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# Keratoconus Treatment Toolbox: An Update

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## Abstract

Keratoconus is a bilateral, asymmetric, progressive disease of the cornea which can lead to visual impairment and blindness as irregular astigmatism increases and corneal scar occurs. Currently, many methods are available for a treatment of keratoconus. The treatment can help enhance visual rehabilitation and prevent progression in keratoconus patients. The treatment options included non-surgical and surgical managements. This review offers a summary of the current and emerging treatment options for keratoconus- eyeglasses, contact lens, corneal collagen cross-linking (CXL), CXL Plus, intrastromal corneal ring segment (ICRS), Corneal Allogenic Intrastromal Ring Segments (CAIRS), Penetrating Keratoplasty (PK), Deep Anterior Lamellar Keratoplasty (DALK), Bowman layer transplantation (BL transplantation) and gene therapy.

**Keywords:** corneal collagen cross-linking, CXL, CXL Plus, intrastromal corneal ring segment, ICRS, PK, DALK, Bowman layer transplantation

## 1. Introduction

Keratoconus is a bilateral, asymmetric, progressive ectatic disease of the cornea characterized by progressive corneal thinning which can lead to visual impairment and blindness as corneal protrusion progresses, irregular astigmatism increases and corneal scar occurs [1]. Keratoconus is often under the radar because of decreased awareness, underdiagnosis and undertreatment. The exact pathological mechanism remains unknown, but both genetic and environmental factors may contribute to development and progression of this disease [2]. The reported evidences of pathogenesis of keratoconus include histochemistry, biomechanics, enzymology, proteomics, and molecular genetics [2]. The disease process starts with fragmentation of the epithelial basement membrane, fibrillation of Bowman's membrane and anterior stroma [3]. Bowman's membrane breakage occurs later together with epithelial abnormality resulting in proteolytic enzymes release that weakens corneal stromal collagen and stromal thinning [3]. The reported prevalence of keratoconus varies between countries and ethnicities, in which Asian is higher than Caucasian about 4.4 to 7.5 times [4, 5]. The prevalence is ranged from 0.3 in 100, 000 to 2300 in 100,000 in Russia and India respectively [6]. However, the prevalence may be higher in tertiary eye care center or refractive

surgery center [7]. Keratoconus is more common in men than women, although both gender are affected [5]. The onset of symptoms usually presents during adolescent and may progress until the 30s. Keratoconus is associated with eye rubbing such as in allergic conjunctivitis, floppy eyelid syndrome, obstructive sleep apnea, Down's syndrome and Leber congenital amaurosis [1, 8–10]. Genetic predisposition accounts for an increased risk of keratoconus in patient that has a positive family history about 15 to 67 times [11].

## **2. Terminology and staging**

Nowadays, there remain many controversies regarding disease definition, diagnosis, and management of keratoconus. Keratoconus is usually a bilateral disease in which the normal contralateral eye is believed to be in the preclinical stage of keratoconus with different terms such as subclinical keratoconus, keratoconus suspect, forme fruste keratoconus [12]. Despite the advancement of the investigations for the diagnosis of keratoconus and subclinical keratoconus, there are no definitive criteria for discriminating subclinical keratoconus from normal cornea currently [13]. The detection of keratoconus and subclinical keratoconus is crucial to prevent ectasia after refractive surgery. Moreover, some treatment modalities such as corneal collagen crosslinking can prevent vision loss in keratoconus if implement in the early stage of the disease [14]. The early stage symptoms may manifest as reduced vision, fluctuation of vision, progressive myopia and astigmatism, increasing higher order aberrations [4, 15]. When the disease progresses into an advance stage, there is a severe visual loss from high myopia, irregular astigmatism and corneal scarring.

The following criteria are mandatory to diagnose keratoconus- abnormal posterior elevation, abnormal corneal thickness distribution and clinical non-inflammatory corneal thinning [10]. However, there is no clinically adequate classification system for keratoconus currently. One of the most popular grading systems is Amsler-Krumeich classification system which classified severity of diseases based on the amount of myopia and astigmatism, corneal thickness or scarring and central keratometry readings [16, 17]. However, Amsler-Krumeich classification system is considered as outdated because it relies on “old” indices (corneal steepness, refractive change, the presence of scarring), and fails to address disease impact [18]. Nowadays, other alternate classification systems are growing in number such as Shabayek-Alio system which is based on corneal higher aberrations and the keratoconus severity score (KSS) which considers average corneal power and root mean square (RMS) [19, 20]. The “ABCD grading system” that incorporates anterior and posterior corneal curvature, thinnest pachymetric values based on the thinnest point and distant visual acuity may better reflects the anatomical change than some previous classification that uses pachymetric value based on apical measurement [21]. In routine clinical practice, the term “advanced keratoconus” usually apply to any case with unacceptably poor spectacle distance vision and contact lens intolerance [18].

## **3. Diagnosis**

The keratoconus diagnosis is bases on the history and clinical examination. However, the investigations are very useful to augment the clinical examination and detect the early stage of disease. Moreover, the accurate diagnosis and early

detection of keratoconus is essential in this era which laser refractive surgery has increased markedly. Failure to detect keratoconus and subclinical keratoconus can lead to ectasia after refractive surgery [22]. Corneal topography is the primary diagnostic tool for keratoconus detection. However, corneal topography is not a faultless method and therefore other diagnostic tools such as corneal pachymetry to characterize the corneal thinning and aberrometry to characterize degradation of the corneal optics should be used as complimentary techniques [22]. Corneal tomography which based on rotating Scheimpflug camera, such as Pentacam, Galilei, or Sirius systems, provide the topographic, pachymetric, and aberrometric information simultaneously as their use is adequate enough for the keratoconus detection [12, 22]. Currently, OCT technology is being used to differentiate between eye with keratoconus and normal eye because it can provide accurate pachymetric characterization, define epithelial thickness irregularity and asymmetry that present in keratoconus [7, 23]. By analyzing the biomechanical properties of the cornea that may precede the anatomical change, the Ocular Response Analyzer and Corvis systems can provide good diagnostic accuracy [22]. Analysis of the Corneal Microstructure change in keratoconic eye from confocal microscopy such as reducing corneal nerve fiber density and nerve fiber length, reducing keratocyte density, increasing corneal stromal nerve thickness, may be useful in detecting structural changes occurring before manifestation of topographic signs [22, 24]. A combination of multiple imaging modalities, including corneal topography, corneal tomography, Scheimpflug imaging, anterior segment optical coherence tomography, and in vivo confocal microscopy will enhance early keratoconus detection. Modalities during investigations but show promise include polarization-sensitive optical coherence tomography, Brillouin microscopy, and atomic force microscopy [25].

