Optimal management of pediatric keratoconus: challenges and solutions

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Abstract: Keratoconus (KC) shows several distinctive features in clinical appearance, disease progression, and treatment in children compared with adults. Therefore, diagnostic, clinical care, and therapeutic approaches are different. However, pediatric keratoconus is often undiagnosed and thus untreated in many cases. Once diagnosis has been made, compliance with treatment recommendations is often poor. Pediatric keratoconus also tends to have more rapid progression than in adults; therefore, early detection and treatment are paramount to prevent serious vision impairment, which can affect the child’s development. This review of pediatric keratoconus discusses important issues such as worldwide epidemiology, clinical features in children compared to adults, and challenges in diagnosis and treatment and focuses on the most appropriate management strategies based on the best available current evidence.

Keywords: cornea, pediatric, keratoconus, crosslinking, corneal transplant, ICRS

Introduction
Keratoconus (KC) is a progressive, bilateral, thinning disorder of the cornea in which biomechanical changes in corneal collagen fibers result in progressive increase in corneal curvature and thinning.¹,² Occurring at an estimated (variable) prevalence in the general population of approximately 1:375 to 1:2,000, patients usually present with a deterioration in visual acuity secondary to myopia and irregular astigmatism. Rupture in Descemet’s membrane, acute corneal edema, and subsequent scarring are other causes of vision loss.³,⁴

Compared to adults, keratoconus in children progresses more rapidly and is usually more severe at the time diagnosis. Hence, prompt management to halt the progression of the disease and enhance visual performance is crucial.

Nonsurgical options such as spectacles and contact lenses (soft, rigid or scleral) in children are not always tolerated and often insufficient to obtain a satisfactory visual acuity. (Table 1)⁵ Furthermore, none of these conservative options halt progression of the disease. Studies on pediatric keratoconus suggest that at the time of diagnosis, 27.8% are at an advanced stage and 88% progress. Thus, interventions with acceptable safety-efficacy profiles (ie, corneal collagen crosslinking [CXL], and its variations) to increase the biomechanical strength and stability of the cornea have been established. However, in the pediatric population, poor compliance and necessary modifications in treatment modalities create challenges that have yet to be overcome.⁶–⁸ This review analyzes the current challenges and solutions in diagnosing and managing pediatric keratoconus.
Table 1 Challenges in pediatric keratoconus

<table>
<thead>
<tr>
<th>Late diagnosis</th>
<th>Faster progression</th>
<th>Unsuccessful conservative care</th>
<th>Control of eye rubbing behavior</th>
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Epidemiology

There is limited evidence regarding the prevalence of Keratoconus (KC) in children. A study in Lebanon reported a prevalence of 1:200,9 and a more recent one in Saudi Arabia found a prevalence of 1 in 2.10 As mentioned previously, the prevalence in the general population is believed to be between 1:375 and 1:2,000.3 The prevalence of keratoconus varies worldwide: from 0.3 per 100,000 in Russia11 to 2,300 per 100,000 in Central India12 and 54.5 per 100,000 in the United States.13 The variability between the results may be due to environmental factors and genetic influence.

A multifactorial etiology has been proposed, although the exact pathogenesis is unclear. Studies have found a correlation between keratoconus and allergic disorders, especially in pediatric patients (Table 2).14–16 Allergic disorders include vernal keratoconjunctivitis, allergic keratoconjunctivitis, and atopic dermatitis, leading to chronic eye rubbing which appears to play an important role in the pathogenesis of the disease.17 Chronic eye rubbing and atopy was first described as a risk factor for keratoconus by Ridley et al in 1959.18 Contact lens wear (particularly with polymethyl methacrylate) is also considered as a precipitating factor due to microtrauma.17,18,19 Although the lack of inflammation has been questioned and recent studies have shown a role of proteolytic enzymes, cytokines, and free radicals, it does not necessarily meet all the classic criteria for an inflammatory disease.20 An increase in inflammatory mediators has also been found in the tear film of patients with keratoconus, suggesting a possible inflammatory etiology.21

