REVIEW ARTICLE

Corneal Cross-linking Protocols in the Treatment of Progressing Keratoconus: A Comparative Systematic Review

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Abstract

Purpose: To compare the efficacy and safety of contemporary corneal cross-linking (CXL) protocols for progressive keratoconus with the standard Dresden epithelium-off protocol (S-CXL).

Design: Systematic review.

Methods: A systematic search of PubMed, the Cochrane Library, Google Scholar, and ScienceDirect was performed to identify comparative studies evaluating CXL protocols for progressive keratoconus. Protocols were categorized as S-CXL, accelerated epithelium-off CXL (A-CXL), transepithelial epithelium-on CXL (T-CXL), customized CXL, and combined procedures [CXL-plus, including photorefractive keratectomy (PRK)/phototherapeutic keratectomy (PTK) + CXL]. Primary outcomes were the rate of maximum keratometry (Kmax) stabilization, defined as the proportion of treated eyes without post-treatment progression in Kmax according to the study-defined threshold, and the mean change in ΔKmax at ≥6 months of follow-up. Secondary outcomes included changes in endothelial cell density (ECD), stromal demarcation line depth, and adverse events.

Results: Across included studies, S-CXL demonstrated the most consistent long-term stabilization, typically exceeding 94%. Accelerated epithelium-off CXL achieved comparable stabilization (93%) with the advantage of a shorter treatment time. Transepithelial epithelium-on CXL protocols demonstrated lower and more variable stabilization (82–86%), consistent with reduced stromal riboflavin penetration and a more superficial treatment effect. Corneal cross-linking-plus approaches produced the greatest improvements in corneal flattening and visual outcomes while maintaining acceptable stability in appropriately selected patients. Endothelial safety was generally preserved across protocols when minimum stromal thickness thresholds were respected, or thin-cornea modifications were applied.

Conclusion: Standard epithelium-off CXL remains the reference standard for durable keratoconus stabilization. Moderately accelerated epithelium-off protocols offer logistical advantages with comparable efficacy, and CXL-plus strategies may provide superior visual rehabilitation in selected patients. Transepithelial approaches remain promising but require further high-quality, long-term comparative evidence before they can be considered equivalent alternatives for patients at high risk of progression.

Keywords: Accelerated corneal cross-linking, Corneal cross-linking, Customized corneal cross-linking, Dresden protocol, Epi-off, Epi-on, Innovation CXL, Keratoconus, Photorefractive keratectomy, Riboflavin.

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Introduction

Keratoconus is a bilateral, asymmetric, ectatic corneal disease that typically manifests and progresses during adolescence and young adulthood.[1,2] As the most common ectatic corneal dystrophy, keratoconus has a prevalence that varies widely, from 0.2 to 4,790 per 1,00,000 people, with an annual incidence of about 1.5–25 per 1,00,000 people.[3] Keratoconus is a lifelong, sight-threatening condition that significantly affects quality of life. The disease is characterized by progressive stromal thinning and a change in corneal shape from a normal convex profile to a conical or irregular shape.[3] These structural changes lead to increased irregular astigmatism and decreased visual acuity, often requiring the use of specialty contact lenses. In advanced stages, disease progression may necessitate a corneal transplantation.[3] The underlying mechanism of keratoconus progression is closely linked to a significant decrease in the biomechanical strength of the corneal stroma.[4] In the 1990s, Seiler, Spoerl, and colleagues in Dresden, Germany, introduced corneal collagen cross-linking (CXL) as a minimally invasive treatment designed to enhance stromal biomechanical stability by inducing additional covalent bonds between collagen fibers.[5–7] Since its introduction, CXL has been demonstrated to be an effective and safe intervention for halting disease progression, with additional evidence showing improvements in patient-reported quality-of-life outcomes following treatment.[6,8–11]

The original protocol, known as the "Dresden Protocol," involves epithelial removal (Epi-off) followed by ultraviolet (UV)-A irradiation of 3 mW/cm² for 30 minutes. This protocol has conclusively demonstrated efficacy in stabilizing keratoconus progression.[6,12,13] However, drawbacks such as prolonged treatment duration, postoperative pain, delayed epithelial healing, and an increased

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risk of infection have driven the development of alternative and modified CXL protocols.[5,8]

The aim of this systematic review is to quantitatively and qualitatively compare the main protocols that have emerged since the first in vivo paper on corneal CXL was published in 2003.[7] These include accelerated, transepithelial, customized, and combined (CXL-plus) approaches, with standardized outcome measures of efficacy (disease stabilization) and safety (endothelial cell integrity).

