

Pediatric keratoconus - Current perspectives and clinical challenges

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Keratoconus is an ectatic corneal disease characterized by progressive stromal thinning, irregular astigmatism, and defective vision. It can be unilateral or bilateral with asymmetric presentation. It starts at puberty and either progresses rapidly to an advanced stage of the disease or stops in case of delayed onset and slow progression. Pediatric keratoconus is more aggressive than in adults and the management protocols differ because of various rationales such as accelerated progression, advanced stage of disease at the time of diagnosis and co-morbidities. It poses a burden to the society as it affects the quality of life, social, and educational development in children. Hence early diagnosis, recognition of progression, and timely intervention with collagen crosslinking is imperative to arrest the worsening. Association with systemic syndromes and ocular comorbidities can be of concern in pediatric keratoconus. Severe ocular allergy when associated hastens progress and complicates timely intervention of crosslinking treatment and compliance to contact lens wear. Keratoplasty in pediatric keratoconus has good outcomes but can encounter frequent suture-related concerns. This article discusses the epidemiology, etiopathogenesis, clinical challenges, and current perspectives of management of pediatric keratoconus.

Key words: Allergy, atopy, corneal collagen crosslinking, DALK, genetics, keratoconus, pediatric, penetrating keratoplasty, vernal keratoconjunctivitis

Pediatric keratoconus (KC) is the corneal ectasia occurring in children less than 18 years or in adolescence between 10 and 19 years of age, though the disease can manifest in any age.^[1]

KC in children [Fig. 1] exhibits several unique clinical features such as faster disease progression and severe visual impairment at the time of diagnosis creating a negative impact on their quality of life. This review provides an update on epidemiology, prevalence, clinical challenges, collagen crosslinking treatment and keratoplasty challenges and outcomes in pediatric keratoconus.

Epidemiology

The prevalence of KC in the general population is 1 in 2000.^[2] According to the Intelligence Research in Sight Registry of AAO, the prevalence of KC in pediatric population is 0.16%.^[3] KC affects Indians, Pakistanis, Arabs, and Polynesians 4.4 times more than the Caucasians.^[4] The prevalence rates of keratoconus exhibits a geographical variation. The prevalence of pediatric KC is 1.1% in Riyadh^[5] and 4.79% in Saudi Arabia.^[6] This difference in the incidence of KC [Table 1]^[7] is due to its variation in genetic, environmental factors, nutrition, and study tools employed in their studies. There is no clear evidence in the literature indicating a gender difference. The CLEK

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study^[8] reported a mean age at diagnosis of 27.3 ± 9.5 years (10 to 39 years) with about 90% of patients being diagnosed by the age of 10 years. The youngest age of KC documented in the literature is a four-year-old girl with Down's syndrome.^[9]

A younger age of onset of KC tends to be associated with rapid progression and more advanced stage of disease at diagnosis.^[10] Leoni-Mesplie *et al.*^[11] report that 27.8% of patients were below 15 years with stage 4 KC (Amsler Krumeich classification) as against 7.8% with age more than 27 years at the time of diagnosis with male predominance. Chatzis *et al.*^[12] observed KC progression in 88% of children by one year of diagnosis mandating an early advocacy of CXL treatment in these pediatric eyes.

Etiopathogenesis

The pathophysiology of keratoconus is poorly understood. Keratoconus is a multifactorial disorder which involves genetic, metabolic, and environmental factors.^[10] The time-honoured definition of keratoconus states that the condition is noninflammatory.^[13] Current evidence, however, suggests a significant role for the inflammatory mechanisms.^[11,13] Altered dynamics of pro- and anti-inflammatory cytokines is perhaps responsible for activating metalloproteinases and promoting apoptosis of keratocytes.^[11,13] The end result is a reduction in

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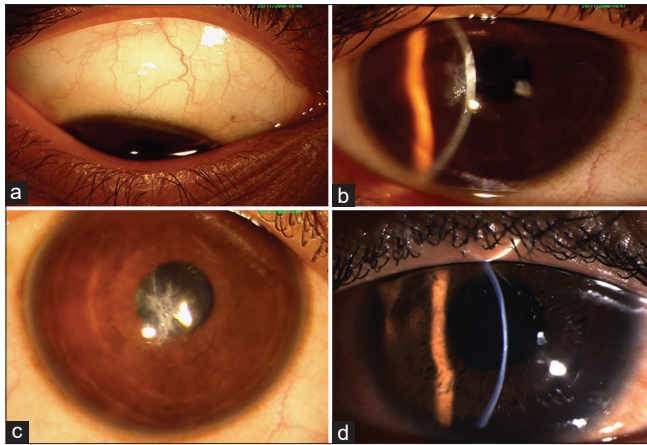


Figure 1: Clinical picture of pediatric keratoconus showing (a) Munson's sign, (b and c) apical scar, and (d) advanced ectasia

collagen cross-linking, resulting in altered corneal rigidity or biomechanical strength.^[14]

Causative factors

The various causative factors implicated in the pathogenesis of KC^[15] include the following:

- 1) Genetic factors
- 2) Environmental factors
- 3) Role of inflammation
- 4) Role of enzymes
- 5) Role of oxidative stress
- 6) Role of hormones

1. Genetic Factors

KC has a genetically heterogeneous distribution. It has been reported to be inherited as autosomal recessive, autosomal dominant, and sporadic^[16] with 10% (range: 5-27.9%) of patients diagnosed with pediatric KC having a family history.^[17] The evidences in support of the genetic basis of KC [Flowchart 1] include the following:

- a) Prevalence of KC in first-degree relatives (20.5%)^[18]
- b) Twin studies in KC that indicate monozygotic twins to have higher concordance than dizygotic twins, with a greater similarity of phenotype^[19]
- c) Associated genetic syndromes are Down's syndrome, Marfan's syndrome, osteogenesis imperfecta, Apert syndrome, Ehlers Danlos syndrome, Leber's congenital amaurosis^[18]

The genes and mutations associated with keratoconus are elaborated in Table 2.^[16,17]

2. Environmental Factors

About 40% of children are affected by systemic allergies.^[20] In the CLEK study,^[8] 52.9% of patients with KC had hay fever or allergies, 14.9% had asthma, 8.4% had atopic dermatitis and 27% had vernal keratoconjunctivitis (VKC), and 40% had abnormal topography. VKC is the most common associated ocular allergy with KC.^[21] The complex mechanism of development of KC in VKC is due to the exposure to allergen, eye rubbing [Flow Chart 2], and the resultant microtrauma to epithelium^[22] that induces increase in the levels of inflammatory mediators [such as matrix metalloproteinases (MMP-1), IL-6, and TNF- α] from both the epithelial and stromal cells, with IL-6 and

Table 1: Incidence of KC in different countries

Countries	Prevalence of Keratoconus
Russia	0.3 per lakh
India	2,300 per lakh
United states	54.5 per lakh
Iran	2,300 per lakh
Columbia	3,900 per lakh

TNF- α , upregulating MMP-1.^[23,24] The pathogenesis [Flow Chart 3] involves the release of specific allergens into the body through conjunctiva, which react with specific IgE on mast cells or basophils. The released vasoactive mediators such as histamine, proteases, TNF- α , and interleukins seem to induce the development and progression of KC.^[23] The eye rubbing in KC has been shown to increase MMP-13 in tears that have an important role in the apoptotic activity of the keratocytes.^[20-22] Keratocyte apoptosis leads to stromal volume loss following degradation of extracellular matrix resulting in thinning and ectasia.^[21]

There also seems to be a higher risk of acute hydrops (40%) in these eyes as compared to primary KC eyes (2.6%).^[25] Early topography evaluations are essential in these eyes as higher corneal elevation, thinner pachymetry, and increased frequency of KC topography patterns are detected in these corneas as compared to normal.^[26,27] Rubbing of eyes for 15 seconds results in 18.4% reduction in central and midperipheral corneal epithelial thickness which explains the association of chronic rubbing and most common site of cone formation (paracentral and inferonasal). Contact lens-induced allergies and eye rubbing can cause KC in genetically predisposed individuals.^[28,29]

3) Role of Inflammation

Increased levels of IL-6, IL-1 β , TNF- α , TNF- γ and reduced levels of IL-10 are noted in keratoconus eyes. The increased levels of gelatinases, collagenases, metalloproteinases, proteases, cytokines, TNF- α and TNF- β have been associated with progressive KC.^[22,23] This upregulation of cytokines and proteases is perhaps due to the underexpression of lactoferrin, an antimicrobial and anti-inflammatory protein.^[24] Enzyme-linked immunosorbent assay (ELISA) analysis of tears in keratoconus patients has shown the elevated levels of inflammatory markers IL-6, TNF- α , and MMP-9.^[29] The tear biomarkers identified in KC are listed in Table 3.^[30]

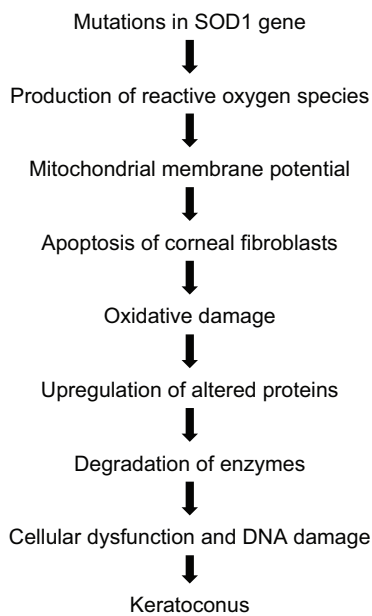
4. Role of Enzymes

MMP-9 is a gelatinase that has been found responsible for the degradation of denatured collagen fibrils.^[31] Immunohistochemistry labelling has identified many biomarkers responsible for keratoconus.^[32] Several studies have observed an upregulation of many MMPs, such as MMP-14, MMP-1, MMP-7, and MMP-2, that cause degradation of fibronectin, membrane glycoprotein, and type I and II collagen.^[31]

Lysyl oxidase (LOX) belongs to the family of amino oxidases also known as lysine-6-oxidase, one of 5 LOX family members, located on chromosome 5q23.2.^[32,33] LOX oxidizes peptide lysine and hydroxyl lysine residues in collagen to peptidyl alpha amino adipic delta semialdehyde, which