There is also a genetic component to the etiology of keratoconus as it is associated with systemic conditions such as Down’s syndrome, Marfan syndrome, mitral valve prolapse, and collagen tissue diseases. Genetic influence with familiar inheritance is also observed.22,23 Patients with first-degree relatives with keratoconus have 15 to 67 times higher risk in developing corneal ectasia compared to patients with no affected relatives.19,24

Ethnicity has been reported to play a role in keratoconus. Asians have 4.4 times the risk for developing keratoconus than Caucasians, and Indians have steeper corneas than Chinese patients with keratoconus.25

Keratoconus is most frequently diagnosed in young adults; it commonly has its onset in puberty and may progress until the third or fourth decade of life. Pediatric keratoconus (onset before 18 years of age) is less common and is more aggressive than adult keratoconus. Few studies about the prevalence and incidence of keratoconus in children have been reported. The youngest case described was a girl with Down syndrome diagnosed at the age of 4 years.26 El-Khoury et al reported 2,972 patients, of which 541 had keratoconus; 16 patients were children 14 years or younger at the time of the diagnosis equating to an incidence of 0.53%, compared to an incidence of 3.78% in adults.9

Clinical features

As previously mentioned, keratoconus is a chronic, progressive bilateral corneal ectasia, most frequently diagnosed in adolescence. In its early stages, the disease can seem unilateral, although posterior corneal elevation is usually detected in both eyes. It is characterized by central or paracentral corneal thinning, irregular corneal astigmatism, and steepening of the cornea, resulting in high myopia and subsequently visual loss. In more advanced cases, rupture in Descemet’s membrane with acute corneal hydrops leads to corneal scarring.20,27

Table 2 Surgical options for pediatric keratoconus

<table>
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<tr>
<th>Transepithelial corneal collagen crosslinking</th>
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<tr>
<td>• Conventional (Dresden protocol)</td>
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<tr>
<td>• Accelerated</td>
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<td>• Pulsed</td>
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<th>Epithelium-off corneal collagen crosslinking</th>
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<tr>
<td>• Conventional</td>
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<td>• Accelerated</td>
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<td>• Pulsed</td>
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<td>• Topography-guided CXL</td>
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<th>Iontophoretic transepithelial crosslinking</th>
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<tr>
<td>Penetrating keratoplasty</td>
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<tr>
<td>Deep anterior lamellar keratoplasty</td>
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<tr>
<td>Sequential intracorneal ring segment ± crosslinking</td>
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Abbreviation: CXL, crosslinking.

Adult vs pediatric keratoconus

The clinical appearance of keratoconus in children is somewhat different from that seen in adults. Morphologically, the ectatic cornea is more centrally located in pediatric cases; thus, irregular astigmatism is less pronounced.28 However, as keratoconus often...
progresses asymmetrically, pediatric patients maintain good binocular visual function until both eyes are affected: the “non-dominant” eye can progress without patients noticing a change in their visual acuity; it is only when their “dominant” eye deteriorates that they become more symptomatic and seek help. Moreover, ocular aberrations generated by the irregular cornea may be partially compensated by internal ocular structures and the high accommodative power (though not commonly seen in myopic patients) present at a younger age. Both of these factors may explain why parents seek ophthalmic care later in the course of the disease, when visual function has deteriorated significantly in their children. Al Suhaibani et al reported an inverse correlation between the severity of the disease and the age of onset. Hence, keratoconus in the pediatric population is more advanced at the time of diagnosis.

Leoni-Mesplie et al described 216 keratoconic patients, where 49 patients were 15 years or younger and 167 patients were 27 years or older. At the time of the diagnosis, 27.8% of the young group had stage IV keratoconus (Amsler-Krumieich classification) versus 7.8% in the adult group. These results were comparable to the study by El-Khoury et al, where 30% of pediatric patients had stage IV keratoconus at the time of the diagnosis. Due to the more rapid progression and severity, children have a higher risk of acute corneal hydrops, leading to an increased need for corneal transplantation to improve vision.