Methods

Study Design

This study is a comparative systematic review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility Criteria and Definitions

Participants

Patients diagnosed with progressive keratoconus, defined as an increase in maximum keratometry (max) of ≥1.0 D within the preceding 12 months.

Intervention

The following major CXL protocols were evaluated:

- Standard CXL (S-CXL; Dresden Protocol): An epithelium-off procedure that involves mechanical epithelial debridement, followed by a 30-minute riboflavin–dextran stromal saturation phase. Ultraviolet-A irradiation (370 nm) is then applied while riboflavin is instilled every 5 minutes. Irradiance is 3 mW/cm^2 for 30 minutes, corresponding to a total energy dose of 5.4 J/cm^2.
- Accelerated CXL (A-CXL): An epithelium-off technique utilizing higher UV-A irradiance (most commonly 9 mW/cm^2) to shorten the irradiation phase to ≤10 minutes, while maintaining an equivalent total energy dose.
- Transepithelial CXL (T-CXL): Protocols designed to preserve the intact epithelium while enhancing riboflavin penetration, using chemically modified formulations (e.g., ethyl alcohol, benzalkonium chloride, trometamol, ethylenediaminetetraacetic acid, and local anesthetics) or iontophoresis. A novel variant is transepithelial accelerated CXL (TE-A-CXL), which combines the transepithelial approach with accelerated irradiation parameters (e.g., 6 mW/cm^2 for 15 minutes).
- CXL-plus: Combined treatment approaches in which CXL is performed immediately or sequentially following adjunctive photoablative procedures, such as topography-guided photorefractive keratectomy (PRK) (the Athens, Cretan, and Tel Aviv protocols).

Follow-up Duration

Studies reporting outcomes with at least 6 months of follow-up were eligible for inclusion.

Information Sources and Search Strategy

A comprehensive literature search was conducted in PubMed, the Cochrane Library, Google Scholar, and ScienceDirect using keywords including "corneal cross-linking," "keratoconus," "accelerated," "CXL plus," "transepithelial," "novel CXL methods," "customized," and "PRK-CXL." Eligible publications included randomized controlled trials, prospective clinical studies, retrospective case series, and systematic reviews and meta-analyses.

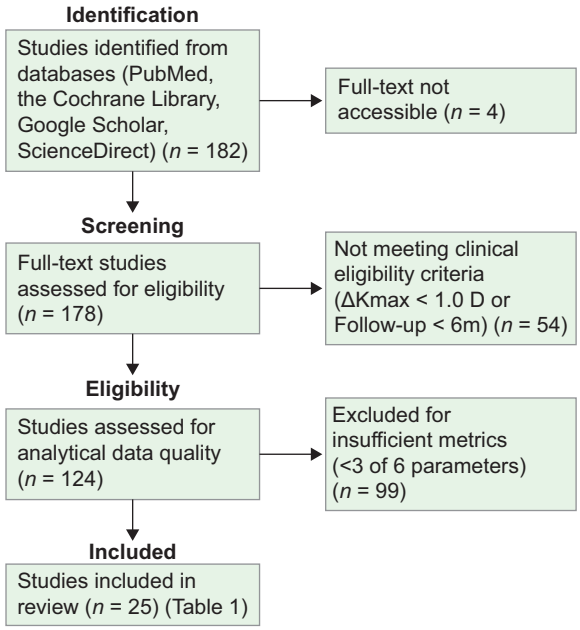

Fig. 1: PRISMA flow diagram of the study selection process

Endpoint Measures

- Primary endpoints (efficacy):
  - Disease stabilization rate: The percentage of treated eyes that demonstrated no progression of Kmax beyond a predefined threshold.
  - Change in ΔKmax: Mean difference in Kmax (D) between preoperative and postoperative measurements.
- Secondary endpoints:
  - Demarcation line depth: Depth of the stromal transition zone following CXL, indicating the transition zone between the cross-linked anterior corneal stroma and the untreated posterior corneal stroma, measured in micrometers (μm).[14]
  - Endothelial cell density (ECD): The percentage change in ECD as a metric for endothelial toxicity.
  - Adverse events: Type and estimated frequency of reported complications.