Table 2: Genetic mutations involved in keratoconus

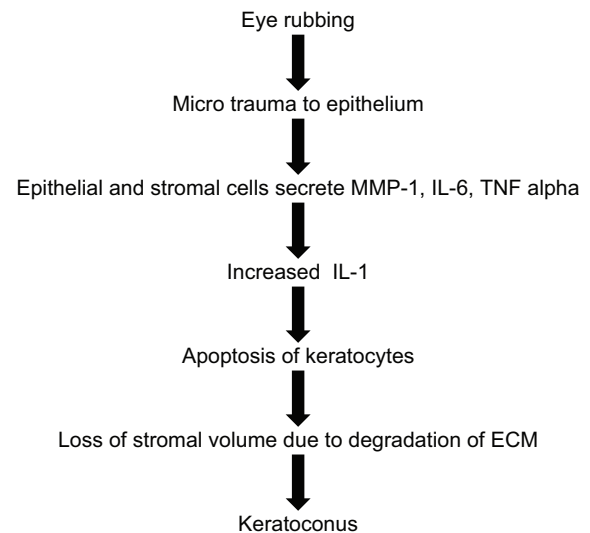
GENE	CHROMOSOME	VARIATIONS	DISEASES
SOD1 (Superoxide Dismutase 1)	21q22	7-base deletion intron-2	KC
ZNF469 (Zinc Finger Protein 469)	16q42	Frame shift mutations/Missense mutations	KC Brittle cornea syndrome type 1
PRMD5 (PR/SET Domain 5)	PR domain containing protein 5	Homozygous mutations linked with ZNF469	Brittle cornea syndrome type 2
TGFBI (Transforming Growth Factor Beta)	5q31 encodes big-h3	c. 1603G4T mutation located in exon12	Corneal dystrophies KC
DOCK9 (Dedicator of cytokinesis 9)	Located in 13q32 along with IPO5 (importin5, OMIM 602008) and STK24 (serine/threonine kinase 24, OMIM 604984)	Mutations	strong candidate gene for keratoconus
MiR184 (micro RNA)	13q32	mutations altering the miR1 (184) seed region	KC & congenital anterior polar cataract
VSX1 (Visual System Homeobox 1)	20p11-q11	Involved in keratocytes-fibroblastic transformation	KC

**Flow Chart 1: Genetic mechanism involved in Keratoconus**

spontaneously combines with vicinal peptidyl aldehydes and forms covalent cross linkages between collagen and elastin fibres.^[32] The lower expression of LOXmRNA is significantly associated with loss of cohesion between collagen fibrils and corneal ectasia.^[33] Copper deficiency has also been hypothesized to be associated with lower LOX activity that causes KC.^[34]

5. Oxidative Stress

The antioxidants protecting ocular tissues against damage are superoxide dismutase enzymes (SOD), low molecular weight antioxidants such as ascorbic acid, ferritin, glutathione, high molecular weight antioxidants, catalase, and glutathione peroxidase.^[35] The concept of oxidative stress has been related to KC with oxidative stress index

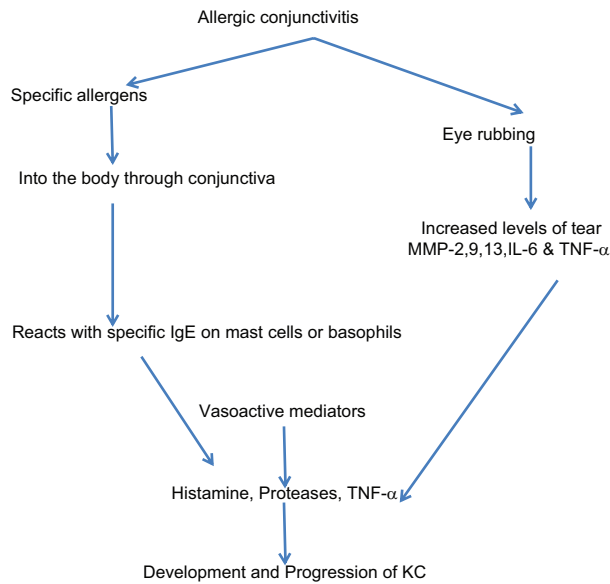
**Flow Chart 2: Pathogenesis of eye rubbing causing Keratoconus**

said to be an indicator for KC progression.^[35] The imbalance between the formation of free radicals and their removal by antioxidants results in the accumulation of aldehydes, peroxy-nitrites, causing the destruction of tissues. IL-1 that is released in tears following eye rubbing also inhibits the synthesis of SOD.^[36]

6. Role of Hormones

The role of sex hormones and thyroid hormones in the pathogenesis of KC has been supported by the following explanations.^[37-39]

- 1) Onset of disease at puberty following changes in hormonal levels
- 2) Progression of corneal ectasia during pregnancy
- 3) Presence of estrogen and progesterone receptors is high in children with vernal keratoconjunctivitis
- 4) Corneal hysteresis and corneal resistance factor measured with ocular response analyser has been noted to decrease during the different stages of menstrual cycles



Flow Chart 3: Pathogenesis of keratoconus in ocular allergies

- 5) Corneal thickness is found to be increased during ovulation
- 6) Higher levels of estrogen mRNA levels in tears
- 7) Reports of progressive KC after infertility treatment
- 8) T4 (Thyroxine) receptors are found in lacrimal gland. The T4 levels have been found to be elevated in tears of patients with KC.

Ocular and Systemic Associations

A number of ocular and systemic disorders are associated with pediatric keratoconus [Table 4].^[16,17]

Ocular associations

Various ocular associations with KC include, blue sclera, ectopia lentis, cataract, retinal detachment, retinitis pigmentosa, macular coloboma, Leber’s congenital amaurosis, aniridia, spring catarrh, and atopic keratoconjunctivitis.^[39]

Leber’s congenital amaurosis (LCA),^[40,41] shows a higher association with KC, the identified gene loci in LCA being 17p13. Other than genetic association, the oculo-digital sign or the Franceschetti sign comprising of eye poking, pressing, and rubbing is also responsible for KC development. The incidence of KC is high in the age group of 15–45 years (30%) as compared to children <14 years (2%) with LCA.^[42]

Systemic disorders

Among the genetic disorders, Down’s syndrome has the highest association with keratoconus, with reported incidence ranging from 0.5 to 15% (10–300 times more common than in the general population).^[43]

Multiple factors have been implicated in the pathogenesis of KC in Down’s syndrome such as genetic predisposition, dryness, blepharitis, persistent styes, infections, punctal agenesis, psychogenesis, mental stress, emotional stress, and blepharoptosis predisposing to eye rubbing and KC.^[42] Delay in the diagnosis of KC in Down syndrome children is due to the unnoticed change in vision by parents and due to the thin cornea due to which CXL could not be done.