#### 4. Disease progression

Keratoconus progression detection is a critical issue because the treatment nomograms have been proposed based on the grading system and ectasia progression [15, 22]. Moreover, the disease progression is differed considerably among individual. The younger the patients are, the higher their risk for rapid progression [26]. Currently, there is no global consensus of ectasia progression. The Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases had defined the definition of “ectasia progression” as a consistent change overtime in at least 2 of the following parameters where the magnitude of the change is above the normal noise of the testing system:

1. Steepening of the anterior corneal surface.
2. Steepening of the posterior corneal surface.
3. Thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point” [10].

Various clinical studies have used different parameters to define disease progression. The most important parameters include: [27, 28]

1. An increase in maximum corneal refractive power ( $K_{\max}$ ) by more than 1 diopter (D) within 1 year

- 2. An increase in (corneal) myopia by more than 3 D or astigmatism by more than 1.5 D within 12 months
- 3. An increase in mean corneal refractive power by more than 1.5 D within 12 months
- 4. A reduction in minimal corneal thickness of more than 5% within 12 months.

The regular topographic/tomographic check-ups can identify keratoconus progression. Regarding the examination intervals, the individual risk profiles need to be taken into consideration. The risk factors that should be considered include eye rubbing, ocular allergies, young age, steep corneal curvature gradient, high astigmatism, marked visual loss, documented progression in the fellow eye, atopic dermatitis or Down’s syndrome [28]. In children, keratoconus tends to be more severe and progress faster requiring closer follow-up intervals [26]. The patient with low risks can be monitored less frequently than the one with high risks. Keratoconus progression is often associated with a decrease in best spectacle-corrected visual acuity (BSCVA), however, a change in both uncorrected visual acuity and BSCVA is not required to document progression [10].

5. Treatment

The important goals of keratoconus management are stopping disease progression and visual rehabilitation [10]. In cases of ocular allergies, patients should be treated with topical antiallergy and lubricants and should be instructed to avoid eye rubbing to halt disease progression. Corneal collagen crosslinking is a promising procedure to stop disease progression with minimal side effects [29]. For the visual rehabilitation, several treatment options corresponding to keratoconus grading have been established. Keratoconus can be treated by both nonsurgical and surgical approaches depend on severity and progression of the disease [15]. The keratoconus treatment toolbox is listed as in **Table 1**.

Nonsurgical treatments	Surgical treatments
<ul style="list-style-type: none"><li>• Glasses</li><li>• Contact lens (CL)<ul style="list-style-type: none"><li>Soft CL; toric, non-toric</li><li>Rigid CL; RGP</li><li>Hybrid lenses,</li><li>Piggyback lens (PBCL)</li><li>Miniscleral</li><li>Semiscleral</li><li>Scleral lenses</li></ul></li></ul>	<ul style="list-style-type: none"><li>• Corneal collagen cross-linking (CXL)<ul style="list-style-type: none"><li>Standard CXL</li><li>Epi-on CXL</li><li>Accelerated CXL</li><li>CXL Plus</li><li>CXL + TG-PRK</li><li>CXL + ICRS</li><li>CXL + TG- PRK + phakic IOLS</li><li>CXL + ICRS + phakic IOLS</li><li>CXL in thin cornea</li></ul></li><li>• Intrastromal corneal ring segments (ICRS)</li><li>• Corneal transplantation<ul style="list-style-type: none"><li>Penetrating keratoplasty (PK)</li><li>Deep Anterior Lamellar Keratoplasty (DALK)</li><li>Bowman layer transplantation</li></ul></li></ul>

RGP = Rigid gas permeable contact lens, IOL = intraocular lenses, PBCL = Piggyback lens, TG-PRK = Topo guided-Photo Refractive Keratectomy.

**Table 1.**  
The keratoconus treatment toolbox.



## 5.1 Nonsurgical treatment

A nonsurgical treatment of keratoconus is spectacles and contact lens. For early stage of disease, those who achieve visual acuity 20/40 or better, spectacles can provide acceptable vision [15]. A toric soft contact lens also provides satisfactory vision for correcting myopia and regular astigmatism in early keratoconus. However, as the diseases progress, spectacles or soft contact lens may not provide acceptable vision because of the higher- order aberrations, in particular vertical coma was increased [30]. Therefore, other special lens such as rigid gas permeable (RGP) contact lens, hybrid lenses, piggy back, miniscleral lens, semiscleral lens or scleral lenses are needed to provide satisfactory vision [31]. The ultimate goal of fitting contact lens in keratoconus is to improve visual acuity without compromise ocular health. However, contact lens use does not slow or stop progression of the disease. In keratoconus, the cone is steeper but the cornea beyond the cone is flatter. In mild keratoconus, traditional RGP lens can provide an ideal fit. However, as the disease progress into advanced stages, it becomes difficult to achieve an ideal fit but compromised fit which is not damage to the ocular surface is acceptable. High oxygen transmissibility lens should be selected to prevent hypoxic-related corneal changes [31].

The type of contact lens selection is based on manifest refraction, degree of keratoconus, and morphology of the cone [31]. Corneal topography can aid in addressing the severity and morphology of the cone. Buxton et al. have classified keratoconus based on keratometry values (K) at the apex of the cone: mild if K is less than 45 D, moderate if K is between 45 and 52 D, advanced if K is more than 52 D and severe if K is more than 62 D [32]. The morphology of the cone is classified as the following [33].

- nipple cone: small, paracentral, steeper located inferiorly or inferonasally
- oval cone: inferiorly or inferotemporally steeper cornea
- globus cone: overall steeper cornea, involves more than three forth of the cornea up to limbus

The three essential parameters in contact lens fitting are power, diameter, and base curve of contact lens.

- Power: Low minus for mild keratoconus, high minus for severe keratoconus
- Base curve: Flatter base curve for mild keratoconus, steeper base curve for severe keratoconus
- Diameter: Based on the cone location, its size and steepness, nipple has a small diameter, usually start with a small diameter such as 8.7 mm, oval cone needs larger diameter lens, globus cone or severe apical displacement need large diameter contact lens.