Results

Literature Search and Study Selection

A systematic search of PubMed, the Cochrane Library, Google Scholar, and ScienceDirect identified comparative studies evaluating CXL protocols for progressive keratoconus, yielding 182 clinical trials and meta-analyses from 2010 to 2025. Full-text articles could not be retrieved for four studies. The remaining 178 reports underwent a full-text eligibility assessment using predefined clinical criteria: documented progression (ΔKmax >1.0 D within the year preceding enrollment) and a minimum follow-up of 6 months. This screening step excluded 54 studies. The remaining 124 reports were then assessed for data completeness, defined as reporting at least three of six key parameters: sample size, follow-up duration, ΔKmax, demarcation line depth, Kmax stabilization rate, and ECD change. Ultimately, 25 studies met this criterion and were included in the final analysis (Fig. 1).

The systematic review included data from primary studies and from systematic reviews. The key clinical outcomes are summarized in Table 1.

Table 1: Summary of key clinical outcomes of CXL protocols

Study (reference)	*Comparison protocol*	*N eyes*	*Follow-up (mo)*	*ΔK max (D)*	*Demarcation line depth (μm)*	*Stabilization rate (%)*	*ECD loss (%)*
Ang et al.[15]	A-CXL	70	12	−0.61	–	100	–
Bordais et al.[16]	S-CXL	89	120	−2.31	–	92	–
Dai et al.[17]	CXL-plus (TG-PRK + ACXL)	30	44	−3.06	–	100	–
Dina et al.[18]	A-CXL	20	12	−1.27	278.90 ± 31.71	100	–
Dina et al.[18]	S-CXL	21	12	−1.46	280.42 ± 47.85	100	–
Eissa and Yassin[19]	A-CXL	34	36	−1.40	–	100	NS ($P > 0.05$)
Eissa and Yassin[19]	S-CXL	34	36	−0.78	–	100	NS ($P > 0.05$)
Elving et al.[20]	Customized CXL high oxygen (Epi-on) vs Customized CXL (Epi-off)	64	24	−1.74 ± 1.31 vs −1.72 ± 1.36	–	100	NS ($P > 0.05$)
Halašová et al.[21]	CuRV (Epi-on) vs A-CXL	179	24	−2.46 ± 2.64 vs −1.38 ± 2.13	–	99 vs 91	NS ($P > 0.05$)
Hersh et al.[22]	S-CXL	78	12	−0.70	–	96	−4.5
Kanellopoulos[23]	CXL-PLUS (TG-PRK+CXL) "Athens" protocol	144	128	−8.68	–	94.4	–
Kobashi and Tsubota[24]	A-CXL vs S-CXL	No data	12	NS ($P > 0.05$)	+102.25 ($P = 0.0003$)	93	NS ($P > 0.05$)
Kymionis et al.[25]	A-CXL vs S-CXL	52	1	–	322.91 ± 48.28 vs 337.00 ± 46.46	–	–
Larkin et al.[26]	CXL-pLUS	30	18	−2.11	–	93	–
Li and Wang[27]	T-CXL vs S-CXL	244	12	Mean difference = −1.05 for S-CXL ($P = 0.02$)	–	S-CXL >T-CXL	–
Lombardo et al.[28]	T-ionto CXL (Epi-on)	22	12	−0.52	–	81.8	NS ($P = 0.39$)
Lombardo et al.[28]	S-CXL	12	12	−0.82	–	91.7	NS ($P = 0.45$)
Matthy et al.[29]	T-CXL (with supplemental oxygen)	34	12	−1.56	–	100	NS ($P > 0.05$)
Mohammadi et al.[30]	CXL (non-specific protocol) in patients with thin corneas (<400 μm)	470	24	−1.40	–	–	−4 ($P > 0.05$)
Ng et al.[3]	T-CXL vs S-CXL	723	12	0.99	–	86	NS ($P > 0.05$)
Rossi et al.[31]	T-CXL vs S-CXL	20	12	1.06 ± 1.00 vs 1.08 ± 2.08	–	100	−2.2 vs −1.2 ($P > 0.05$)
Seiler et al.[32]	Customized CXL vs S-CXL	40	12	−1.70 ± 2.00 vs −0.90 ± 1.30	338 ± 77 vs 357 ± 51	94.7 vs 100	NS ($P > 0.05$)
Serrao et al.[33]	T-ionto CXL vs S-CXL	35	12	0.52 ± 1.30 vs 0.82 ± 1.20	–	–	NS ($P > 0.05$)
Turunç et al.[34]	A-CXL (7.2 J/cm2)	113	6	−1.06	–	–	−0.01 ($P = 0.14$)
Vilares-Morgado et al.[35]	TE-ACXL	41	48	0.61	–	32.1	–
Vinciguerra et al.[36]	T-ionto CXL vs S-CXL	40	12	−0.31 ± 1.87 vs −1.05 ± 1.51	–	100	NS ($P > 0.05$)
Wittig-Silva et al.[13]	S-CXL	46	36	−1.03	–	97.8	−4.50 ($P = 0.49$)
Zhang et al.[37]	T-CXL (Epi-on) vs S-CXL	183	24	0.79 (95% CI: 0.04–1.53)	–	–	−32.01 ($P = 0.34$)