Table 3: Tear biomarkers in Keratoconus

Protein	Expression
BY ELISA ANALYSIS	
IL-6	Increased
TNF-ALPHA	Increased
MMP-9	Increased
MMPs-1,3,7,13	Increased
IL-4,5,6,8	Increased
TNF-alpha, beta	Increased
SFRP1	Decreased
BY LCMS ANALYSIS (Liquid chromatography-tandem Mass spectrometry)	
SCGB2A1	Increased
MMP1	Increased
AZGP1	Decreased
LTF	Decreased
CYSTATINS	Decreased
LCN	Increased
AZGP1	Increased
PIP	Increased

Table 4: Ocular and Systemic conditions associated with paediatric KC

Ocular Conditions	Systemic Conditions
Atopy	Apert syndrome
Aniridia	Atopy
Blue sclera	Crouzon’s syndrome
Congenital cataracts	Down’s syndrome
Ectopia lentis	Ehlers Danlos Syndrome
Microcornea	False chordae tendinae
Leber’s congenital amaurosis	Leber’s congenital amaurosis
Retinitis pigmentosa	Marfan’s syndrome
Retinopathy of prematurity	Mitral valve prolapse
Vernal keratoconjunctivitis	Noonan’s syndrome
Fuchs dystrophy	Osteogenesis imperfecta
Posterior polymorphous dystrophy	Raynaud’s syndrome
	Syndactyly
	Xeroderma pigmentosa

Among connective tissue disorders the most commonly associated is Ehlers Danlos syndrome with KC patients displaying joint hypermobility in comparison to age-matched controls (12%).^[44,45] Mutations in COL5A1 or COL5A2, that codes for Type V collagen - α 1 and α -2, are responsible for ocular abnormalities (eyelid and conjunctival abnormalities, keratoglobus, corneal thinning, keratoconus, dry eyes, pathologic myopias, angiod streaks, retinal detachment, scleral atrophy, and globe perforation). Collagen V accounts for 10%–20% of the total collagen in cornea.

Histopathology

Histopathological abnormalities have been documented in every layer of the KC cornea.^[46] Immunohistochemical studies reveal characteristic histological findings such as thinned out epithelium with irregular loss of basal cells and presence of apoptotic cells over the cone. Breaks and fibrillations are seen in Bowman’s layer. Stroma shows altered orientation of collagen fibrils and loss of lamellae. Increased visibility of nerve fibers is due to corneal thinning. The architecture of sub basal nerve plexus are altered with fragmentations and

reduced density. Localized thickening of nerve fibers with wrapping of anterior keratocytes around the nerve is also a characteristic finding in KC. Keratocytes are fewer in number due to apoptosis. DM ruptures and folds are also seen in KC. Endothelium is normal, but may have intracellular dark structures, pleomorphism, and elongation of cells in few cases.

Clinical Concerns in Pediatric Keratoconus

Although KC in children differs from adults in few distinct clinical features, particularly time of presentation, rate of progression of the disease and treatment protocols, children share most of the common signs and symptoms of adult KC. The symptoms include, mild blurring of vision, which improves on squeezing of both eyelids to improve the precision of visual acuity, polyopia, distorted images and defective vision. Clinical signs of pediatric KC^[37] are tabulated [Table 5]. The difference of pediatric KC from adult onset KC is elaborated in Table 6.^[17,21,39] In contrast to adult KC, pediatric KC tends to present early, usually in the latter part of first decade of life, a positive family history, systemic syndromic association, ocular allergy and atopy with presence of significant eye rubbing, more significant rapid progression, and the presence of some amount of amblyopia resulting from the early onset of the disease causing visual deprivation, especially in cases with asymmetrical involvement or unilateral presentation.^[47] Sometimes acute corneal hydrops may be the presenting feature in children, with the KC going unnoticed earlier [Fig. 2]. Reliable clinical diagnostic testing also becomes a difficulty in pediatric cases. Pediatric keratoconus occurring in patients with severe allergic keratoconjunctivitis present with higher association of ocular co-morbidities such as corneal scarring [Fig. 3], steroid induced cataract and glaucoma.

Table 5: Clinical signs of keratoconus

Clinical sign of KC	Clinical Details
External signs	Munson's sign Rizzotti's sign
Slit lamp findings	Stromal thinning Posterior stress lines (Vogt's) Iron ring (Fleischer's ring) Epithelial/Sub epithelial scarring
Retroillumination signs	Scissoring reflex Oil droplet sign (Charleaux sign)
Photokeratoscopy signs	Compression of mires inferotemporally (Egg shaped) Compression of mires inferiorly and centrally
Videokeratoscopy signs	Localised increase in surface corneal power Inferior-superior asymmetry Skewing of steepest radial axes above and below horizontal meridian

Table 6: Differences between pediatric and adult keratoconus

Paediatric Keratoconus	Adult keratoconus
Diagnosis of PKC is late due to scarcity of symptoms	Adult onset KC presents earlier than PKC
The Progression of PKC is explosive in nature, because the biochemical rigidity is inversely proportional to age	The progression is slower and stabilises after third or fourth decade
PKC patients are commonly associated with systemic and ocular diseases	Comparatively lower incidence of systemic and ocular associations
PKC usually associated with 8.8% to 36% of VKC in KC	Adult KC is usually associated with hormonal disturbances
PKP in Advanced PKC has poor prognosis	Comparatively better prognosis

Blurring of vision and polyopia are due to the ocular aberrations caused by irregular astigmatism in KC. It is compensated by the natural anatomy, the physiological optics of internal ocular structures, and the high accommodative power in most of the children.^[48] Another hypothesis is that the irregular astigmatism is less due to centrally placed cone in children. Late presentation with corneal scarring requires early corneal transplantation.^[49] The rate of progression of ectasia tends to be more aggressive in children compared to adult due to higher rate of corneal collagen remodelling and associated ocular allergies.^[50] They are also at high risk of developing acute hydrops probably due to eye rubbing.