Increased corneal curvature has also been reported in pediatric patients compared to adults. Chatzis and Hafezi noted that in 59 keratoconic eyes in patients between the ages of 9 and 19 years, there was an increase in corneal steepening (Kmax) greater than 2 dioptres in 1 year, with a progression rate of 88%. Another characteristic observed in children is that central cones are more common, with this group progressing more rapidly than peripheral cones.

In many cases, these groups of patients require surgical treatment an earlier age: in mild-to-moderate ectasia, corneal crosslinking is recommended to stop progression of the disease whereas in severe cases with corneal scarring, corneal keratoplasty for visual rehabilitation is indicated (Table 3).

**Diagnostic challenges**

Keratoconus can be clinically diagnosed on slit-lamp findings (ie, corneal steepening, thinning, Vogt’s striae, and Fleischer ring). However, these changes are seen mainly in moderate-to-severe stages of the disease. Conversely, there may be no obvious changes in the earliest stages of keratoconus, leading the majority of these patients, and importantly, pediatric patients to remain undiagnosed.

Several classification systems for keratoconus exist. One of the earliest is the Amsler–Krumieich classification system, which is divided into 4 stages according to the severity of the disease, incorporating myopia, astigmatism, keratometry readings, central corneal thickness, and the transparency of the cornea. Although this system is widely used among ophthalmologists, it has limitations. It only measures the anterior corneal surface at the center of the cornea. Patients with keratoconus commonly have para-central corneal thinning; therefore, a full corneal thickness map is more useful for classification purposes.

Modified Rabinowitz–McDonnel indices are also helpful. It incorporates central keratometric reading (K) and inferior–superior dioptic asymmetry (I/S index). Values higher than K >47.2D and I/S index >1.2 are suggestive of keratoconus.

Placido disc-based corneal topography had previously been described as the gold standard tool. However, it has the restriction of only measuring the anterior corneal surface. With the advent of newer imaging technologies such as Scheimpflug, optical coherence tomography (OCT), and slit-scan tomography, the anterior and posterior cornea can be measured and are now accepted as the best and widely available tests to diagnose early keratoconus.

Consequently, developing newer classifications and staging systems is necessary. Using Scheimpflug technology (Pentacam, Oculus, Germany), the Belin/Ambrosio Enhanced Ectasia Display (BAD) program assesses the likelihood that a cornea is ectatic. It uses the pachymetry map and anterior and posterior elevation maps and compare it with the standard best-fit-sphere (BFS) from the central 8 mm. Additional improvements to this program to enhance the reference surface have subsequently been implemented.

<table>
<thead>
<tr>
<th>Table 3 Risk factors in pediatric keratoconus</th>
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<tr>
<td>Lower thinnest corneal thickness</td>
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<td>Higher average central corneal keratometry</td>
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<tr>
<td>Increased posterior elevation</td>
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<tr>
<td>Frequent eye rubbing</td>
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<td>Allergic eye disorders</td>
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Belin et al have also reported the ABCD grading system, a newer tomographic method of staging keratoconus.\textsuperscript{35} It measures tomographic data and anatomical and functional changes and classifies keratoconus into stages 0–5. The tomographic data are the anterior curvature, posterior curvature, and pachymetry map; the functional changes measure the best-corrected distance visual acuity; the anatomical criteria take into consideration the absence or presence of corneal scarring.

Although corneal tomography is the gold standard for keratoconus screening, in early stages of the disease, it can sometimes be misdiagnosed with topography or tomography alone. High-resolution optical coherence tomography (HR OCT) and high-frequency ultrasound can detect epithelium, stromal, and corneal thickness changes in subclinical keratoconus, which may be more sensitive in diagnosing keratoconus in its earliest stage.\textsuperscript{35,37}