A contact lens type is selected based on the manifest refraction and the degree of keratoconus. The contact lens of choice for keratoconus patients is RGP lens. However, if the patients develop intolerance or discomfort, customized soft toric contact lens, PBCL, hybrid lens or scleral lens can be considered. The indications, advantages and disadvantages of each contact lens type are summarized as in **Table 2** [30, 31, 34]. Fitting contact lens in keratoconus can improve vision and

Contact lens types	Indication	Advantages	Disadvantages
Soft/ Soft toric	<ul style="list-style-type: none"><li>• For mild KC</li><li>• High myopia associated with KC</li><li>• Intolerance/ discomfort with RGP</li><li>• Prior to PBCL</li></ul>	<ul style="list-style-type: none"><li>• Comfort</li></ul>	<ul style="list-style-type: none"><li>• Cannot correct irregular astigmatism</li></ul>
RGP	<ul style="list-style-type: none"><li>• First lens of choice for KC patient</li></ul>	<ul style="list-style-type: none"><li>• First lens of choice for visual improvement</li><li>• Can correct irregular astigmatism</li></ul>	<ul style="list-style-type: none"><li>• Less comfortable than other CLs</li><li>• Need lens adaptation</li><li>• Inappropriate fitting can compromise ocular health</li><li>• May associated with increase keratoconus progression [35]</li></ul>
Hybrid lens	<ul style="list-style-type: none"><li>• RGP intolerance</li><li>• Inability to obtain optimal RGP fitting</li><li>• Poor RGP centering</li><li>• Reduced wearing time with RGP</li></ul>	Comfort	<ul style="list-style-type: none"><li>• Risk of hypoxia, corneal edema, neovascularization</li></ul>
Piggyback lens (PBCL)	<ul style="list-style-type: none"><li>• Discomfort or RGP intolerance</li><li>• Irregular cornea where RGP lens fitting are not possible</li><li>• (unstable RGP on the eye, popping out of lens</li><li>• 3 and 9 o’ clock staining with RGP</li><li>• Corneal scarring</li></ul>	Comfort	<ul style="list-style-type: none"><li>• Lost RGP</li><li>• GPC</li><li>• Risk of hypoxia, corneal edema, neovascularization</li><li>• Punctate keratitis</li><li>• Difficult handling and maintaining</li></ul>
Scleral lens	<ul style="list-style-type: none"><li>• All options fail to improve vision</li><li>• Inability to get an optimum fit with RGP</li><li>• RGP intolerance</li><li>• 3 and 9 o’ clock staining with RGP</li><li>• Vascularization with PBCL</li><li>• Advanced keratoconus</li><li>• Corneal scarring</li><li>• Associated ocular diseases</li></ul>	<ul style="list-style-type: none"><li>• Comfort</li><li>• Stable VA</li><li>• Delays or obviates the need for keratoplasty</li></ul>	<ul style="list-style-type: none"><li>• Difficult in care regimen (require different removal and insertion technique)</li><li>• Contraindicate in corneal edema, acute hydrops, post filtration surgery</li></ul>

RGP = Rigid gas permeable, Hybrid lens = rigid lens in the center and a soft skirt in the periphery, PBCL = Piggy back lens (RGP lens sitting on top of a soft contact lens) KC = keratoconus, GPC = giant papillary conjunctivitis, VA = visual acuity.

**Table 2.**  
Contact lens in keratoconus (KC).

delay the need for keratoplasty. Moreover, contact lens in keratoconus patient also have a role in correcting residual refractive error after Corneal collagen cross-linking (CXL), after Intrastromal corneal ring segments (ICRS) or post-keratoplasty [31].

## 5.2 Surgical treatment

Even though the specialized imaging device can provide grading scheme of keratoconus, for practical purposes, the term “advanced keratoconus” may apply to any cases that have unacceptably poor spectacle distance vision and contact lens intolerance. As the diseases progress, spectacles or contact lens cannot provide acceptable vision. This group of patients requires a surgical management such as Corneal collagen cross-linking (CXL), Intrastromal corneal ring segments (ICRS), and Corneal transplantation to restore vision and/or stabilize progression of diseases.

The special considerations in surgical management of keratoconus are listed in Table 3.

### 5.2.1 Corneal collagen cross-linking (CXL)

Keratoconus typically progresses until the fourth decade, when most but not all, slows or stabilizes [36]. Corneal crosslinking (CXL) has been proposed as a new treatment modality to stop progression of keratoconus since the late 1990s [27]. Currently, CXL is the gold standard and only minimally invasive surgical procedure that halt the progression of keratoconus [27]. The indications for CXL are progressive keratoconus in adults and postoperative ectasia, central corneal thickness more than 400  $\mu\text{m}$ ,  $K_{\text{max}}$  58 D or less [36, 38]. However, the procedure is not approved for stable keratoconus currently. CXL is the promising treatment that can prevent progressive visual loss due to disease evolution and delay invasive surgical procedures such as corneal transplantation. The mechanism of cornea strengthening is a photochemical reaction of corneal collagen by the Riboflavin as a photosensitizer in the photopolymerization process and ultraviolet A irradiation (UVA). The interaction between Riboflavin and UVA can increase the formation of intrafibrillar and interfibrillar carbonyl-based collagen covalent bonds [37].

The standard Dresden protocol was proposed as a treatment option for keratoconus by Wollensak et al. in 2003 [38]. This standard technique is conducted under topical anesthesia. The central corneal epithelium is removed followed by application of 0.1% riboflavin solution (0.1% riboflavin in 20% dextran solution) as a photosensitizer every 5 minutes for 30 minutes. Then the cornea is exposed to 370 nm UVA with an irradiance of 3  $\text{mW}/\text{cm}^2$  or 5.4  $\text{J}/\text{cm}^2$ , during which time riboflavin solution is re-applied every 5 minutes. After the treatment, topical antibiotics eye drops are applied and bandage contact lens placed upon the eye [38]. Although this standard protocol has been proven to be an effective procedure to halt keratoconus progression [39], it is a time-consuming procedure, may create patient discomfort and has post-operative complications related to corneal abrasion. The reported complications in association with CXL include corneal haze, corneal infection, corneal edema, and corneal melting. Adverse effects are common but mostly transient and of low clinical significance [40]. However, anterior corneal stromal haze is a typical postoperative finding that often occurs in the first month after treatment and typically resolves after 12 to 20 weeks [41]. The posterior aspect of this haze is an indistinct hyperreflective demarcation line seen in the mid stroma that represents the depth of CXL [37]. Two trends have emerged to modify the standard Dresden protocol. The first is a tendency to shorten treatment times [42]. Alternative treatment protocols with different formulations of riboflavin solution