A-CXL, accelerated CXL; CuRV, customized remodeled vision; CXL-plus, CXL combined with TG-PRK; ECD, endothelial cell density; –, not reported; NS, not statistically significant; S-CXL, standard CXL; T-CXL, transepithelial CXL; TE-ACXL, transepithelial accelerated CXL

Table 2: Summary of adverse effects of CXL protocols

The protocol	*Primary advance events*	*Estimated frequency (%)*	*Notes*	*Study ref.*
S-CXL (Epi-off)	Pain, infection (mainly due to postoperative handling), corneal scaring, delayed epithelial healing, transient stromal haze, photophobia, vision loss (more than two lines)	Haze: 4–5% Infection:<2% Vision loss: 4.6% Corneal scarring: 8.6%	High efficacy, requires ≥400 µm corneal thickness Non-infectious corneal infiltrates: 2%	[5,38–46]
A-CXL (Epi-off)	Similar to S-CXl but less painful	Similar to S-CXl	Procedure time is shorter, higher UV-A irradiance	[45,47–49]
T-ionto CXL (Epi-on)	Decreased pain, less delayed healing, haze, need for retreatment	Haze: 1–2%	Lower efficacy, fewer acute adverse events	[48–50]
T-CXL (Epi-on) chemical enhancers	Corneal melting	Enhanced by high UV-A radiation	Reduced stromal thinning, stromal haze and infections compared to Epi-off protocols	[51–53]
CXL-plus (PRK + CXL)	Haze, delayed epithelial healing, infection, loss of vision lines	Haze: 5–10% Delayed healing: 10% Vision loss: 2–8%	Significant improvement in UDVA*/CDVA**, similar ectasia progression rate to CXL alone, haze mostly transient	[54–62]
Sub-400 protocol (thin-cornea)	Haze, endothelial cell loss, corneal melting, mild pain	Rare	Modified protocols, safe, no evidence of major complications	[30,52,63–65]

*UDVA, uncorrected distance visual acuity.**CDVA, corrected distance visual acuity

Summary of Key Findings

Standard epi-off CXL; Dresden protocol: Remains the reference standard, demonstrating the most consistent and durable long-term stabilization, with reported rates typically ranging from 94 to 98%.[13,18,22,24,28–30,32]

Accelerated CXL

Moderately accelerated protocols (e.g., 9 mW/cm^2) achieve stabilization outcomes comparable to those of S-CXL, while substantially reducing procedure time and maintaining an acceptable safety profile.[16,18,21,24]

Transepithelial CXL

Protocols involving iontophoresis or chemical enhancers consistently yielded lower stabilization rates (82–86%) compared to Epi-off techniques.[3,27,28,37] This reduced efficacy is primarily attributed to insufficient stromal riboflavin concentration, leading to a shallower demarcation line and potentially a weaker biomechanical effect.[8] Regarding TE-A-CXL, a substantial proportion of eyes with progressive keratoconus demonstrated post-treatment progression and required additional interventions to achieve disease control.[35]

Customized CXL

Customized irradiation patterns targeting the ectatic cone were associated with greater Kmax reduction, improved corneal surface regularization compared with uniform irradiation strategies, and faster epithelial recovery in comparative reports.[8,20,21,32]

CXL-plus (PRK + CXL)

The combined protocols achieved the largest mean corneal flattening effect (ΔKmax) and the most significant improvement in visual acuity, suggesting excellent simultaneous refractive and stabilizing effects in appropriately selected patients.[17,23,26]

Safety profile

All protocols demonstrated a favorable endothelial safety profile. No statistically significant change in ECD was reported ($p > 0.05$), provided that the minimum stromal thickness threshold of 400 µm was maintained or appropriately compensated for Table 2.

