

New clinical pathways for keratoconus

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REVIEW

Abstract

Pre-2000, the clinical management of keratoconus centred on rigid contact lens fitting when spectacle corrected acuity was no longer adequate, and transplantation where contact lens wear failed. Over the last decade, outcome data have accumulated for new interventions including corneal collagen crosslinking, intracorneal ring implantation, topographic phototherapeutic keratectomy, and phakic intraocular lens implantation. We review the current evidence base for these interventions and their place in new management pathways for keratoconus under two key headings: corneal shape stabilisation and visual rehabilitation.

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Conventional keratoconus management

For the age group 10–44 years, the prevalence of keratoconus in white Europeans has been estimated 1 in 1750, rising to 1 in 450 in South Asians.¹ Until 2000, disease progression in keratoconus was managed with spectacles until irregular astigmatism necessitated rigid contact lens fitting, then corneal transplantation where contact lenses failed. No interventions were available to arrest or slow disease progression, and corneal transplantation was required in up to 21% of keratoconic eyes.² Using established techniques (Markov modelling), the lifetime cost of conventional keratoconus treatment has been estimated at US\$25 168 per patient, with the likelihood of primary and repeat corneal transplantation being the key cost determinants.³ Given the relatively high prevalence of keratoconus and the frequency with which corneal transplantation is required, this represents a significant health economic burden.³

While penetrating keratoplasty (PK) for keratoconus generally achieves good visual

outcomes, long-term graft survival in keratoconic eyes declines rapidly after the second decade. Primary graft survival rates from the Australian Graft Registry are 89% at 10 years, 49% at 20 years, and 17% at 23 years.⁴ These rates fall further with repeat grafts. Ten-year survival rates are 53% for second and 33% for third grafts.⁵ Most grafts for keratoconus are performed in relatively young patients. In an effort to reduce the rate of repeat transplantation and associated complications, many surgeons now use deep anterior lamellar keratoplasty (DALK), with preservation of the host endothelium, as the transplantation procedure of choice in keratoconus. Accelerated long-term endothelial cell loss observed after PK does not occur after DALK.⁶ Extrapolation from observed endothelial cell loss rates predicts a median graft survival of 49 years for DALK *vs* 17 years for PK.⁷ But current DALK techniques are technically challenging. Intraoperative complications and conversion to PK are common. A recent UK transplant registry comparison of results for PK and DALK in keratoconus showed a high early failure rate for DALK.⁸ This was attributed to the learning curve in the surgical transition from PK to DALK for many surgeons in the period studied (1999–2005). Where transplantation is successful, irregular astigmatism and high postoperative anisometropia commonly prevent successful visual rehabilitation in spectacles without recourse to further surgical intervention.⁴

Corneal transplantation is an effective but costly intervention in advanced keratoconus (stage IV modified Krumeich classification,⁹ anterior 3 mm zone steep keratometry [K] > 55D; Table 1), with an estimated incremental cost-utility ratio of between \$1942¹⁰ and \$3025¹¹ per quality-adjusted lifeyear. The life impact of repeat intervention, and slow, often incomplete, visual rehabilitation after transplantation should not be underestimated.¹² Transplantation costs, and evidence for reduced quality of life in contact lens wearers,¹³

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Table 1 Modified Krumeich classification of keratoconus⁹

Stage	Characteristics
I	Eccentric corneal steepening Induced myopia and/or astigmatism <5D Corneal radii ≤48D Vogt's striae, no scars
II	Induced myopia and/or astigmatism >5D, <8 D Corneal radii ≤53D No central scars Corneal thickness ≥400 μm
III	Induced myopia and/or astigmatism >8D, <10D Corneal radii >53D No central scars Corneal thickness 200–400 μm
IV	Refraction not measurable Corneal radii >55D Central scars, perforation Corneal thickness <200 μm

Abbreviation: D, dioptres.

Note that on a Pentacam scan result, K1 represents corneal curvature in the flat central 3 mm zone, K2 represents the steep curvature in the 3 mm zone; Kmax (denoted by the white diamond symbol) represents the steepest point over the entire scanned anterior corneal surface. Thresholds for progression used in contemporary studies (Table 2) refer to Kmax (or Kmin), as opposed to the above classification which is equivalent to the 3-mm zone K2.

underline the need for a new, more proactive approach to keratoconus management.

New pathways for keratoconus management

Over the last decade, outcome data have accumulated for new interventions in keratoconus which promise to reduce transplantation rates significantly, arrest disease progression, and save many patients from long-term reliance on rigid contact lens wear. These interventions include corneal collagen crosslinking (CXL), intracorneal ring implantation (ICRS), topographic photorefractive keratectomy (topoPRK), and phakic intraocular lens (pIOL) implantation. They all require that ocular surface inflammation (eg, atopic keratoconjunctivitis) associated with keratoconus is well controlled before treatment, and none is applicable to advanced (stage IV) disease with corneal scarring. Beyond these basic common requirements, definition of the indications, timing and sequence for new interventions in keratoconus continues to evolve. Based on the current evidence base, we outline new proactive pathways for keratoconus management addressing two essential aims: shape stabilisation and visual rehabilitation.