Considerations	Details
Corneal thickness (Corneal thinness)	<ul style="list-style-type: none"><li>• <b>CXL:</b> CCT &gt; 400 µm can use standard Dresden protocol CCT &lt; 400 µm</li><li>• Hypotonic riboflavin solution Epi-on CXL</li><li>• Pachymetry-guided epithelial debridement Decreasing the UVA irradiance dose</li><li>• Reducing the duration of riboflavin soaking Increasing the riboflavin concentration or a combination of the above</li><li>• <b>ICRS:</b> minimum corneal thickness at the site of their insertion and along the length of their path &gt;400 µm</li><li>• <b>Bowman layer transplantation:</b> do not affect</li><li>• <b>DALK:</b> Prefer Melles manual dissection than Anwar “big-bubble” technique</li><li>• <b>PK:</b> not suitable for significant peripheral thinning DALK or modified procedure “tuck-in lamellar keratoplasty” may be preferable</li></ul>
Kmax	<ul style="list-style-type: none"><li>• <b>CXL:</b> risk of failure, continue progression in <math>K_{max} &gt; 58</math> D, increase risk of losing vision in <math>K_{max} &gt; 55</math> D</li><li>• <b>ICRS:</b> associated with poorer visual outcomes and more complications in <math>K_{max} &gt; 58</math> D</li><li>• <b>Bowman layer transplantation:</b> do not affect</li><li>• <b>DALK:</b> central curvatures &gt;60 diopters (D) may experience worse outcomes</li><li>• <b>PK:</b> do not affect</li></ul>
Preoperative BCVA	<ul style="list-style-type: none"><li>• <b>CXL, ICRS, Bowman layer transplantation:</b> rarely do the visual gain exceed 1 or 2 lines</li><li>• <b>DALK or PK:</b> extremely poor vision</li></ul>
Endothelial health	<ul style="list-style-type: none"><li>• <b>CXL:</b> risks of endothelial damage if CCT &lt; 400 µm</li><li>• <b>ICRS, Bowman layer transplantation, DALK:</b> No or mild endothelial dystrophy</li><li>• <b>PK:</b> advanced KC and a failed endothelium</li></ul>
Lens status	<ul style="list-style-type: none"><li>• <b>CXL, ICRS, Bowman layer transplantation:</b> not promote cataractogenesis, preferable options for phakic eyes</li><li>• <b>DALK:</b> No/less cataractogenesis than PK</li><li>• <b>PK:</b> cataractogenesis, may be the least desirable option for phakic eyes</li></ul>
Patient age (Pediatric)	<ul style="list-style-type: none"><li>• <b>CXL:</b> modest corneal flattening effect, mild visual benefit without any additional complications, smaller gain and less durable than adults</li><li>• <b>ICRS:</b> approved for age &gt; 18 years (worldwide), 21 years in US, no difference between visual outcome or corneal topography between different age groups</li><li>• <b>Bowman layer transplantation:</b> extraocular procedure, one of the safest options</li><li>• <b>DALK:</b> similar outcomes with adults</li><li>• <b>PK:</b> outcomes are slightly worse, principally attributable to higher rates of graft rejection, failure</li></ul>

Considerations	Details
Ability to cooperate (Mental disability)	<ul style="list-style-type: none"><li>• <b>CXL</b>: risk of postoperative complications, only patients capable of reliable cooperation, with good family support</li><li>• <b>ICRS</b>: less risky and fewer postoperative requirements than CXL, DALK, PK but aware of ICRS stem from migration/ superficialization from eye rubbing</li><li>• <b>Bowman layer transplantation</b>: less risky and fewer postoperative requirements than CXL, DALK, PK</li><li>• <b>DALK</b>: may be preferred over PK</li><li>• <b>PK</b>: worse outcomes from higher incidence of postoperative complications</li></ul>
Pre-existing corneal scarring (previous hydrops)	<ul style="list-style-type: none"><li>• <b>CXL</b>: may be less successful, cannot replace corneal scar then central corneal scar is a relative contraindication</li><li>• <b>ICRS, Bowman layer transplantation</b>: central corneal scar is a contraindication, may arrest disease progression and permit continued CL wear in non- visually disabling scarring</li><li>• <b>DALK</b>: may be preferred over PK, prefer Melles manual dissection, Anwar “big-bubble” technique is contraindicated</li><li>• <b>PK</b>: outcomes tend to be worse (not be considered mandatory to replace endothelium)</li></ul>

*CCT = central corneal thicknesses, Epi-on CXL = Epithelium-On Corneal collagen cross-linking, ICRS = Intrastromal corneal ring segments, DALK = Deep Anterior Lamellar Keratoplasty, PK = Penetrating keratoplasty, D = diopter, KC = keratoconus, K<sub>max</sub> = Maximal corneal steepness, BCVA = best corrected visual acuity. Adapted from Surv Ophthalmol. 2015 Sep;60(5):459–80. [18] J Cataract Refract Surg. 2015 Apr;41(4):842–72 [37]. \*currently little to recommend UV-CXL in corneas thinner than 400 μm [18].*

**Table 3.**  
*Special considerations in surgical management of keratoconus.*

and delivery methods by altered UV exposures have been proposed. These newer techniques can shorten duration times, reduce patient discomfort, and minimize postoperative complications. The second trend is “epi-on” approach, such that the epithelium remains intact during CXL. These modifications were described in the following sections.

5.2.1.1 Accelerated CXL (ACXL)

According to Bunsen- Roscoe law of photochemical reciprocity, which states that “the same photochemical effect can be achieved with a reduced irradiation interval provided the total energy level is kept constant through a corresponding increase in irradiation intensity” [37]. ACXL is a modified CXL technique that increase the intensity of ultraviolet A (UV-A) irradiation and shortening the exposure time without altering the total energy delivered. Currently commercial devices now offer ultrafast settings such as 43 mW/cm<sup>2</sup> for 2 minutes [42]. Using this setting, would achieve the standard Dresden protocol energy dose of 3.4 J or a radiant exposure of 5.4 J/cm<sup>2</sup> within 2 minutes [42]. However, it ignores the requirement of oxygen in the CXL reaction, the time needed for oxygen replenishment, and potential physical damage due to higher irradiance [36]. The reduced efficacy of ACXL is believed to be due to depletion of oxygen in these high-fluence treatments [43]. The efficacy, safety, and treatment protocols of accelerated CXL are still being investigated and in evolution.