Progressive KC is defined by an increase of one or more dioptre of K-max over a period of 12 months.^[51] The association of VKC, atopy, and eye rubbing in children are the risk factors for rapid progression.^[20,21] Control of allergies with topical medications and early diagnosis of KC with topography is challenging in them. Topography imaging in children is challenging with poor repeatability of the testing, poor cooperation, and ability to focus, with decentration and shadows negatively affecting the image capture. Children with ocular allergy are also poor candidates for reliable topography imaging on serial follow-ups. Apart from ocular allergy, associated co-morbidities such as secondary glaucoma and cataract are to be managed. Counselling and education of the parents for a long-term follow-up, control of allergy with regular medications, and avoidance of eye rubbing remain crucial in successful rehabilitation of pediatric KC patients.

The Corneal Ectasia preferred Practice Pattern and the Pediatric Eye Evaluations Preferred Practice pattern of AAO recommend early screening and treatment in pediatric patients due to poor visual outcomes of unmanaged KC.^[3,52]

Mass screening for KC is recommended for children with the following risk factors, for early diagnosis and treatment:

- Allergic eye disease
- Children living in high altitude/high UV exposure
- Geographic areas with high incidence of KC
- Children with Down's syndrome
- Family history of KC
- School children with myopia and myopic astigmatism.

The screening tools include retinoscopy, VKG, corneal tomography, wave-front aberrometers, ocular response analyzer, and ASOCT.

Differential diagnosis

Keratoconus has to be distinguished from other ectatic disorders such as pellucid marginal corneal degeneration disorder (PMCD), Terrein marginal corneal degeneration (TMCD), Brittle cornea syndrome and keratoglobus (KG).^[53] PMCD and TMCD are

common adult onset ectatic disorders, rarely occurring in children and present with distinct clinical features. KG is a congenital true ectatic disorder of cornea that needs to be differentiated from pediatric KC, since management and prognosis is different in both these conditions [Table 7].^[51] Brittle cornea syndrome (BCS) is a rare autosomal recessive disorder characterized by deafness, joint hypermobility, and ocular features such as extreme corneal thinning, blue sclera, keratoconus, keratoglobus, and high myopia usually presents with recurrent spontaneous perforations [Fig. 4]. It is imperative to identify this condition early and manage with protective spectacles to prevent irreversible blindness.^[54]

Management Protocol

Management of pediatric keratoconus centres on visual rehabilitation with contact lenses, rigid gas permeable in early cases, and multicurve contact lenses in moderate cases and corneo-scleral/scleral contact lenses in advanced cases. Spectacle correction often does not give best results except in early cases

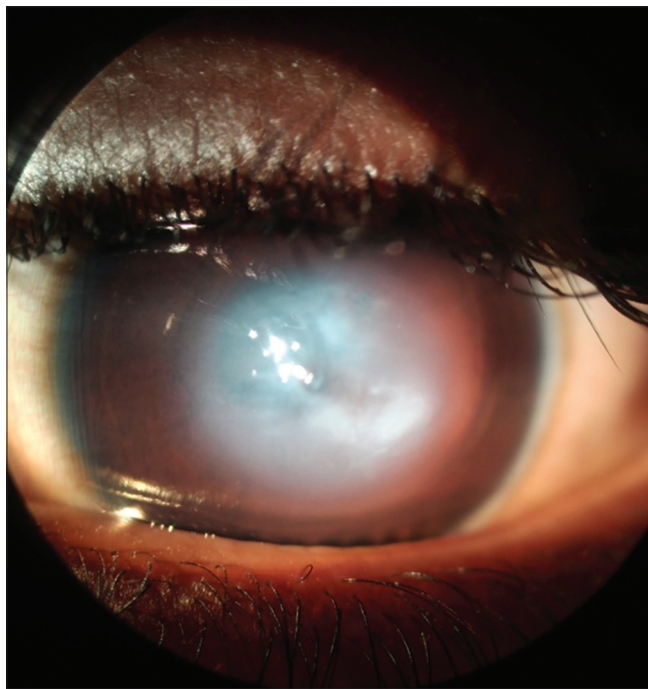


Figure 2: Acute hydrops in a case of pediatric keratoconus

due to the irregular astigmatism. Treatment advice should highlight the importance of avoidance of eye rubbing, continued topical antiallergic therapy (in indicated cases), and frequent follow-up for topographic imaging to monitor progress. In pediatric keratoconus, several physicians prefer to offer early collagen crosslinking therapy in view of the aggressive nature of the disease.^[55] There needs to be a cautious approach in view of the post crosslinking concerns related to sterile infiltrates and infectious keratitis in pediatric KC cases. Active ocular allergy needs to be well controlled before considering crosslinking treatment in pediatric KC cases associated with allergic keratoconjunctivitis. Early surgical intervention may be essential in cases with advance ectasia and incompatibility to contact lens rehabilitation due to ocular allergy.