Methodology

We searched MEDLINE (1950–2012) and the Cochrane Central Register of Controlled Trials using the following search terms: keratoconus; corneal crosslinking;

crosslinkage; intracorneal ring segment; topoPRK; and pIOL. For the meta-analysis, two authors (DG and AS) independently assessed the search results for randomised-controlled trials (RCTs) of corneal crosslinking in keratoconus. The authors of one RCT¹⁴ were contacted for clarification of one trial methodology and they provided additional unpublished data. A risk of bias assessment was performed on studies and only studies with a low risk of selection, performance, detection, and attrition bias were included. Data extraction was done independently by DG and AS. Data synthesis was performed using a meta-analysis software package, Review Manager (RevMan, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2008). The effect of the intervention was expressed as odds ratios and confidence intervals (CIs) were calculated. The Mantel–Haenszel fixed-effect method of meta-analysis was used.

Defining disease progression—monitoring keratoconus

Defining disease progression and the threshold for surgical intervention in keratoconus patients under observation remains a challenge. Assuming no diurnal variation in corneal shape, the coefficient of repeatability (CoR) should correspond closely to the limits of agreement for successive measures of corneal tomography indices,¹⁵ defining a threshold beyond which there is a 95% probability that an observed difference reflects disease progression rather than measurement inaccuracy. Keratometry measurement repeatability in keratoconic eyes (stage II, 3 mm zone steep $K \leq 53D$) has been shown to be significantly poorer than in normal corneas, with a 1D CoR for steepest keratometry (Kmax) using Fourier-domain anterior-segment OCT (Casia SS-1000 Tomey Corp., Nagoya, Japan) and 1.5D using a Scheimpflug-based imaging device (Pentacam HR, Oculus GmbH, Wetzlar, Germany).¹⁶ This compares with CoR values in normal corneas of <0.5D for both imaging devices.¹⁶ Based on this, a change in Kmax of +1.5D vs measurement at presentation on Pentacam image comparison maps may be a useful contemporary threshold indication for CXL using a widely available corneal tomography device. A lower threshold (+1D vs baseline Kmax) is used in contemporary studies (Table 2). Changes in other criteria used to define disease progression (Table 2) may tip the balance in favour of intervention where the observed increase in Kmax is < +1.5D.

The frequency with which patients should be screened and the optimum corneal tomography method also require additional research. After diagnosis, we are currently monitoring six monthly for 2 years with annual review subsequently. More frequent initial monitoring

may be valuable in younger patients at high risk of rapid progression. Where possible, rigid contact lenses should be left out for a minimum of 2 weeks before each topography examination to reduce corneal warpage.

Shape stabilisation

Standard crosslinking

Corneal collagen crosslinking (CXL) using the standard, epithelium-off protocol originally described by Wollensak *et al*¹⁷ is effective in arresting disease progression (52% stabilizing, 45% regressing) with 3% of eyes progressing despite treatment.^{14,18} Long-term outcomes (mean 52 months follow-up, range 48–60 months) for standard CXL have been reported in the Siena Eye Cross Study,¹⁹ a prospective, non-randomised study of 44 eyes with progressive keratoconus treated with CXL and fellow eye controls. Control eyes, in which disease progression was less rapid than treated eyes before assignment, were observed initially then crossed over to CXL after 2 years. Their data confirmed a halt in

ectatic progression in all treated eyes, with a mean reduction in Kmax of 2 dioptres (D), while fellow eyes progressed by a mean 1.5D for 24 months (before crossover) before also demonstrating comparable reductions in Kmax after CXL. Refraction stabilised at 2 years and spectacle corrected distance visual acuity (CDVA) improved 2 ± 1 Snellen lines (mean \pm SD).¹⁹ Two-year outcome data from an uncontrolled prospective study²⁰ in 40 children (mean age 14.2 ± 1.7 years) with mild disease ($3 \text{ mm zone steep } K \leq 53\text{D}$) confirmed similar findings with both UDVA and CDVA improving by two lines (logMAR) and a reduction in Kmax of 1.27D.

Further evidence for the efficacy of standard, epithelium-off CXL is found in three RCTs with fellow eye controls that have published 12-month results.^{14,18,21} Excluding one study¹⁸ in which control eyes were crossed over to treatment after just 3 months, we combined 1-year post-CXL keratometric and acuity outcome data for patients ($n = 31$) in the remaining two trials. Clinically significant ectatic progression (increase in $K_{\text{max}} \geq 1\text{D}$ at 12 months) was observed in 32% untreated control eyes and 3% eyes treated with CXL ($P = 0.01$, z-test); whereas significant regression (decrease in $K_{\text{max}} \geq 1\text{D}$ at 12 months) was seen in 45% of CXL treated eyes and 10% untreated control eyes ($P = 0.005$, z-test) (Figures 1a and b). After conversion of 12 month acuity data to logMAR values, combined data showed a statistically significant improvement in CDVA for patients treated with CXL ($P = 0.04$, z-test).