#### *5.2.1.2 Epi-on CXL/transepithelial CXL*

Due to the epithelial debridement is a major contributor to the postoperative complications of CXL, such as infective keratitis and an abnormal wound-healing response [37]. This issue has perpetuated interest in epithelium-on technique. Epi-on CXL has less discomfort to the patient and reduces postoperative complications [43]. This CXL technique has low complication rate, 0% to 3.9% of the patients has only transient haze [37]. According to the hydrophilic property of riboflavin solution, the penetration through the intact hydrophobic corneal epithelium is difficult. The standard formulations show minimal penetration through intact epithelium. The modifications by adding various additives, such as benzalkonium chloride, topical anesthetic, tris(hydroxymethyl) aminomethane (trometamol), sodium ethylenediaminetetraacetic acid, have been proposed to improve epithelial permeability to riboflavin [36]. Riboflavin penetration can be improved by increased riboflavin concentration and iontophoresis [36]. Since even the low amount of riboflavin surface films will markedly block UV-A transmission, transepithelial formulations are often rinsed from epithelial surface before irradiation [36]. The iontophoretic delivery system uses of mild electrical current for delivering riboflavin through the epithelium [36]. It allows greater and deeper riboflavin penetration in the corneal stroma than the conventional epithelium-on technique. Overall, the effectiveness of transepithelial techniques has been disappointing [27]. Epi-on CXL has limited keratocyte apoptosis, shallower demarcation line and less biomechanical rigidity than standard epi-off CXL [37]. In general, better outcomes can be achieved by standard epithelium off technique and epi-on CXL have resulted in progression of the disease after treatment [36, 44]. However, recent research with innovative transepithelial CXL system achieved 4-fold higher corneal stromal concentrations of riboflavin than commercially available epi-on CXL system, and this level is theoretically adequate for effective CXL [44].

#### *5.2.1.3 Pulsed-light accelerated CXL (PLA-CXL)*

Due to the presence of oxygen is required for CXL, but high-exposure doses of UVA light cause a decrease in the oxygen concentration rapidly [45]. The recent technique has focused on pulsing the UVA light with “on” and “off” periods to increase the efficacy of CXL treatment by replenishing the consumed oxygen [46]. This technique is an effective treatment modality to stop progression in progressive keratoconus but regresses some of the cases [46].

#### *5.2.1.4 CXL plus*

Despite the fact that CXL can halt the progression of keratoconus and provide corneal stability, functional visual acuity remains a problem [47]. Recent data from the systematic review disclosed that conventional epi-off CXL can flattening cornea 2 D approximately and improving visual acuity 2 lines or 10 letters on average [48]. CXL normalizes the corneal shape by changing the physical properties of the cornea, resulting in reduction of all corneal aberrations, high order and low order. The improvement in uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) are related to improvement in the total corneal aberrations and only high-order aberrations respectively [49].

In order to address this issue, CXL can be performed alone or in combination with topo guided photorefractive keratectomy (PRK), ICRS, phakic IOLS or Topo guided PRK plus ICRS for better improvement of visual acuity [15].

- CXL + Topo guided PRK

Kanellopoulos et al. reported the first case of topography-guided PRK performed 1 year after CXL for treatment of keratoconus and showed visual acuity improvement [50]. On the contrary, the Athens protocol which combines accelerated UV-CXL with same-day photorefractive keratectomy (PRK) was more effective with improvement in UDVA and CDVA of 20/45 or better (2.25 logMAR) was founded in 83% of patients at last follow up [51]. However, this study was conducted in post-LASIK ectasia [51]. Same-day simultaneous topography guided PRK CXL in progressive keratoconus appears to be superior to sequential CXL with later PRK (6 months later) in the aspect of UCVA, BSCVA, spherical equivalent (SE) and mean reduction in K [52]. This combined technique also prevents regression of keratoconus and reduce the risk of keratectasia and might be suitable for eyes requiring improvements in irregular astigmatisms but still have good CDVA [47, 53].

- CXL + ICRS

The CXL can be performed before, simultaneously or after the ICRS. The advantage of performing the CXL first is slowing the progression of the keratoconus and selects the best alternative way to treat the residual refractive error [54]. The recent systematic review and meta-analysis demonstrated that simultaneous ICRS implantation and CXL may provide better outcomes in term of refraction and keratometry. However, UDVA, BCVA and cylindrical refractive error were similar between combined technique and staged procedure [55]. The combined procedure of CXL plus ICRS implantation appears safe and efficacious for the treatment of progressive keratoconus with significant improvements in visual acuity, keratometry values, and refractive error [54]. This technique might be effective for eyes with more irregular astigmatism and worse CDVA [53].

- CXL + Topo guided PRK + phakic IOLS

The simultaneous topography-guided photorefractive keratectomy (PRK) and crosslinking (Athens protocol) followed by phakic intraocular lens (IOL) implantation 2–4 months later for managing keratoconus improved and stabilized visual performance in patients with keratoconus. The  $K_{\text{mean}}$ , SE, UDVA, CDVA improved significantly. At last follow-up, all eyes could achieve CDVA of 0.3 or better [56].

- CXL + ICRS+ + phakic IOLS

Three steps treatment of keratoconus by ICRS implantation, CXL and phakic IOLS significantly improve UDVA, CDVA, higher order aberrations and corneal shape in moderate to severe keratoconus [57]. Moreover, keratometry ( $K_{\text{steep}}$ ,  $K_{\text{flat}}$ ,  $K_{\text{max}}$ ) and refraction (sphere, SE, but not cylinder) were also improved [58]. The time interval between ICRS implantation and CXL was 4–6 weeks and ICL implantation was performed 6–8 months after CXL [57, 58].

#### 5.2.1.5 CXL in thin cornea

The 0.1% riboflavin in 20% dextran solution is used in original Dresden protocol. Only the anterior 300  $\mu\text{m}$  of stroma can be treated [38, 59]. This standard technique requires corneal pachymetry more than 400  $\mu\text{m}$  after de-epithelization to decrease complications such as corneal stromal scar and corneal



endothelial cytotoxicity [47, 60]. In order to combat this issue, there are various modifications to the conventional CXL protocol for CXL in thin cornea. These modifications include hypoosmolar riboflavin, transepithelial CXL, iontophoresis-assisted CXL, Customized epithelial debridement technique, Lenticule-assisted CXL, contact-lens-assisted CXL (CACXL) and individualized corneal CXL [60–67].

Hypoosmolar riboflavin has lower colloidal pressure (310 mOsmol/L vs. 402.7 mOsmol/L in isotonic riboflavin) that causes stromal swelling to double its thickness where stromal bed is less than 400  $\mu\text{m}$  [60]. However, the efficacy of CXL using hypoosmolar riboflavin was lower than traditional CXL with isotonic riboflavin. The possible theory to explain is that in hydrated corneas (using hypoosmolar riboflavin) concentration of collagen fibrils is decreased, hence fewer collagen fibrils are available for CXL [60, 61]. By changing the osmolarity of the riboflavin solution, while maintaining the concentration at 0.1%, probably does not alter the final riboflavin concentration in the cornea. On the contrary, modifying other parameters to obtain a more shallow depth of treatment; ie, the intensity of the UVA light, the duration of treatment, or the intensity of riboflavin concentration will alter the final riboflavin concentration in the cornea and require new dose–response assays [61]. Unfortunately, these modified techniques have not yet distinguished themselves as more effective than any other in terms of topographic or visual outcomes.