Collagen crosslinking

Collagen crosslinking (CXL) is a technique that uses ultraviolet A (UV-A) light and riboflavin (photosensitizer, vitamin B2). The goal of therapeutic collagen cross-linking treatment of the cornea increases the biomechanical rigidity of the cornea and arrests the progression of the ectasia.

Riboflavin is non-toxic, precursor of various co-enzymes, that increases the absorption of UV-A by the corneal stroma [Table 8]. When exposed to UV-A the resulting excitation of riboflavin generates reactive oxygen such as singlet oxygen and superoxide anions. These react with available groups with the generation of additional chemical bonds between amino acid residues.^[56,57] This increases cross-linking between proteoglycans and collagen^[54] with the resultant photopolymerization of collagen fibrils improving biomechanical properties. Both Young’s modulus and corneal rigidity increase after collagen cross-linking.^[56]

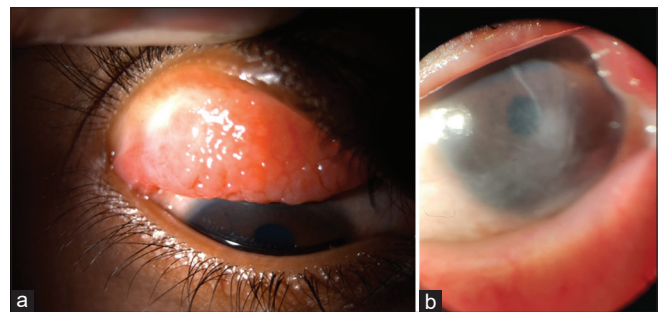


Figure 3: Clinical picture of GPC (a) and corneal opacity (b) in two different cases of pediatric keratoconus with vernal keratoconjunctivitis

Table 7: Differences between keratoglobus and keratoconus

Keratoglobus (KG)	Keratoconus (KC)
Entire cornea is thinned out in KG	Central and paracentral thinning occurs in KC
Bilateral, presents since birth	Bilateral or Unilateral, presents at any age after birth usually in second or third decade
Non- Progressive disorder	Progressive condition
No association with Down’s syndrome commonly	KC is common in Down’s syndrome children (incidence is 5.5% - 15%)
Associated with autosomal recessive pattern of inheritance	Usually isolated condition
Prone for rupture following trivial trauma	Corneal rupture is uncommon in KC
Optical rehabilitation with glasses is usually indicated in KG	Contact lens rehabilitation can be offered for visual rehabilitation in KC patients
Keratoplasty carries poor prognosis due to proximity of limbus. Recommended surgical techniques such as Tuck-in lamellar keratoplasty (TILK) are more demanding	Keratoplasty and DALK procedures carry the good prognosis in advanced cases

Histopathologically, there is an increase in the diameter of the collagen fibrils.

The original protocol was based on the removal of epithelium followed by the application of riboflavin and then ultraviolet light in a sequential manner (Dresden protocol).^[57] Long-term stabilization of KC in the “epi-off” procedure is well-documented both in adult & pediatric KC.^[57] However, the alternate method of achieving the same result without the removal of the epithelium; the “epi-on” technique, cites potential advantages such as reduced post-operative pain, reduced risk of infection, and the potential to perform the procedure as an outpatient technique. Moreover, de-epithelialization has potential risks such as corneal haze, 2.8%^[57] ulceration, infection, reactivation of herpes keratitis, and sterile infiltrates.

However, there exist many pertinent issues regarding the efficacy of epi-on cross-linking. The epithelial barrier function restricts the entry of substances with a molar mass greater than 100 g/mole. Riboflavin has a molar mass of 376 g/mole. It cannot penetrate the tight junctions of the epithelium. Moreover, while riboflavin is hydrophilic the epithelium is lipophilic. The riboflavin in the epithelium can also absorb the UV-A, thus decreasing the actual UV-A power within the stroma. The concentration of riboflavin is therefore uneven in the stroma. Oxygen is an important component of the crosslinking process and an intact epithelium restricts the entry of oxygen. In the epi-on procedure, 0.1% riboflavin in 15% dextran solution is supplemented with trometamol and EDTA (Ricrolin-TE), whereas in the epi-off procedure iso-osmolar 0.1% solution (10 mg riboflavin-5-phosphate in 20% dextran) (Ricrolin; Sooft, Montegiorgio, Italy) is used. In both procedures, riboflavin loading is done for 30 minutes followed by the application of UVA 370 nm at 3 mW/cm² for 30 minutes.^[58-61]

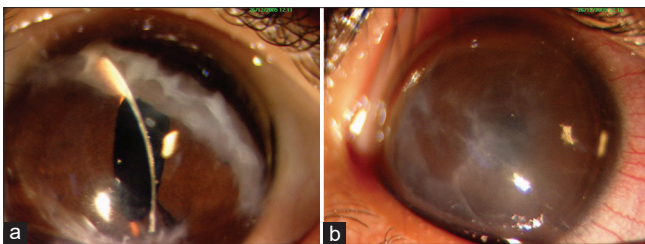


Figure 4: Slit lamp photograph of a case of Brittle cornea syndrome bilateral keratoglobus with multiple repaired corneal tears (a) and healed hydrops (b)

