectasia), debriding the cornea only in areas thicker than 400 µm, leaving the corneal epithelium intact in thinner areas. Post-CXL, corneal healing occurred within 5 days. Corneal topography was stable at 9 months, with no significant alteration in endothelial cell density on confocal microscopy. Pachymetry-guided epithelial removal may enhance safety in thin corneas (< 400 µm), but concerns

remain regarding long-term efficacy, riboflavin penetration and incomplete treatment beneath residual epithelium. The study showed that localised pachymetry-guided de-epithelialisation is successful and does not negatively impact the outcome of CXL.[54]

In August 2011, Kanellopoulos and his colleagues administered same-day topography-guided partial PRK and CXL to stabilise keratectasia and progressive post-LASIK ectasia, and the results were promising.[18] The procedure is known as *the Athens Protocol* and involves performing topography-guided partial PRK and CXL on the same day. Photorefractive keratectomy involves the removal of the corneal epithelium and reshaping of the anterior corneal stroma to change the refractive power of the cornea, utilising an excimer laser. Although CXL results in corneal flattening, residual astigmatism may persist. Topography-guided partial PRK can be used to regularise the cornea and improve BCVA, with minimal stromal removal (≤ 50 µm) and correction of up to 2.50 D of astigmatism and 1.00 D of myopia. Results of the Athens Protocol showed less PRK-associated scarring and a deeper CXL outcome, with greater corneal flattening.[18]

Implications and recommendations

The chronological synthesis of the literature demonstrates a clear evolution from a single, standardised protocol to a spectrum of individualised approaches. Early studies established the biomechanical efficacy and safety margins of the Dresden protocol, which explains its continued role as the benchmark technique. Subsequent innovations: accelerated, transepithelial and thin-cornea protocols did not arise from inadequacy of the standard approach, but rather from clinical pressures to reduce treatment time, postoperative morbidity and exclusion of advanced cases. The persistence of *epi-off* CXL as the comparator in modern trials underscores that newer techniques represent strategic compromises rather than outright replacements. This evolution reflects a broader shift in KC management towards personalised care, in which biomechanical stability, visual rehabilitation, patient comfort and resource availability must be balanced.

Corneal crosslinking has shifted the management of KC and other ectasias from predominantly rehabilitative strategies to proactive biomechanical stabilisation. The demonstrable reduction in progression rates and consequent decline in keratoplasty demand underscore CXL's public-health relevance, particularly in regions with limited access to donor tissue and subspeciality surgical care. Early identification of progression and timely referral for CXL are therefore critical clinical imperatives for optometrists and ophthalmologists alike.

Pre-operative screening is fundamental to the selection of an appropriate CXL protocol and must precede any intervention. Screening includes confirmation of ectatic diagnosis, documentation of disease progression, assessment of stromal thickness at the thinnest point, ocular surface status, patient age, atopic history and tolerance for postoperative discomfort. Tomographic evidence of progression, commonly defined as an increase in maximum keratometry (Kmax) of ≥ 1.0 D over 12 months with alterations in corneal thickness and posterior elevation, remains a key trigger for intervention.

Clinical implications include a move towards earlier intervention, the need for protocol individualisation (standard Dresden vs. accelerated regimens; *epi-off* vs. *epi-on*; modified approaches for thin corneas) and long-term follow-up to verify stability. The evidence base supports *epi-off* CXL as the benchmark for efficacy,[8,14,32,38,39] but patient comfort, healing time and risk profiles justify selective use of alternative protocols.

Selection of an appropriate CXL protocol is intrinsically linked to pre-operative screening and should be individualised rather than uniform. The initial decision point is confirmation of progressive KC, typically defined by documented tomographic or keratometric progression over time. Corneal thickness at the thinnest point then becomes the primary determinant of protocol eligibility. In corneas with a minimum stromal thickness of ≥ 400 µm, the epithelium-off Dresden protocol remains the reference standard owing to its well-established biomechanical efficacy, predictable treatment depth and long-term stability.

Accelerated protocols have emerged primarily in response to the prolonged treatment time and postoperative discomfort associated with the standard protocol. While these regimens reduce procedure duration and improve patient tolerance, the shallower demarcation lines reported in several studies suggest reduced crosslinking depth, which may have implications for long-term biomechanical stability, particularly in rapidly progressive disease.

For patients with thin corneas (< 400 µm), pre-operative screening necessitates careful risk stratification, as endothelial safety becomes the dominant concern. Modified approaches such as hypo-osmolar riboflavin swelling, CACXL and customised irradiation protocols expand treatment eligibility but require meticulous intraoperative pachymetry and acceptance of potentially reduced stiffening effects.