**Treatment**

**Intracorneal ring segment implantation**

Only a few retrospective interventional case series have been published regarding intracorneal ring segment (ICRS) implantation for the treatment of pediatric keratoconus, with varying results.\textsuperscript{39–42} The most recent study combined ICRS and crosslinking and examined visual, refractive, and keratometric outcomes in 12 patients aged 14 years or younger. Corrected distance visual acuity improved 0.18 logMAR (logarithm of the minimum angle of resolution) and unaided visual acuity improved 0.47 logMAR; refraction and keratometry values also improved after 6 months. All parameters stabilized between 6 months and 4 years postoperatively, except for a small but significant improvement in cylinder and uncorrected distance visual acuity after 4 years. The surgery was well tolerated by most patients, and no intraoperative or postoperative complications were reported, except for one ring segment that had to be removed after 2 years due to vascularization and corneal thinning. According to the results of this study, ICRS implantation with cross-linking is a safe and effective procedure for visual rehabilitation in children with keratoconus and poor corrected distance visual acuity. As over 20% of all keratoconus patients demonstrate contact lens intolerance, ICRS implantation could be offered in selected cases, and especially in adolescent patients, assuming a 400-micrometer corneal thickness at the mid-periphery and in the absence of central corneal scarring. As in adults, ICRS results in good visual and topographic results in pediatric patients. However, ICRS alone does not halt the progression of keratoconus.\textsuperscript{40} Despite promising results, ICRS implantation is not commonly used in the pediatric age group due to the aggressive nature of keratoconus, frequent eye-rubbing, poor patient compliance, unpredictability of results, and the lack of nomograms adapted to pediatric keratoconus.\textsuperscript{43}

**Corneal transplant**

Diagnosis of keratoconus before adulthood is a poor prognostic factor for disease progression, increasing the probability of the need for a corneal transplant. Corneal transplants for keratoconus in the pediatric population represent 15–20% of all corneal transplants,\textsuperscript{55} and those with progressive disease have a seven-fold higher risk of requiring a corneal transplant in the future. However, transplantation at a young age is associated with a higher risk of rejection and a poor visual prognosis. It is also a perioperative challenge for the corneal surgeon: preoperative risk factors must be assessed such as age of diagnosis, the existence of any form of allergic disease, the presence of associated genetic or connective tissue disorders, steep keratometric values, patient co-operation, and availability for frequent follow-up visits. Intraoperative challenges such as positive vitreous pressure, low scleral rigidity, and increased fibrin reaction must also be considered. If a transplant is performed at a very young age (although less likely in cases of keratoconus), postoperative care may require multiple examinations under anesthesia which is a risk in itself.\textsuperscript{27} If patients have a low risk of amblyopia or are beyond the age of amblyopia reversal, then corneal transplantation should be postponed as long as possible.

The interval from the onset of the disease to the development of an advanced stage of keratoconus with visual symptoms is shorter and faster in the pediatric age group. Therefore, every child with a history of atopy, eye rubbing, ocular allergy, or family history should be a suspect for keratoconus and screening is advised from a young age with frequent follow-up visits. An early diagnosis could prevent the progression of the disease and visual loss.

**Preventing progression in pediatric keratoconus: solutions**

After the diagnosis of keratoconus, it is of paramount importance to prevent progression in order to prevent deterioration of visual acuity and dependency of visual aids. One strategy for halting the progression of keratoconus is to perform corneal CXL.
CXL increases the mechanical strength of the affected cornea using a photosensitizer (riboflavin) and ultraviolet-A irradiation (370-nm wavelength light), which produce ROS, leading to crosslinking of interfibrillar collagen and increasing corneal biomechanical rigidity.\textsuperscript{44,45} CXL is usually performed for disease progression, although there is no standard definition of progression. It is most commonly defined as an increase in maximum keratometry of at least 1 diopter over 1 year, based on topographic findings. This value of 1 diopter was chosen because of the amount of variability in corneal topography measurements.\textsuperscript{46} Therefore, “progression” of 0.2 diopters within 1 year might very well be related to measurement error. The measurement error increases with keratoconus severity, leading to substantial amounts of uncertainty in cases with keratometry values above 55 diopters.\textsuperscript{47}

Another important factor to consider when interpreting keratometry values is contact lens wear. Contact lenses alter the shape of the cornea, mostly by remodeling the epithelial surface. The usage of scleral lenses can alter maximum keratometry values by more than a diopter.\textsuperscript{48} Contact lenses that are placed directly on the cornea, such as rigid gas-permeable contact lenses that are often used in keratoconus, could influence the shape of the cornea even more. Therefore, pediatric contact lens wearers are usually instructed not to wear their contact lenses for one or several weeks before keratometry measurements. The ideal discontinuation time before measurements has not been established partly due to the fact that many keratoconus patients are heavily dependent on contact lenses and are unable to cease lens use for extended periods of time.