A number of studies have documented the efficacy of epi-off in pediatric KC. On follow-up of 77^[58] and 152^[59] patients (10 – 18 years) for a period of 36 and 48 months, respectively (Siena protocol) in two studies, Caporossi *et al.* noted visual improvement in 80% of patients and^[58] 90% stabilization achieved in four years. Zotta *et al.*'s long-term results of 20 eyes of (14.34 ± 2.14 years) followed for a period of 89 months noted that K1, K2 and the topographic cylinder remained stable at 7.5 years.^[62] Vinciguerra *et al.*^[63] in a prospective, interventional study of 40 patients (mean age 14.2 ± 1.7 years) over two years follow-up noted that the significant improvement in both UDVA and CDVA with both K1 and K2 decreasing with the reduction in K-max being more significant. Significant reduction in total, corneal, higher-order, and astigmatic wave-front aberrations were also observed. The epi-off procedure also seems to be effective in steep corneas. In a study of 43 pediatric patients, 25 eyes having K-max values of 60 dioptres (D) or greater showed significant K-max reduction from 64.94 ± 4.99D to 62.25 ± 4.42D at 2 years follow-up.^[64]

Variable results of transepithelial collagen cross-linking for pediatric KC has been reported. Caporossi *et al.* noted the stability in 24 patients who underwent transepithelial crosslinking (TE-CXL) to last only for a year.^[65] In contrast, Salman's excellent results over a 12-month period with reduction in K-max of 2.3D and flattening of the anterior elevation as well as the increased stability of the cornea^[66] prompted him to recommend epi-on procedure in the pediatric age group. Buzzonetti in a study of efficacy of TE-CXL in the pediatric age group (mean age 14.4 ± 3.7 years) spanning 18 months noted worsening of K-max showing that it does not effectively halt the KC progression compared to standard CXL.^[67]

The general consensus is that the epi-on procedure is of doubtful; it does not appear to stop the progression of KC. The procedure may be considered in uncooperative patients and when pachymetry values are less than 400 microns. However, given some of the stated advantages, efforts have been made to improve the penetration of riboflavin by various innovations such cross-hatched grid pattern for epithelial debridement, benzalkonium (BAK), and benzoate application, iontophoresis, contact lens-assisted crosslinking etc., Not much work has been done in these areas in the pediatric population. BAK-assisted TE-CXL has been reported by Koppen *et al.*^[68] in the pediatric age group with significant improvement in CDVA at six and 12 months in progressive, but observed progression of K-max throughout the study.

Recently, accelerated cross-linking is been accepted worldwide to shorten surgical time. For pediatric KC, accelerated

Table 8: Collagen Crosslinking Protocols

Procedure	Riboflavin Concentration	Riboflavin saturation	UV-A application	Fluence
Standard Dresden Protocol	Iso osmolar 0.1% solution (10 mg riboflavin-5-phosphate in 20% dextran) Ricrolin	30 mins (every 2 min for 30 mins)	30 mins riboflavin (every 2 mins for 30 mins)	3 mw/cm ² 5.4 J/cm ²
Accelerated protocols epi-off	Ricrolin	10-30 mins every 2 mins	30 mw/cm ² , 3 mins	5.4 J/cm ²
Trans epithelial	0.1% riboflavin in 15% dextran with trometamol (Ricrolin+)	10 mins	30 mins	3 mw/cm
Transepithelial iontophoresis assisted CXL	0.1% riboflavin, no dextran, trometamol, EDTA	10 mins	30 mins	3 mw/cm
Hypotonic	0.5% riboflavin No dextran	30 mins	30 mins	3 mw/cm

CXL is not much effective with increase in K-max and posterior elevation values noted at 36 months post procedure.^[69]

Soeters *et al.* has observed that in pediatric KC, thinner corneas ≤ 450 microns and centrally located cones responded better to cross-linking treatment.^[69] However, it is almost imperative to note that the longest period of follow-up available in this age group is 7.5 years. Stability has been noted but there were no changes in the keratometry values.^[70] However, a number of studies document corneal steepening noted to begin three years after the procedure.^[12] An indirect extrapolation as to the efficacy of cross linking can be made from the fact that the number of transplants for KC is decreasing as evidenced by data from transplant registers. Italy's Corneal Transplant Epidemiological Study noted a 27-percent reduction in corneal grafting for keratoconus over a six-year period starting from 2002.^[71] Caporossi *et al.*'s observed the need for re-epi-off treatment to manage progression in 50% of children who had epi-on CXL earlier^[72] points towards the need for robust follow-up post cross-linking. Reports of retreatments both in the adult and pediatric population are scarce.

VKC with KC is a relative contraindication for CXL. It would be advisable to control the allergic process before cross-linking. Nonhealing epithelial defects and predisposition to infection are more likely, if uncontrolled. Currently, standard CXL is advised if the corneal thickness is more than 400 microns and the hypotonic variant, if the pachymetry is at least 360 microns.

It is evident that a large number of protocols and options exist for cross-linking. Collagen cross-linking with hypo-osmolar riboflavin is reportedly successful in children but long-term data is lacking. Future directions in cross-linking in pediatric KC would be directed toward establishing the safety and efficacy of current protocols, and the relevance of protocols such as epi-off pulsed accelerated crosslinking, where higher irradiation applied in on-off mode would not only shorten treatment times but would obtain comparable efficacy as the standard Dresden protocol.^[56,57] To summarize, the current consensus is that KC progresses much faster in children and therefore the procedure can be offered as soon as progression is documented to obviate the need for transplantation.

Concerns in surgical interventions in pediatric keratoconus

In cases where contact lens wear is not possible due to ocular allergy, and in advanced ectasia, surgical intervention is recommended. KC progresses rapidly in children (88%) compared to adults (8%).^[11,12,73] KC is the most common acquired nontraumatic indication of 23%–67% of pediatric keratoplasty.^[73] In Indian children with acquired nontraumatic causes, requiring penetrating keratoplasty, KC (37%) follows postinfectious keratitis adherent leukoma (63%) as the leading indications for surgery.^[74] However, a recent study from Eastern China^[75] noted KC (67.2%) to be the most common indication for pediatric keratoplasty.