Spontaneous disease regression does not normally occur in keratoconus, and apparent disease regression (decrease in $K_{\text{max}} \geq 1\text{D}$) in 10% of control eyes in RCTs may simply reflect limitations in measurement accuracy for contemporary topographers¹⁶—a problem compounded by corneal warpage in rigid contact lens

Table 2 Criteria for keratoconus progression *vs* baseline measurement used in contemporary clinical trials of corneal collagen crosslinking^{14,18,21}

Kmax $\geq 1\text{D}$ increase
Kmax – Kmin $\geq 1\text{D}$ increase
Kmean $\geq 0.75\text{D}$ increase
Pachymetry $\geq 2\%$ decrease in CCT
Corneal apex power $> 1\text{D}$ increase
MRSE $> 0.5\text{D}$

Abbreviations: CCT, central corneal thickness; D, dioptres; Kmax, steepest keratometry; Kmin, flattest keratometry; MRSE, manifest refractive spherical equivalent.

Kmean = (Kmax + Kmin)/2; corneal apex power is measured with cone location and magnitude index (CLMI).

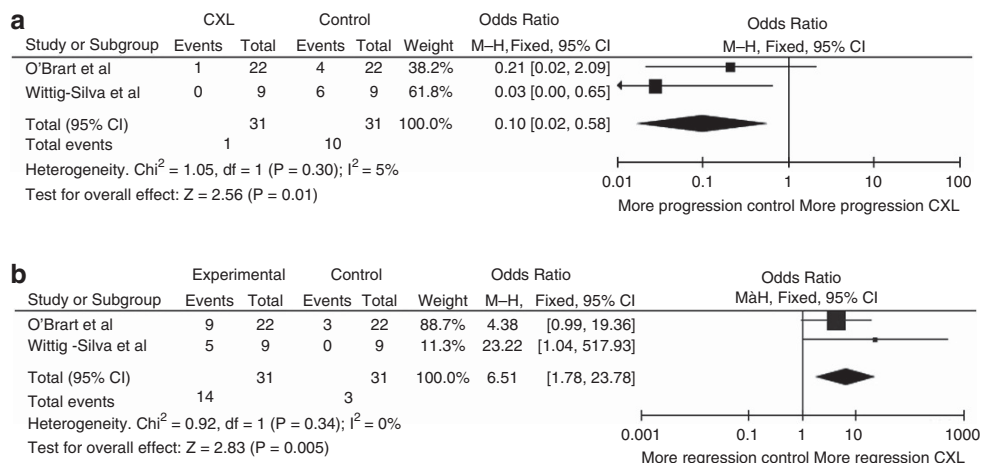


Figure 1 Forest plot of meta-analysis of 12 month results from placebo-controlled randomised trials showing (a) disease progression (defined in these trials by an increase in maximum keratometry ($K_{\text{max}} \geq 1\text{D}$) is significantly less likely after collagen CXL; and (b) disease regression (reduction of $K_{\text{max}} \geq 1\text{D}$) is significantly more likely after CXL.

wearers. These limitations and varying inclusion criteria (Table 2) in contemporary studies underline the problem of defining disease progression in keratoconus and defining thresholds for intervention.

Although generally safe,^{14,18,19,21,22} a range of complications is seen after standard, epithelium-off CXL. Sterile corneal infiltrates, thought to be an immune reaction to bacterial antigen deposition, were observed in 7.6% of patients in a prospective series of 117 eyes with 12 month follow-up after CXL reported by Koller *et al.*²² Culture-proven bacterial keratitis with permanent loss of vision has also been reported.²³ Mild stromal haze is common after CXL and typically resolves within a year without detriment to visual acuity; but mid-stromal scarring was observed in 3% of cases by Koller *et al.*,²² and 3% (95% CI 1–9%) lost two or more lines of Snellen CDVA. Although the mechanism of visual loss was not identified, risk factors for loss of vision in this study were age > 35 years and pre-operative CDVA > 20/25.

Keratocyte and endothelial cell toxicity

Keratocyte apoptosis has been observed at up to 350 μm depth in experimental and clinical studies of the standard CXL protocol in which UVA light at 370 nm is applied at an irradiance of 3 mW/cm² for 30 min.²⁴ Rates of endothelial cell loss similar to background age-related change were recorded in the Siena Cross Study¹⁹ where treated corneas had $\geq 400 \mu\text{m}$ central thickness after epithelial removal, but significant cell loss and corneal endothelial failure have been reported in thinner corneas.^{25,26} Shielding by riboflavin saturation in a 400- μm -thick cornea reduces irradiance at the endothelial level to 0.18 mW/cm²,²⁴ well below the cytotoxic threshold of 0.35 mW/cm² previously established in porcine endothelial cell cultures.²⁷ Hypotonic riboflavin is now commonly used to increase corneal thickness before UVA exposure in thinner corneas. This technique was originally described by Hafezi *et al.*²⁸ They reported no complications or progression of ectasia at 6 months in a series of 20 eyes with > 320 μm initial corneal thickness after epithelial removal. Similar encouraging 1 year results for CXL using hypotonic riboflavin in thinner corneas were reported by Raiskup *et al.*²⁹ in a prospective series of 32 eyes.