Due to the uncertainty of topography measurements alone, other variables are often incorporated to determine whether there is progression of keratoconus. Variables that are often included are corneal thickness, posterior curvature of the cornea, manifest refraction, uncorrected and corrected distance visual acuity, and patient age.\textsuperscript{35}

An inverse relationship has been found between patient age and disease progression; in general, pediatric keratoconus is more likely to progress, and this progression can be very rapid and devastating.\textsuperscript{31} The Global Consensus on Keratoconus and Ectatic Diseases states that CXL can be beneficial upon diagnosis in young patients with keratoconus.\textsuperscript{49} However, there is concern about the efficacy and long-lasting effect of CXL in children.\textsuperscript{8}

When counseling pediatric patients and their parents, it is important to understand that the level of evidence for pediatric CXL is inferior to the level of evidence in adults since no randomized controlled trials have been performed in children. Furthermore, the efficacy of pediatric CXL may not be equivalent to the efficacy of CXL in adults; the risk of keratometric progression after pediatric CXL is approximately 22% compared to 2–10% in adults.\textsuperscript{50} One of the boundaries to performing a randomized, controlled trial in children is that it may be considered unethical to withhold CXL from a child with progressive keratoconus in a control group in order to prove that care without CXL is inferior to care that includes CXL since treatment efficacy has been demonstrated in multiple randomized, controlled trials in adults.\textsuperscript{51}

### Conventional vs modified CXL

The original crosslinking protocol included the removal of the central corneal epithelium, application of riboflavin 0.1% as a photosensitizer and an irradiation time of 30 mins using 370 nm ultraviolet-A (UVA) light with an irradiance of 3 mW/cm$^2$.\textsuperscript{45} This protocol is commonly referred to as the Dresden protocol. Adaptations of this protocol aimed at avoiding the need for epithelium removal (trans epithelial CXL) and shortening the treatment time (accelerated CXL). This was attempted in order to prevent postoperative pain and the risk of infection due to epithelium removal and to circumvent the need for the patient to lie still for an extended period of time. This is especially relevant for children because the tolerance of pain and the ability to lie still are usually less at this age. However, the efficacy of transepithelial CXL in halting the progression of keratoconus is inferior to CXL with epithelial removal.\textsuperscript{52} This is mostly due to the fact that the inability of riboflavin to pass through the intact epithelium. A method that aims to circumvent the removal of the epithelium while enabling the riboflavin to penetrate the cornea stroma is iontophoresis-assisted trans epithelial CXL. However, interest in this treatment has diminished since it has been demonstrated to be less effective than standard CXL with epithelium removal in a head-to-head comparison.\textsuperscript{56}

### Pulsed CXL

A recent novelty is the introduction of pulsed CXL. During photosensitization, oxygen in the corneal stroma is an important component of the chemical reactions. In accelerated CXL protocols where the irradiation time is markedly reduced, it is thought that there may be insufficient time for replenishment of oxygen levels in the stroma, leading to decreased treatment efficacy. Therefore, by pulsing the UVA irradiation during the exposure time allows oxygen to diffuse deeper into the
corneal stroma during pauses in the UVA, which may increase the treatment depth and the resultant corneal stiffening. Literature on pulsed CXL is limited, and although the depth of treatment might be deeper in rabbit corneas, the added clinical value of pulsed CXL compared to conventional CXL has not been proven.53

Many studies have been published on the efficacy of accelerated CXL compared to the original Dresden treatment protocol with varying results. However, a head-to-head comparison in randomized, controlled trials with sample sizes large enough to detect small but potentially relevant differences in efficacy is still lacking. Therefore, crosslinking with epithelium removal remains the current gold standard, although alternative photosensitizers are under investigation.