Discussion

This review highlights the effectiveness of S-CXL and the clinical rationale for modern protocol innovations.[7,10,39] Over time, several visual rehabilitation options have been developed for the management of keratoconus, such as scleral lenses and intracorneal ring segments (ICRS).[66–68] The evolution of CXL reflects a broader shift in keratoconus management, from a focus on visual rehabilitation toward a more patient-centered approach that balances biomechanical effects, procedural burden, and safety.[4,6,69] Contemporary protocols aim to minimize postoperative morbidity, streamline clinic workflow, and address refractive limitations that persist even when progression is arrested.[1,16,37,45,46,60,69–71]

Evaluating biomechanical efficacy (S-CXL vs A-CXL), the S-CXL protocol remains the traditional benchmark for biomechanical efficacy, high stabilization rate, high disease-arrest rate, and the deep, homogeneous demarcation line it produces.[8,13,72] The shift to A-CXL offers significant logistical improvements and cost savings for both clinics and patients in terms of surgery duration. Nonetheless, reduced efficacy observed at very high irradiances (such as 45 mW/cm^2) is a critical point. This phenomenon is well explained by the exceedingly rapid oxygen consumption in the stroma, which can limit the formation of cross-links (Type II aerobic reaction).[8] This observation is biologically plausible and aligns with current mechanistic understanding that oxygen availability is a key limiting factor in the photochemical cross-linking reaction. Higher irradiances can rapidly deplete stromal oxygen and constrain cross-link formation, particularly that mediated by oxygen-dependent pathways. Therefore, while A-CXL represents a practical and widely adopted alternative, mainly for convenience, the degree of acceleration should be selected cautiously, and longer-term outcomes, especially for pediatric and highly progressive disease, should continue to be closely monitored.[18,19,24,25,34,45,46,50,72]

Transepithelial (epithelium-on) CXL was developed to reduce postoperative pain, expedite recovery, and mitigate

the risk of infection by avoiding epithelial debridement.[1,3,27] Earlier epithelium-on protocols, relying on chemical enhancers or iontophoresis, often reported lower and more variable stabilization rates than epithelium-off approaches, consistent with the epithelium's role as a significant barrier to stromal riboflavin diffusion and oxygen availability.[1,5,28,29,35,51] These limitations may lead to reduced stromal riboflavin concentration, diminished UV-A absorption, and yield a more superficial CXL effect, contributing to the less robust biomechanical response observed in some comparative studies.[33,37] However, T-CXL is rapidly evolving, and newer proprietary systems have been specifically designed to enhance riboflavin bioavailability without epithelial removal.[8,21,54] Notably, the EpiSmart (EpiOxa, USA) platform has introduced a formulation and delivery strategy intended to overcome traditional diffusion constraints, and early clinical data are emerging. In a Phase 2 study of EpiSmart CXL for keratoconus, Epstein and colleagues reported encouraging outcomes supporting the feasibility and potential effectiveness of a next-generation epithelium-on approach.[5,73] While these findings suggest that modern epi-on systems may narrow the performance gap observed with earlier transepithelial protocols, the current evidence base remains limited by relatively short follow-up, and a lack of extensive head-to-head randomized comparisons against standard epithelium-off CXL.[1,35,46] Consequently, epithelium-on CXL should still be interpreted as a promising and advancing modality, but one that requires further high-quality comparative trials and longer-term data before it can be considered equivalent for patients at high risk of progression, particularly pediatric and rapidly progressive keratoconus.[19,26,34] Emerging strategies, including supplemental oxygen ("hyperoxic" transepithelial CXL), represent a promising direction by directly addressing oxygen limitation and potentially improving cross-linking depth and uniformity.[20,29] However, these innovations require additional high-quality, long-term comparative evidence before they can be recommended as equivalent alternatives for high-risk progression, particularly in younger patients.[1,20]

Toward Personalized Treatment: Customized CXL and CXL-Plus

A major conceptual advance in contemporary CXL is the recognition that keratoconus is spatially localized and biomechanically heterogeneous rather than uniformly distributed across the cornea.[4,8] This has motivated the development of customized CXL protocols that aim to selectively increase treatment intensity within the ectatic cone while minimizing unnecessary irradiation of more stable regions.[32] By concentrating UV-A energy at the area of maximal biomechanical weakness, customized approaches may achieve greater reductions in Kmax and improved corneal regularity compared with homogeneous treatment, with the potential for greater functional benefit, especially in patients with ultrathin corneas, where individualized energy distribution is critical for safety.[15,18,20,64,65]