Rapid crosslinking

Rapid treatment protocols for CXL based on shorter UVA exposure times and higher irradiances are emerging. The underlying premise in rapid CXL is that delivering a similar total energy over a shorter period of time will not compromise safety or efficacy in comparison with the standard protocol (30 min at 3 mW/cm²). Stress-strain measurements on porcine corneal strips treated using a

rapid protocol (9 min at 10 mW/cm²) demonstrated equivalent increases in corneal stiffness in comparison with the standard protocol.³⁰ In a recent prospective randomised trial,³¹ contralateral eyes of 21 patients with progressive keratoconus were randomised to either conventional or rapid CXL (7 mW/cm² for 15 min). A halt in ectasia progression was seen in all cases at a mean follow-up of 46 months. Both groups responded similarly: CDVA improved from 20/60 to 20/40, UDVA from 20/30 to 20/25, mean sphere reduced by 2.4D and Kmax reduced from 49.5D to 46.1D. Endothelial cell loss was less in the rapid CXL group (– 100 cells/mm²) than in the conventional CXL group (– 250 cells/mm²).

Transepithelial crosslinking

Transepithelial CXL, in which riboflavin is delivered using enhancers of epithelial permeability rather than epithelial debridement, promises to deliver the benefits of standard epithelium-off treatments without the painful rehabilitation and complications of epithelial removal. Epithelial-toxic agents used include benzalkonium chloride (BAC), sodium ethylenediaminetetraacetic acid (EDTA), tetracaine, proparacaine, ethanol, and gentamicin. A non-toxic reversible synthetic non-selective ion channel-forming peptide, NC-1059, has also been shown in a chick corneal model to enhance riboflavin permeability across an intact epithelium.³² Two prospective, paired-eye studies in humans have documented small, but significant improvements in CDVA over fellow untreated eyes at 12 and 18 months, respectively, with a trend towards deterioration in topographic and acuity measures in non-treated control eyes.^{33,34} Improvements in corneal curvature (~2D mean reduction in Kmax) were similar to those seen after epithelium-off CXL. Statistically significant improvements in CDVA were also observed in an uncontrolled prospective study,³⁵ though the authors recorded conflicting keratometric results depending on the imaging device used (progression by Scheimpflug, no change by Placido disc). In addition to drug-induced epithelial disruption, Stojanovic *et al.*³⁶ described the use of a riboflavin-soaked polyvinyl acetal pledget (Merocel sponge, Medtronic, Inc., Minneapolis, MN, USA) inserted into the conjunctival sac to produce microabrasions of the superficial epithelial layers with eyelid blinking. In conjunction with proparacaine, gentamicin, and BAC, their 12-month results showed significant improvements in UDVA, CDVA, refraction, and keratometric indices.

Optical coherence tomography (OCT) imaging suggests that crosslinking may be concentrated in the anterior corneal stroma after transepithelial CXL,³⁴ with a demarcation line typically visible at around 100 μm

depth as opposed to $\sim 250 \mu\text{m}$ after epithelium-off CXL. Transepithelial and standard, epithelium-off CXL may, therefore, be complimentary. Filippello *et al*³⁴ argue that since crosslinking appears to be concentrated at different stromal levels for the two modalities, transepithelial treatment could be used where epithelium-off CXL fails. Conversely, provided further clinical evidence continues to support comparable efficacy and enhanced safety *vs* standard, epithelium-off CXL, we believe that transepithelial CXL could have an important *first-line treatment* role in shape stabilisation for newly diagnosed keratoconus, with the back-up of epithelium-off CXL if ectatic progression still occurs (Figure 2).

Until now, the conventional approach has been to intervene with CXL only for patients with documented disease progression. Factors predictive of an increased risk of disease progression in keratoconus include young age (≤ 35 years), steep keratometry, high astigmatism, reduced CDVA (irregular astigmatism), ethnicity other than white European, and documented progression in the contralateral eye.^{37–39} These risk factors for disease progression are often present at presentation, and may be compounded if further disease progression is allowed to occur. Based on this, the proven efficacy of CXL,^{14,18,19,21,22} the higher risk of CXL-related visual loss aged > 35 years,²² and the relative safety of transepithelial treatment,^{33,34} we believe that there is a rational argument for transepithelial CXL at presentation for patients ≤ 35 years of age with keratometric stage II disease (Figures 2 and 3).⁹ For patients over 35 years without other risk factors, the risk of progression is lower (and CXL-related complications higher), so no intervention is required at presentation.