Topography-guided CXL
A treatment protocol that has the potential to replace the standard CXL protocol is topography-guided CXL. The rationale of this treatment is that CXL can be altered based on each individual’s cone shape; the ultraviolet light intensity is augmented based on the corneal topography which can result in more flattening of the ectatic area of the cornea. Topography-guided CXL (photorefractive intrastromal crosslinking, PiXL) has led to superior results in spherical equivalent and visual acuity after 12 months compared to standard CXL in a randomized controlled trial.54

Postoperative management
All patients require antibiotics and topical steroids after CXL. However, some considerations should be taken into account regarding pediatric patients. Children must be under observation for possible intraocular pressure elevation during the topical steroid treatment. Children should not resume the use of contact lenses until complete corneal epithelialization.

Acute pain management is frequently necessary within the first 24–48 hrs after surgery and is particularly important in children where pain tolerance may be lower. Management options include systemic and topical nonsteroidal anti-inflammatory medications, cycloplegic drops, and an eye patch (when only one eye was treated) or a bandage contact lens to improve comfort in these patients.

Challenges after crosslinking
Corneal healing
Complete epithelialization is generally achieved 4 days after the procedure. A mild haze can be observed in a majority of patients on slit-lamp examination, but it does not have any effect on the visual acuity and usually decreases with topical steroid treatment by 2 months after surgery.

Endothelial cell loss
Endothelial cell density (ECD) has not been shown to be affected after CXL in pediatric subjects after 2 years of follow-up.55,57

Failure
In adults, CXL treatment results in a complication rate (loss of 2 or more Snellen lines) of approximately 2.9%.58 Failure of CXL to arrest keratoconus progression may be attributed to different genetic patterns, biomechanical modifications occurring in the corneal stroma, and the negative influence of other conditions such as allergy and atopy. A preoperative maximum keratometry reading of less than 58.0 diopters may reduce the failure rate, and restricting patient age may further reduce the complication rate to 1%.59,60 Other complications include visually significant haze, scarring, and keratitis.

In children, there are limited reports about failure to arrest progression. Shetty et al reported on accelerated CXL outcomes in children younger than 14 years and observed failure in 17.6% of treated cases. Failure was associated with a history of allergic conjunctivitis, where persistent eye rubbing may “nullify” the effect of CXL. Therefore, it is important to actively treat underlying allergic eye disease with topical steroids and topical mast cell stabilizers when it is necessary.57,61

Limbal stem cell damage
There is concern that CXL may potentially damage limbal stem cells. Attention should be paid to the ultraviolet irradiation area at all times, particularly in children, as distraction may lead to inadvertent limbal irradiation. On the other hand, children with concomitant vernal or atopic keratoconjunctivitis may have preexisting subclinical limbal stem cell deficiency; therefore, it is recommended to use a limbal guard to prevent further damage.57

Conclusion
As in adults, several management options are available for the treatment of pediatric keratoconus. The main objectives in children are to halt the progression of the disease, visual loss prevention, and ultimately avoid corneal transplantation.

Currently, the only known treatment that has been proven to prevent progression is crosslinking. CXL performed in
children has shown similar initial efficacy as adults in terms of improvement of visual and topographic outcomes; however, long-term outcomes are more variable. CXL can potentially prevent visual loss and prevent the need for corneal transplantation. Allergic eye disease in children with keratoconus should be treated aggressively, especially if they are undergoing CXL. Although there is limited evidence, accelerated CXL appears to show results comparable to those of conventional CXL in arresting the progression of keratoconus in pediatric patients. The optimal CXL protocol for children will depend on the severity of the disease, patient cooperation, and availability of riboflavin and irradiation devices in order to meet the individual patient’s needs.

Due to the scarcity of randomized, controlled trials in pediatric keratoconus, the majority of data are inferred from clinical trials and case series with adult patients. Therefore, currently, authors have been unable to determine a gold standard for the treatment of keratoconus in children.

Author contributions
All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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Date: 2019-01-01


Persistent Link: http://hdl.handle.net/11343/249672

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