Similarly, transepithelial and iontophoresis-assisted techniques may be preferentially selected in paediatric patients, individuals with significant pain sensitivity or those at higher risk of epithelial healing complications, despite their comparatively lower biomechanical impact. 'CXL Plus' strategies promise refractive gains but raise concerns about haze and require careful case selection and informed consent.

Thus, protocol selection is not algorithmic in isolation, but is intrinsically linked to pre-operative screening findings. Optimal outcomes depend on matching disease severity, corneal thickness, patient factors and rate of progression to the most appropriate CXL technique, rather than applying a uniform approach.

Recommendations for practice

- Screen earlier and more systematically: Incorporate tomography, pachymetry and Kmax monitoring into routine assessments of at-risk patients (e.g. adolescents with allergies or eye rubbing, positive family history of KC).
- Define progression *a priori* (e.g. ≥ 1.0 D Kmax increase in 12 months), anterior corneal steepening, posterior corneal steepening, and thinning and/or an increased pachymetric rate of change, and refer promptly.[4,10]
- Apply a protocol-selection algorithm: Base choice of protocol on stromal thickness, patient age, rate of documented progression of KC, pain tolerance and ocular surface status. Reserve epi-on or iontophoresis-assisted methods for cases where epithelial removal poses undue risk, acknowledging the lower, shorter-term stiffening effect.[42]
- Manage thin corneas cautiously: Use hypo-osmolar riboflavin swelling, CACXL or customised or depth-modulated irradiation only in centres experienced with these techniques, and document intraoperative thickness rigorously.[41]
- Standardise peri- and post-operative care: Adopt uniform riboflavin formulations, UVA fluence and soak and irradiation times; ensure adequate analgesia, prophylaxis against infection and scheduled follow-ups (e.g. 1 week, 1 month, 6 months, yearly). Track demarcation lines with Anterior Segment Optical Coherence Tomography (AS-OCT) when possible as a surrogate of treatment depth.[20,45]
- Integrate with visual rehabilitation: After biomechanical stabilisation, coordinate timely optical correction (RGP corneal lenses or scleral lenses) to maximise functional outcomes.[56]

By embracing early detection, evidence-based protocol selection and coordinated visual rehabilitation, clinicians can leverage CXL to meaningfully alter the natural history of KC. Concurrently, rigorous research and policy support will refine protocols, safely extend indications and entrench CXL as a sustainable component of comprehensive ectasia care.

Conclusion

Over the last 100 years, the treatment and management of KC have substantially evolved. While it would be ideal to offer a quick, pain-free CXL procedure, the slow irradiation time of the Dresden protocol has been found to be the most successful. Currently, the *epi-off* procedure with 9 mW/cm^2 for 10 min using constant light appears to work best.[31] The effect of treatment has been observed to remain stable for up to 10 years in the original Dresden cohort.[41]

Early detection and assessment of KC progression are vital. If it is progressive, the progression of KC needs to be halted. Corneal crosslinking has played a phenomenal role in changing the way we prevent the progression of KC. If corneas are more than 400 µm thick at their thinnest point (when KC is in its early or moderate phase), CXL can be implemented to prevent progression. Thereafter, patients can be referred to an optometrist for the fitting of RGP corneal lenses or scleral lenses to improve VA.[57] Corneal crosslinking is significant because it reduces the need for surgical interventions such as a keratoplasty.[41] However, if KC is detected in the advanced stage, keratoplasty may sometimes be the only option.

This narrative review synthesises evidence from 58 publications and demonstrates a clear evolution from the standard *epi-off* Dresden protocol to a diverse range of accelerated, transepithelial, thin-cornea and combined treatment strategies. While newer protocols improve patient comfort, reduce treatment time and expand eligibility, the Dresden protocol remains the benchmark against which efficacy is measured.

Despite substantial progress, important research gaps remain. Long-term comparative data beyond 5–10 years are limited for accelerated, transepithelial and thin-cornea techniques.

The biomechanical durability of reduced-fluence or epithelial-on protocols in rapidly progressive disease, particularly in paediatric populations, requires further investigation. In addition, standardised outcome measures and consensus definitions of treatment success would strengthen inter-study comparability. Future research should focus on well-designed prospective trials, longer follow-up periods and the development of validated clinical algorithms to guide protocol selection. Addressing these gaps will further refine CXL as a personalised, evidence-based intervention in the management of KC.

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the article, contributed to the discussion of results, approved the final version for submission and publication, and take responsibility for the integrity of its findings.

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