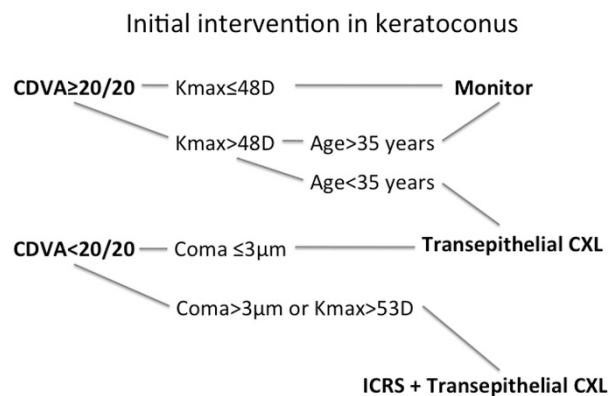


Figure 2 A decision tree for intervention at presentation in keratoconus. We are currently exploring the role for transepithelial collagen CXL at presentation for younger patients with keratometric stage II disease; and ICRS in combination with transepithelial CXL to provide a gross shape correction in patients with reduced spectacle CDVA at presentation and higher levels of coma or keratometric stage III disease.

As transepithelial CXL protocols continue to develop, further clinical trials documenting safety and efficacy are required to develop the evidence base for early intervention strategies.

Visual rehabilitation

In the future, early intervention with CXL should greatly reduce the numbers of patients dependent on rigid contact lenses and corneal transplantation for visual rehabilitation in keratoconus. For the present, many patients are already past the point at which they still have good spectacle corrected or unaided acuity. Current strategies for contact lens fitting in keratoconus are comprehensively described by Barnett and Mannis,⁴⁰ and summarised briefly below. While transplantation remains the principal treatment for contact lens intolerant patients with stage IV keratoconus, newer interventions can be combined for earlier stage disease with the aim of restoring good spectacle corrected or unaided vision.

Contact lens fitting

Soft lenses and soft toric lenses can provide good visual rehabilitation in early keratoconus; but RGP lenses are generally required to neutralise significant corneal surface irregularity. RGP lenses provide good tear exchange, but lens stability deteriorates as the corneal profile steepens in more advanced keratoconus. Traditional corneal RGP lenses are between 8 and 10 mm in diameter. Newer intralimbal RGP lenses (10.5–12 mm diameter) can improve corneal coverage and centration in some patients,⁴¹ but the increased diameter may make application and removal more difficult. ‘Piggyback’

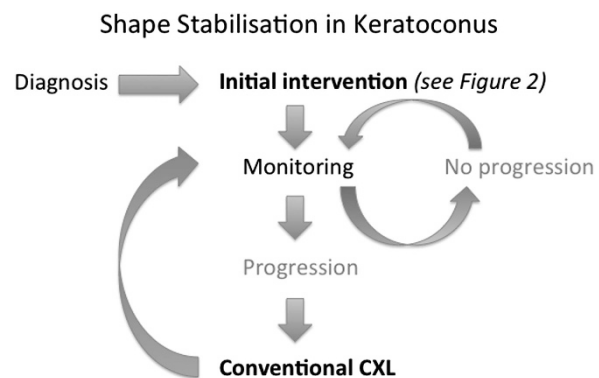


Figure 3 A pathway for shape stabilisation after initial intervention in keratoconus. Emerging transepithelial corneal CXL protocols avoid most of the complications associated with epithelium-off CXL but may be less effective.^{33,34} CXL can be repeated if there is continued disease progression.

(soft beneath RGP) lens combinations and hybrid (RGP centre and a soft skirt) lenses can improve wearing time in patients with poor RGP lens tolerance. Where these options fail, RGP scleral (and semi-scleral) lenses, which vault clear of the corneal surface, are a solution applicable to almost any corneal shape.⁴² Scleral lenses can rescue vision in patients with late stage disease—particularly where technical obstacles such as a thin peripheral cornea limit options for corneal transplantation.

Despite advances in contact lens fitting for keratoconus, contact lens dependence may be associated with significant impairment of vision-related quality of life that continues to decline over time.¹³

Gross corneal shape adjustment—intracorneal ring segments

Intrastromal corneal ring segments (ICRS) are effective in flattening the corneal shape and improving vision for most recipients with keratoconus, but the magnitude of effect is highly variable; and inclusion of different implantation techniques, different types of ICRS, and patients with late stage disease in earlier studies^{43–46} makes the existing evidence base for ICRS harder to interpret.

Many surgeons now use smaller diameter ICRS designs (Table 3) and femtosecond laser assisted implantation. Earlier case series reporting manual implantation of the original Intacs ICRS (designed for simple myopic rather than keratoconus correction) are therefore not considered here. Femtosecond laser channel cutting has, by ensuring a consistent cut depth, both facilitated and enhanced safety in ICRS implantation.⁴⁷ Flattening of central curvature with ICRS implantation increases with smaller ring diameter and greater segment thickness. The penalty for using a smaller diameter ring

is a greater potential for dysphotopsia. The triangular profile used in Ferrara and Keraring ICRS is designed to reduce forward light scatter by total internal reflection of incident light, but further clinical studies are required to quantify dysphotopsia-associated with ICRS implantation.