Despite the fact that CXL has a promising clinical outcomes, risk factors for ongoing ectasia include the application of isotonic riboflavin solution to thicken a thin cornea prior to treatment, corneas steeper than 58 D and age > 35 years [18, 68]. The most frequent definition of treatment failure is the continual progression of keratoconus with an enhancement of  $K_{\text{max}}$  reading of 1.0 D or 1.5 D over the preoperative value [40, 47]. The outcomes of different CXL techniques are listed as in **Table 4**.

### *5.2.2 Intrastromal corneal ring segments (ICRS)*

Intrastromal corneal ring segments (ICRS) were FDA-approved in 1999 for the treatment of low myopia. ICRS implantation causes displacement of the collagen fibers resulting in flattening of the central cornea and tissue adjacent to the ring is displaced forward [37]. ICRS are segments of polymethylmethacrylate (PMMA) plastic available in numerous arc-lengths, thicknesses, and designs. Five types of ICRS are available for keratoconus: 1) Intacs (Addition technology Inc.) 2) Intacs SK (Addition technology Inc.), 3) Ferrara Rings (Ferrara ophthalmics) and 4) Keraring (Mediphacos). 5) MyoRing (Dioptex, GmbH, Linz, Austria). The devices are inserted into stromal tunnels that may be created manually using a corkscrew blade or femtosecond laser with no difference in results (except that channels tend to be slightly shallower when created manually and more often decentered when created by laser) [37]. The objective of ICRS implantation is to improve visual and topographic outcomes and restoration of contact lens tolerance [15, 18, 37]. Maximal flattening effect occurs with segments at 60–79% corneal thickness. Shallower than 60%, the effect may be lessened and can induced ocular surface complications. On the contrary, deeper than 80%, there may have no topographic effect [88]. The outcome achieved is directly proportional to the thickness of the ICRS and inversely proportional to its diameter [37]. ICRS can be used alone or used in combination with other treatment options such as CXL for stabilizing disease progression [15]. The outcomes of ICRS are listed as in **Table 4**.

Although, ICRS has good visual and topographic results, some complications have been reported. Intraoperative complications rate are low, but can occur and



Treatment	Visual outcomes	Refractive outcomes	Topographic outcomes	Disease progression
Standard CXL	<ul style="list-style-type: none"><li>• VA either remains unchanged or improves by 1–2 lines [18, 38, 48, 49]</li><li>• Corneas steeper than 58 D, no benefit in UDVA or BCVA [68]</li></ul>	<ul style="list-style-type: none"><li>• Small reduction in astigmatism &lt;0.5 D [18, 70]</li><li>• variable, unpredictable corneal astigmatic correction [71]</li><li>• Sphere and cylinder was less negative, SE was more positive [49]</li></ul>	<ul style="list-style-type: none"><li>• Evening out of corneal parameters and a decline in overall surface variability [72]</li><li>• Flattening Kmean and Kmax by 1–2 D [18, 38, 48, 49]</li><li>• KFlat did not change [49]</li><li>• advanced KC may demonstrate changes more frequently than mild disease [18]</li><li>• Shortly after therapy, CCT may decline till 3 months but rebounds to baseline at 1 year [39]</li></ul>	<ul style="list-style-type: none"><li>• Stop progression &gt; 90% -100% [68, 69, 74]</li><li>• Stop progression 75% in pediatric patient [63]</li></ul>
Epi-on CXL/ Transepithelial CXL	<ul style="list-style-type: none"><li>• Improvement of UDVA and CDVA (logMAR) [49]</li><li>• 3 months: 0.06</li><li>• 6 months: 0.17</li><li>• 12 months: 0.05</li><li>• 0.07 logMAR more improvement in CDVA than standard CXL [69]</li><li>• Similar or lower UDVA with standard CXL [62, 69]</li></ul>	<ul style="list-style-type: none"><li>• No changes for the sphere, cylinder, and SE up to 12 months after CXL. [49]</li><li>• Lower SE than standard CXL [69]</li><li>• Similar increase refractive cylinder by 1.5 D and spherical refraction by 1.0 D as standard CXL [69]</li></ul>	<ul style="list-style-type: none"><li>• Less effective than standard CXL to reduce Kmax (mean difference = 1.05D) [62]</li><li>• Kmax was reduced by 1.9–2.2 D, 1 and 3 months after CXL but not later [49]</li><li>• Stable Kmax (no flattening) or Kmax increase by 1.1 D [69, 73]</li><li>• Kmin was reduced by 0.6 to 0.8 D, 1 and 3 months after CXL, and not later [49]</li><li>• Ksteep was reduced by 1.9 and 1.2 D, 6 and 12 months, respectively, after CXL. [49]</li><li>• Kavg was not changed [49]</li><li>• Kflat, Ksteep increase slightly overtime (but decrease slightly overtime in standard CXL) [69]</li><li>• Similar change in CCT with standard CXL or stable CCT [62, 69]</li></ul>	<ul style="list-style-type: none"><li>• 23–55% progression of the disease between 1 year- 3 years after treatment [44, 69, 73]</li><li>• Stop progression 50% in pediatric patient with Iontophoretic Transepithelial CXL [63]</li></ul>

Treatment	Visual outcomes	Refractive outcomes	Topographic outcomes	Disease progression
Accelerated CXL	<ul style="list-style-type: none"><li>No improvement in UDVA, BCVA [49]</li><li>UDVA and BCVA increased 1 Snellen line at 30 months [75]</li><li>Compare to standard CXL at 5 years [76]</li><li>Similar improve in UDVA by 0.08 logMAR</li><li>Similar improve in BCVA by 0.06 logMAR</li></ul>	<ul style="list-style-type: none"><li>Similar reduction in astigmatism by 0.8–0.9 D, SE by 0.9 D when compare to standard CXL at 4 years [76]</li><li>Cylinder increased by 0.7 D 3 months after CXL, SE was more positive after 36 months by 1.07 D, sphere data were not reported [49]</li></ul>	<ul style="list-style-type: none"><li>Similar reduction in K with standard CXL (Kflat, Ksteep Kmean by 1 D and Kmax by 1.7–2.2 D, at 5 years) [49, 76]</li><li>Greater reduction in Kmean than standard CXL [78]</li><li>Epi-on was less effective than Epi-off Accelerated CXL to reduce Kmean, Kmax [75]</li><li>Epi-on: stable CCT</li><li>Epi-off: decreased during the first 6 months and return to baseline at 1 year [75]</li><li>Less or similar corneal thinning than standard CXL [78, 79]</li><li>No significant changes in corneal topography parameters [49]</li></ul>	Conflicting findings [75]
Pulsed-Light Accelerated CXL	<ul style="list-style-type: none"><li>CDVA improved by 0.11 logMAR at 6 months [49]</li><li>BCVA improved by 0.2 logMAR at 1 year [77]</li><li>BSCVA improved by 0.17 logMAR at 2 years [46]</li></ul>	<ul style="list-style-type: none"><li>Corneal astigmatism increased by 0.3 D at 1 year [77]</li></ul>	<ul style="list-style-type: none"><li>Kmax reduced by 1.2D at 1 year [77]</li><li>Flattening of Kmean and Kmax by 0.58 and 0.75 D at 2 years [46]</li><li>Thinnest corneal pachymetry reduced by 7–16 µm at 1–2 years [46, 77]</li><li>CCT reduced by 6 µm at 2 years</li></ul>	All eyes show stability of $K_{max}$ , 30% show small increase in $K_{max}$ at 12 months [77]