In parallel, CXL-plus strategies, combining CXL with adjunctive refractive surface procedures such as topography-guided PRK and/or PTK, appear to provide the largest gains in visual acuity by addressing both disease progression and optical irregularity.[23,59,60] Protocol variations, including the Cretan protocol plus (transepithelial PTK followed by conventional PRK and simultaneous CXL), have demonstrated encouraging outcomes, including corneal stabilization with improved visual performance in appropriately selected keratoconus patients.[69,74] However, these combined procedures may increase the risk of postoperative complications, including persistent stromal haze, delayed epithelial recovery, and more rarely, loss of lines of corrected distance visual acuity, with a higher risk in patients with atopy or predisposition to corneal scarring.[42,52,53,55,57,58,63,75] Future progress in this area will likely depend on the development of validated, individualized nomograms that integrate disease stage, corneal thickness, age, refractive profile, and patient-specific visual needs to optimize outcomes while minimizing risk.[17,76,77] Importantly, additional prospective, long-term randomized trials are required to define durability, safety, and standardized indications for customized and CXL-plus protocols, particularly across diverse patient populations and keratoconus phenotypes.[17,60,69,75]

Addressing Thin Corneas, The Sub400 Protocol

Corneal thickness remains a critical determinant of procedural safety in CXL, and the traditional "400-µm rule" remains a widely accepted threshold to minimize endothelial UV-A exposure and toxicity.[5,47,71] The Sub400 protocol is an important advancement in the management of patients with ultrathin corneas who would otherwise be excluded from standard epithelium-off treatment.[64] By intentionally swelling the cornea, typically using hypo-osmolar riboflavin solutions, to achieve a safe stromal thickness during irradiation, Sub400 expands access to biomechanical stabilization in advanced keratoconus.[71,78] This approach may reduce the likelihood of progression to keratoplasty in eyes with severe thinning, although careful pachymetric monitoring and strict adherence to safety parameters remain essential to prevent complications such as endothelial damage or corneal melting.[41,52,63–65] Recent data further suggest that individualized UV-A irradiation based on intraoperative pachymetry (the Sub400 nomogram) can effectively stabilize these thin corneas without clinical evidence of endothelial toxicity.[64,65]

Study Limitations

Comparisons across CXL protocols remain challenging due to substantial heterogeneity in UV-A irradiance and exposure time, epithelial management, oxygen availability, riboflavin formulations, and variability in baseline disease severity and follow-up duration. Definitions of progression and treatment failure vary across studies and centers, and reporting of key secondary outcomes (e.g., demarcation line depth, endothelial cell density, standardized adverse event rates) is often incomplete, limiting reliable quantitative synthesis and increasing susceptibility to reporting and publication bias. These constraints are particularly relevant for emerging epithelium-on innovations, where follow-up is often shorter and head-to-head randomized comparisons with standard epithelium-off CXL remain limited.

Conclusion

While the landscape of CXL has diversified significantly over the last quarter-century, our analysis confirms that the S-CXL maintains its status as the most robust benchmark for durable keratoconus stabilization. Accelerated, customized, and CXL-plus approaches offer meaningful advantages in efficiency and visual rehabilitation, while transepithelial techniques remain promising but require stronger long-term comparative evidence. Future multicenter trials with standardized endpoints are needed to refine patient-specific protocol selection.

Clinical Significance

Corneal cross-linking protocol selection should be individualized based on progression risk, corneal thickness, and the patient's visual

rehabilitation needs. In rapidly progressive disease, particularly in children and adolescents, epithelium-off CXL (standard or moderately accelerated) remains the preferred strategy to maximize durable stabilization. For selected adult patients with functional limitations from optical irregularity or contact lens intolerance, CXL-plus approaches may offer meaningful visual improvement, while thin-cornea adaptations (e.g., Sub-400) expand eligibility for treatment in advanced ectasia when standard safety thresholds cannot be met.

Declarations

Conflict of Interest

The authors declare that they have no conflicts of interest relevant to this work.

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AI Use Declaration Statement

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Authors' Contributions

(CRediT Format) Ori Shapira: Conceptualization, Methodology, Investigation, Data Curation, Writing- Original Draft, Writing- Review and Editing, Project Administration. Yishay Weill: Investigation, Data Curation, Writing- Review and Editing. David Zadok: Supervision, Writing- Review and Editing, Validation.

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