In a series with 12-month postoperative results of 50 consecutive femtosecond laser Keraring ICRS cases reported by Coskunseven *et al*,⁴⁸ approximately two-thirds of patients gained spectacle CDVA compared with pre-implantation levels (1–4 Snellen lines). Only two patients lost two lines of spectacle CDVA, and neither wanted the implants removed because of gains in UDVA. Overall improvement in mean keratometry was ~3D (50.6 ± 4D pre-ICRS; 47.6 ± 4.5D post-ICRS) with larger gains for cases with a steeper initial shape (stage III, 3 mm zone steep *K* > 53D) in which thicker ICRS was implanted. Asymmetric ICRS implantation (asymmetric arc length and thickness in superior and inferior ICRS) or single ring implantation can be used in patients with reduced spectacle CDVA associated with high pre-operative coma (cone decentration). Results in a smaller series of 21 cases of femtosecond laser Keraring ICRS implantation reported by Shabayek and Alio⁴⁹ were similar, with significant gains in overall higher order aberration levels for patients with high starting levels of coma (>3 microns). A retrospective series⁵⁰ of 173 femtosecond laser cut eyes comparing Intacs SK and Keraring SI6 (both with a 6 mm diameter optical zone) observed comparable improvements in vision and keratometry, with no statistically significant differences between the two ICRS models.

Femtosecond ICRS implantation has a good safety profile. A recent multicenter retrospective review⁴⁷ of 850 eyes with femtosecond Keraring ICRS implantation using an Intralase femtosecond laser for ring channel creation reported a 5.7% overall complication rate.

Table 3 Characteristics of available intracorneal ring segments (ICRS)

Name	Manufacturer	Internal diameter/mm	External diameter/mm	Arc length/degree	Profile	Thickness/mm
Intacs	Addition Technology Inc. Sunnyvale, CA, USA	6.8	8.1	150	Hexagonal	0.25–0.45 (0.05 increments)
Intacs SK	Addition Technology Inc. Sunnyvale, CA, USA	6.0	7.3	150	Oval	0.4 and 0.45
Ferrara	Mediphacos Ltd, Belo Horizonte, Brazil	4.4	5.6	160	Triangular	0.2–0.35
Kerrarings SI5	Mediphacos Ltd, Belo Horizonte, Brazil	5.0	—	90, 120, 160, and 210	Triangular	0.15–0.35
Kerrarings SI6	Mediphacos Ltd, Belo Horizonte, Brazil	5.5, 6.0	—	90, 120, 150, and 210	Triangular	0.15–0.35
MyoRing	Diopex GmbH, Linz, Austria	5–8	—	360	Triangular ^a	0.2–0.4 (0.02 increments)

^aConvex anteriorly and concave posteriorly.

Intraoperative complications did not result in failure to complete ICRS implantation. Incomplete ring channel formation was the commonest complication (2.7%). In these cases, ring channels can be completed manually allowing ICRS implantation to proceed. Endothelial perforation was evident in 0.6% cases. In this circumstance, channel creation 90 μm superficial to the initial attempted depth can be completed 1 month after surgery. The target depth for femtosecond Keraring implantation is 80% of corneal thickness at the location of the ring channel (5 mm diameter). Ultrasound pachymetry was used in this study. Availability of more accurate regional pachymetry methods, OCT in particular, may eliminate the risk of perforation. Postoperative complications occurred in 1.6% of cases. Within-channel migration of ring segments was noted in seven eyes and treated successfully with repositioning and a sutured vertical incision closure. Four cases of stromal thinning over the ICRS and two cases of corneal melting required implant removal. As with endothelial perforation, melting was attributed to inaccurate regional pachymetry and superficial channel creation in relatively thin corneas. Infection (an infiltrate at the entry site) was seen in one case in this series and treated without ICRS explantation. Problems for this study are lack of acuity, refractive, and keratometric outcome data. The authors also do not state the follow-up period studied or whether these were consecutive cases. Nonetheless, data from this and smaller prospective series^{47,49} indicate that sight-threatening complications are rare.

Very little long-term data are available for ICRS, and any effect of ICRS implantation on disease progression remains uncertain. In a case series of Intacs ICRS with 3-year follow-up in 13 eyes, significant increases in average K values were observed between 6 months and 3 years, indicating that disease stabilisation was not achieved by ICRS alone.⁵¹