Treatment	Visual outcomes	Refractive outcomes	Topographic outcomes	Disease progression
Intrastromal corneal ring segments (ICRS)	<ul style="list-style-type: none"><li>Improve 1–2 lines of BSCVA and BCVA</li><li>Newer segment designs such as INTACS SK and Kerarings, visual gains still rarely exceed 1–2 lines and may increase visual aberrations. [18]</li><li>10% lost <math>\geq 1</math> line of UDVA, and 20% lost <math>\geq 1</math> line of BCVA [80]</li></ul>	<ul style="list-style-type: none"><li>Sizable reduction in corneal astigmatism from 1 to 3 D</li><li>Significant changes between 6 and 12 months</li><li>Full refractive effect is not seen before 1 year postoperatively</li><li>Appears stable, at least through 10 years of follow-up [18]</li></ul>	<ul style="list-style-type: none"><li>Standard INTACS reduce mean Ks by 3–5 D [18]</li><li>INTACS SK, Kerarings, Ferrara ring, and Myoring reduce mean Ks by 2–9 D (smaller internal diameters and are placed closer to the corneal center) [18]</li></ul>	Stop progression >90% for mild to moderate KC at 5 and 10 years [68, 80, 83]
Penetrating keratoplasty (PK)	<ul style="list-style-type: none"><li>UDVA 20/50 to 20/100 [18]</li><li>BCVA 20/30 to 20/40 [18]</li></ul>	<ul style="list-style-type: none"><li>Average astigmatism 3 to 5 D but may exceed 10 D [18]</li><li>20% require refractive surgery after surgery [18]</li><li>Suture removal tends to result in large unpredictable swings in the amount of astigmatism</li></ul>	Donor button is <ul style="list-style-type: none"><li>oversized 0.5 mm; mean K around 45.5 D</li><li>same-sized; mean K around 42.5 D [18]</li></ul>	Approximately 10% of eyes will display recurrent KC 20 years after PK; some diseased recipient cornea is left unremoved [84, 85]
Deep Anterior Lamellar Keratoplasty (DALK)	<ul style="list-style-type: none"><li>Descemetic DALK; Similar/better UDVA, BSCVA, BCVA to PK [18, 81]</li><li>Pre-descemetic DALK; inferior visual results to PK</li><li>Fewer higher aberrations than PK [18]</li></ul>	<ul style="list-style-type: none"><li>Same refractive outcomes or more myopia than PK [18, 82]</li></ul>	2 D steeper than if they had received a similarly sized PK [18]	NA

Treatment	Visual outcomes	Refractive outcomes	Topographic outcomes	Disease progression
Bowman layer transplantation	<ul style="list-style-type: none"><li>BSCVA typically improves by 1–2 lines</li><li>BCVA usually remains unchanged [18]</li></ul>	<ul style="list-style-type: none"><li>Slight hyperopic shift with no significant effect on corneal astigmatism [86, 87]</li></ul>	<ul style="list-style-type: none"><li>Mean reduction in anterior simulated Ks 5 D</li><li>max corneal power 5 to 7 D</li><li>K max 8–9-D [86, 87]</li><li>Non- significantly increase CCT, thinnest pachymetry [86]</li><li>These topographic changes occur within the first post-operative month and appear stable through at least 2 years</li></ul>	<ul style="list-style-type: none"><li>Stop progression</li><li>90% [87]</li></ul>

CXL = Corneal collagen cross-linking, PRK = Photorefractive keratectomy, IOL = intraocular lenses, UDVA = Uncorrected Distance visual acuity, CDVA = Corrected Distance visual acuity, BCVA = Best Corrected Visual Acuity, BSCVA = Best Spectacles Corrected visual acuity, D = Diopter, SE = spherical equivalent.  
Other than standard CXL, formulation of riboflavin solutions, riboflavin concentration, total UVA energy that was used for each study may be different.

**Table 4.**  
Outcomes of surgical treatment of keratoconus.

usually relate to corneal tunnel creation such as insufficient tunnel depth, asymmetry or decentration, or Bowman's layer perforation [15]. The post-operative complications have been reported such as corneal neovascularization, keratitis, deposits around ring segment, corneal haze, halos, pain, corneal melting or edema, segment extrusion, visual fluctuation, and photophobia [15]. This procedure is reversible and not preclude from further surgeries such as CXL and/or corneal transplantation. Due to complications such as stromal necrosis, segment extrusion of synthetic ICRS material, corneal allogenic ICRS (CAIRS) combined with CXL has been reported. Instead of using PMMA to create segment, CAIRS is trephined from donor cornea. CAIRS were implanted into mid-depth corneal tunnel that was created by femtosecond laser, followed by ACXL [89]. This procedure has a promising result in term of improvement of UDVA by 2.79 lines, CDVA by 1.29 lines. Moreover, this procedure demonstrated improvement of SE,  $K_{\max}$ ,  $K_{\text{steep}}$  and topographic astigmatism and halt progression in all cases during follow period [89].

### 5.2.3 Corneal transplantation

Treatment options for advanced keratoconus that has corneal thickness less than 400  $\mu\text{m}$ ,  $K_{\max}$  more than 58 D may be limited to corneal transplantation that can stabilize the cone and enable continued contact lens wear [86]. The keratoplasty techniques may be penetrating keratoplasty (PK), Deep Anterior Lamellar Keratoplasty (DALK) or Bowman layer transplantation.