Combined ICRS and CXL

ICRS implantation can be combined with CXL,^{52–56} but the treatment sequence is important: ICRS appears more effective in improving corneal shape before the cornea is stiffened with CXL. Coskunseven *et al*,⁵² in an RCT comparing CXL first and ICRS later (group 1) with ICRS first and later CXL (group 2), showed significantly greater improvements (mean 7 months follow-up) in spectacle CDVA (three line gain (group 1); two line gain (group 2), $P < 0.01$) and manifest astigmatism (2.48D mean absolute cylinder reduction (group 1); 1.76D reduction (group 2), $P < 0.05$) where ICRS was performed first. Simultaneous CXL and ICRS may be equally effective. El-Raggal showed a trend towards greater improvement at 12 months in mean K values where

simultaneous ICRS and CXL was performed *vs* CXL 6 months after ICRS ($50.2 \pm 3.8\text{D}$ to $44.9 \pm 2.9\text{D}$ simultaneous treatment; $50.4 \pm 3.8\text{D}$ to $47.3 \pm 3.5\text{D}$ delayed CXL, $P = 0.046$), although there were no differences in UDVA, CDVA, or refractive error.⁵⁴ But this study was underpowered ($n = 8$ each arm). More evidence is required to determine the optimum interval between ICRS and CXL in combined treatment; but the practical advantages to combining ICRS with transepithelial treatment in particular are clear. An interesting variation here has been described by Saelens *et al*⁵³ who augmented stromal riboflavin penetration by injection into the ring channels before transepithelial CXL.

ICRS implantation protocols

With increasing availability of femtosecond laser technology, OCT regional pachymetry, and intraoperative guidance systems to help reduce axial misplacement during implantation, ICRS implantation should become safer and more predictable. Several important gaps in the evidence base for this intervention exist, but there are already strong arguments for ICRS implantation for gross corneal shape correction in keratoconus patients with reduced CDVA—particularly if they are contact lens intolerant. Disease progression after standard, epithelium-off CXL is more likely for patients with later stage III disease (3 mm zone steep $K > 53\text{D}$),²² and most patients with stage III keratometric changes already have reduced CDVA. Because contemporary ICRS implantation has a good safety profile and results are better if implantation is performed simultaneously with or before CXL, the balance of existing evidence suggests a role for ICRS implantation in combination with transepithelial CXL at presentation for patients with keratometric stage III keratoconus, or for earlier stage disease if vision is reduced (spectacle CDVA $\leq 20/25$) in association with high levels of coma ($> 3 \mu\text{m}$) (Figure 2).

Inclusion criteria in Coskunseven's recent prospective series of femtosecond Keraring ICRS implantation include a minimum central corneal thickness of 350 and 450 μm at the incision site.⁴⁸ No upper limit for keratometry values was specified. Neovascularisation has not been reported after femtosecond Keraring ICRS implantation and 5 mm diameter ICRS are within the block of tissue normally removed in any subsequent transplantation procedure. Where corneal thickness is adequate and there is no central scar, it is probably reasonable to consider ICRS implantation with CXL in patients with advanced stage III disease since there should be no increased risk of failure in any subsequent corneal transplant. But a stratified analysis of patients with contact lens fitting problems associated with steep

keratometry is required to determine whether ICRS is a viable alternative to corneal transplantation for this group or whether there is an upper limit to the Kmax for ICRS. For the present, limits for ICRS implantation are probably best defined by Coskunseven's pachymetric inclusion criteria above.⁴⁸

Thermal keratoplasty

Microwave thermal keratoplasty is being explored as a possible alternative to ICRS and transplantation for gross corneal shape correction in advanced keratoconus. Although large initial shape improvements can be obtained, almost complete regression is seen within a year. Kato *et al*⁵⁷ treated 21 advanced keratoconic eyes with topography guided conductive keratoplasty (with intraoperative keratometric monitoring): mean keratometry values were 55 ± 8D at baseline, 45 ± 9D at 1 week, 50 ± 7D at 1 month, and 54 ± 7D at 3 months. Studies are in progress to determine the extent to which shape regression after thermokeratoplasty can be modulated by combination with CXL.

Fine corneal shape adjustment—PRK

Combination with CXL may allow safe application of surface excimer laser ablation techniques to fine tune corneal shape in keratoconus. To date, topography-guided PRK has been studied in combined therapy.^{58–60} But wavefront ablation would be a viable alternative in cases with good aberrometry data.

For simultaneous combined treatment, in which CXL is applied immediately after PRK, the aim is to improve CDVA by reducing irregular astigmatism rather than to correct spherocylindrical error fully. Reasons for this are the requirement for a 400-µm residual stromal bed *after ablation* to allow safe CXL, and the danger of hypermetropic overcorrection if spherical equivalent reductions induced by CXL are not anticipated. Simultaneous combined treatment has clear advantages for patient comfort (the epithelium is only removed once), but takes no account of improvements in corneal regularity and spectacle CDVA that might normally be produced by CXL alone.