#### 5.2.3.1 Penetrating keratoplasty (PK)

Penetrating or lamellar keratoplasty techniques are used depending on the extent of corneal scarring [15]. PK provides long term good vision but has slow visual rehabilitation from residual astigmatism and anisometropia [15]. Both PK and DALK tend to worsen any existing ocular surface problems, as both involve surface incisions, injury of corneal nerves, placement of long-lasting sutures, and requiring post-operative topical corticosteroids [18]. Despite the facts that long term graft survival following PK for keratoconus is good, averaging 97% at 5 years, 90% at 10 years and 80% at 20–25 years, most of the patients with advanced KC are transplanted early in life, therefore it is more likely that more than one graft may be required over their lifetime ultimately [18].

#### 5.2.3.2 Deep anterior lamellar keratoplasty (DALK)

The visual outcomes of BCVA, UDVA for DALK remains debated. The recent data from systematic review and meta-analysis demonstrated that the visual outcomes were worse [90] or better [81] than those for PK. The outcomes of DALK for keratoconus are better than PK [81] or equivalent [81] in terms of refractive error, astigmatism and rejection rate. Fifty percent of eyes may encounter Descemet membrane perforation which is the most significant intra-operative complications [18]. Other complications such as a double anterior chamber and persistent corneal edema have been reported. DALK may be less prone to secondary ocular hypertension because of their lower steroid requirement (owing to the smaller risk of rejection) [18]. Another advantage DALK is the lack of endothelial rejection because there is no endothelial defense reaction [15]. The reported rates of postoperative complications such as graft rejection, secondary glaucoma, complicated cataracts, and constant endothelial cell loss are lower with DALK than PK [15].



Classification* Disease progression	Management			
	Stage 1	Stage 2	Stage 3	Stage 4
Non- progressive	Spectacles	Spectacles		
	CL	CL	CL	CL
			CL intolerance	CL intolerance
	ICRS	ICRS		
			BL transplantation	BL transplantation
				DALK/PK
Progressive	Spectacles	Spectacles		
	CL	CL	CL	CL
			CL intolerance	CL intolerance
	CXL	CXL	CXL	
	ICRS	ICRS		
			BL transplantation	BL transplantation
				DALK/PK

Adapted from JAMA Ophthalmol. 2014 Apr 1;132(4):495–501.  
The classification of keratoconus was based on Krumeich JH et al.A. Live-epikeratophakia for keratoconus. J  
Cataract Refract Surg. 1998 Apr;24(4):456–63. [17]  
Stage 1  $K_{max} < 48$  D, thickness  $> 500\text{ }\mu\text{m}$ , absence of scarring.  
Stage 2  $K_{max}$  48–53 D, thickness 400–500  $\mu\text{m}$ , absence of scarring.  
Stage 3  $K_{max}$  54–55 D, thickness 200–400  $\mu\text{m}$ , absence of scarring.  
Stage 4  $K_{max} > 55$  D, thickness  $< 200\text{ }\mu\text{m}$ , central corneal scarring.

**Table 5.**  
Management algorithm in various stages of keratoconus.

5.2.3.3 Bowman layer transplantation

The PK or DALK may be disrupted by complications such as suture-related problems, graft rejection, epithelial wound-healing abnormalities, corneal curvature changes due to progression of KC in the peripheral host cornea resulting in disappointing visual results [86]. In KC corneas, pathological changes include the reduction of number of keratocytes, organization of the stromal lamellae, fragmentation or absent of Bowman’s layer (BL) [91] It has been suggested that the BL may be the strongest biomechanical element of the human cornea followed by the anterior third of the cornea [92]. Therefore, the BL may play a structural role in maintaining the shape/tectonic stability in KC corneas [87]. This procedure was first described in 2014, Bowman’s layer graft was positioned inside the recipient corneal stroma in a sandwich technique, without corneal incision or sutures, to pull the anterior corneal surface flatter and create homogeneous corneal topography [86]. BL transplantation can be performed under local anesthesia and low dose topical steroid can stop within 1 year post-operative, minimizing the risk of glaucoma development or cataract formation [86, 87, 93]. The reported complications are low such as intraoperative microperforation of the Descemet’s membrane [87, 93]. Because of the transplanted tissue is acellular, no episodes of allograft rejection have been observed [86, 87]. This procedure may postpone penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) and potentially allowed long term contact lens wear [86]. Although graft preparation and surgical technique can be challenging, assisted technologies, such as femtosecond laser and intraoperative anterior segment optical coherence tomography (OCT), may

help conquer these barriers [94, 95]. “Bowman layer onlay,” a recently developed surgical technique in which an isolated Bowman’s layer graft, is positioned onto the patient’s anatomical Bowman’s layer or anterior stroma, has demonstrated the rapid re-epithelization and integration of the tissue and comparable clinical outcomes to intrastromal transplantation [96]. The outcomes of each keratoplasty techniques are listed in **Table 4**.

There are a variety of nomograms for the treatment of keratoconus which are mainly focused on the keratoconus grading, risk factors, the progressive nature of the disease, and contact lens tolerance [15]. The management algorithm in various stages of keratoconus is shown in **Table 5**.

## 6. Future directions

Treatment for advanced KC has trended away from invasive procedures such as PK and even DALK toward minimally invasive procedures such as CXL, ICRS or BL transplantation. Although keratoconus is a multifactorial disease, the pathogenesis of the disease is very much affected by genetic factors and positive family history [2, 8, 97]. By identifying pathogenic genes and changing the structure of cell proteins, gene therapy may be a very promising and effective treatment modality to change the course of the disease [15].

## 7. Conclusion

The two most important goals of management of keratoconus are stopping disease progression and visual rehabilitation. An ocular allergy should be treated. Care providers should instruct the patients to avoid eye rubbing to halt disease progression. A careful follow up is needed to document disease progression and provide prompt treatment. A nonsurgical treatment of keratoconus includes spectacles or contact lens. Contact lens use does not slow or halt progression but can provide satisfactory vision in early stages of keratoconus. A contact lens type is selected based on the manifest refraction and the degree of keratoconus.

The five operations (CXL, ICRS, PK, DALK and BL transplantation) currently represent the available surgical treatment options for advanced KC. Treatment for advanced KC has trended away from invasive procedures such as PK and even DALK toward minimally invasive procedures such as CXL, ICRS or BL transplantation. CXL and ICRS were once regarded only for mild to moderate keratoconus, their roles are now expanding in advanced diseases as well.

PK and DALK provide long term good vision but has slow visual rehabilitation and may be disrupted by complications such as suture-related problems and graft rejection. BL transplantation was introduced for advanced KC with extreme thinning/steepening. This novel procedure may postpone penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) and potentially allow long term contact lens wear. Since genetic factors play significant roles in KC, advances in gene therapy may soon yield innovative treatments of this disease.

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