In a large comparative case series with minimum 2-year postoperative follow-up, Kanellopoulos⁶⁰ compared outcomes of 198 eyes treated with topography-guided PRK followed immediately by CXL (simultaneous combined treatment) with an earlier series of 127 eyes treated with topography-guided PRK a minimum of 6 months after CXL (sequential combined treatment). Simultaneous combined treatment produced greater improvement across a range of measures: LogMAR CDVA improved from 0.39 ± 0.3D to

0.11 ± 0.2D, with a reduction in spherical equivalent of -3.2 ± 1.4D and mean keratometry of -3.5 ± 1.3D. This compares with the sequential group's CDVA improvement from 0.41 ± 0.3D to 0.16 ± 0.2D, spherical equivalent reduction of -2.5 ± 1.2D and mean keratometry reduction of -2.75 ± 1.3D. Haze scores were also significantly better for simultaneous combined treatment. In all, 20 s intraoperative applications of mitomycin C were used throughout, and the maximum ablation depth was limited to 50 µm. The essential problem for this comparison is that the time interval between CXL and PRK for sequential treatment was not specified, and may have been considerably shorter than the 2-year period in which refractive results typically continue to improve after CXL alone.¹⁹ Further study is required to quantify any gain in spectacle CDVA over CXL alone for simultaneous combined CXL and PRK, and to determine whether increased haze scores for sequential combined treatment observed by Kanellopoulos are still evident where PRK is performed later in the post-CXL wound healing cycle, a minimum of 2 years after treatment.

The current evidence base does not allow a clear recommendation with regard to the place for simultaneous combined CXL and PRK. But topography-guided or wavefront-driven PRK is a reasonable option to choose once refraction is stable after CXL if spectacle CDVA remains poor (Figure 4).

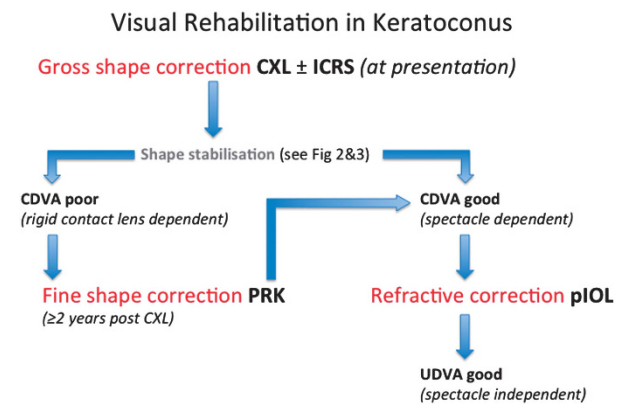


Figure 4 A pathway for visual rehabilitation in stage II and III keratoconus. Initial intervention in keratoconus (Figure 2) may include collagen CXL ± intracorneal ring segment implantation (ICRS). Neither intervention provides a predictable shape change. After a 2-year period to allow shape stabilisation post-CXL,^{19,76} further fine shape correction with topographic PRK^{58–60} may therefore be required to achieve good spectacle CDVA. If CDVA is good but uncorrected distance vision remains poor (UDVA) remains poor, then patients may opt for pIOL implantation^{61–66} to complete visual rehabilitation.

Refractive correction—pIOL implantation

For patients with a stable corneal shape and good CDVA, pIOL implantation can be used to complete functional visual rehabilitation. A number of recent papers have reported effective refractive correction using pIOLs in keratoconus (post-operative spherical equivalent range -0.08 ± 0.4 to $+0.1 \pm 0.4$; 64–67% within 0.5D and 84–100% within 1D of target refraction)^{61–66} and for post-keratoplasty ametropia.⁶⁷ Of the pIOLs available,⁶⁸ the Visian ICL (Staar Surgical, Monrovia, CA, USA) offers the longest safety track record for an injectable pIOL and is available in a wide range of powers (including toric correction up to 6D). Pesando *et al*⁶⁹ reported retrospective 10-year follow-up data in 59 ICL-implanted hypermetropic eyes, showing a mean endothelial cell loss of 4.7%, mostly occurring within the first few weeks of implantation and remaining almost unchanged thereafter. Edelhauser *et al*⁷⁰ reported prospective, multicenter, 4-year follow-up data on 526 eyes with a 2–3% cell loss rate over the first 3 years, followed by a cell increase of 0.1% between years 3 and 4, suggesting that endothelial remodelling and stability may have been achieved.

Combined ICRS and pIOL implantation has been described,^{71–74} but refractive correction with pIOLs is highly predictable,⁷⁵ whereas the refractive effect of ICRS implantation is highly variable.^{43–46,52–56} We would therefore argue for gross shape correction with ICRS implantation followed by CXL, fine shape correction with PRK if necessary, then finally pIOL implantation as a logical pathway to visual rehabilitation in grade II–III keratoconus (Figure 4).

Summary

Thick case note files documenting the progression of keratoconus towards corneal transplantation may soon be a historical anecdote among ophthalmologists. While recent advances in contact lens technology have benefited many patients, the last few years have also seen new and exciting developments in both stabilizing and reversing ectasia, with interventions for visual rehabilitation originally developed in refractive surgery finding new applications in keratoconus. The clinical pathways we outline here attempt to clarify the positioning of new interventions in the treatment of keratoconus with reference to an incomplete evidence base. Clinical pathways for keratoconus will continue to evolve with further innovation and the guidance of future research.

Conflict of interest

The authors declare no conflict of interest.

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