There are very few studies that have reported the use of ICRS for pediatric KC. ICRS, although safe and effective in children with poor visual acuity, it does not seem to be preferred in pediatric cases with VKC due to the risk of aggressive nature of the disease, tendency for eye rubbing and risk of extrusion.^[73]

Improvement in refractive and visual outcomes following four years of ICRS and CXL, which has been done one month apart, has been reported.^[76] Kera ring implantation with accelerated CXL using femto-laser for tunnel creation,

showed increased visual outcomes in 42.9% of children.^[77] Complications include extrusion and migration of the device, infections, and KC progression.^[77]

Penetrating keratoplasty (PK) [Fig. 5a] can be challenging in children due to low scleral rigidity and increased vitreous positive pressure. However, well-controlled general anesthesia, low intraocular pressure by massage and intravenous mannitol, and use of Flieringa scleral ring can render the surgery safer.^[78] Same sized grafts are preferred in PK or DALK in children. Rapid wound healing causes early suture loosening which mandates suture replacements or removal. Hence, 10.0' nylon interrupted sutures are to be performed.^[77-79]

Deep anterior lamellar keratoplasty (DALK) [Fig. 5b] has become the preferred procedure of choice because of better structural stability and less immune rejection.^[80] DALK can be performed with mechanical trephining or as Femtosecond laser-assisted procedure.^[80,81] The stromal dissection can be done by manual method up to the pre-Descemet's layer as in pre-Descemetic DALK (pd-DALK) or by barring Descemet's membrane (DM) (d-DALK) either by air (Anwar's big bubble technique), hydro, or visco dissection.^[82,83] DALK is technically challenging, and intraoperative DM perforation can lead to a double anterior chamber and interface problems such as infection or vascularization with poor visual outcome and graft failure. Conversion to PK may also be required.^[84]

The reported success rate with big bubble range was around 75% to 80% in KC corneas that underwent DALK in children.^[84,85] Feizi *et al.*^[85] had done successful big bubble in 75% of the eyes and the rest were pd-DALK. DM perforation was noted in 11.4% (5 eyes) of DALK procedure, either while air injection or deep stromal dissection. Urretts Zavalia Syndrome (UZS) is a well-recognized but rare postoperative complication following keratoplasty for KC patients. The low rigidity and intrinsic abnormality of keratoconic eyes allows the occlusion of vessels at the root of the iris within the sclera during surgery.^[86] Feizi *et al.*^[85] reported UZS in 2.3% (one eye) of pediatric DALK maintained clear graft with BCVA 20/30 after appropriate management. Arora *et al.* attempted big bubble DALK in 20 eyes of 16 patients (mean age of 14.4 years) with advanced keratoconus.^[87]

Another common concern that is frequently faced in eyes with ocular allergy that undergo PK or DALK is the predisposition for a significantly rapid suture loosening which tends to recur despite repeated suture replacements [Fig. 6]. This necessitates earlier suture removal or the resultant focal thinning at this graft host junction region of repeated affliction causing a higher postoperative astigmatism. It is imperative to ensure that the ocular surface allergy is well controlled before considering surgical intervention in cases of KC with VKC.

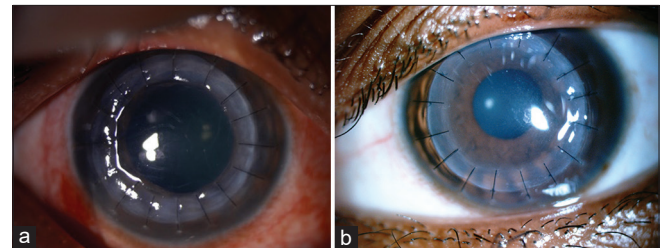


Figure 5: Postoperative clinical picture of penetrating keratoplasty (a) and deep anterior lamellar keratoplasty (b) in pediatric keratoconus cases

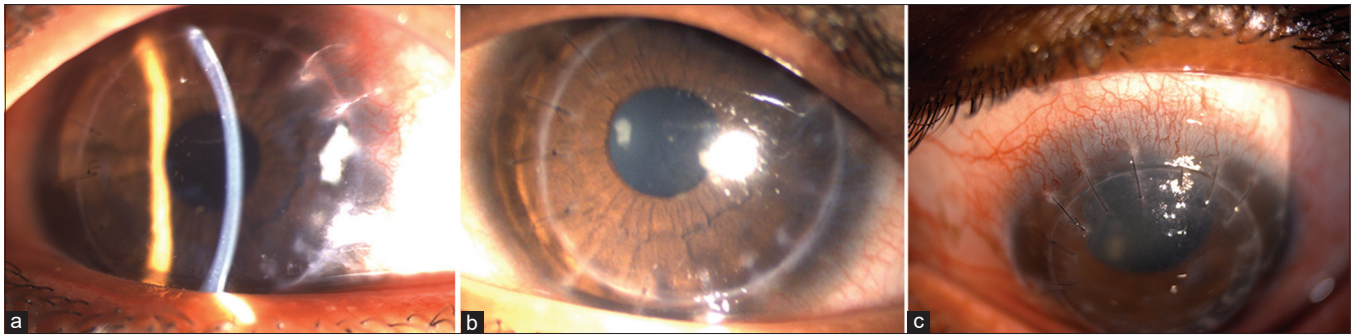


Figure 6: Slit lamp photograph of post-DALK (at 3 months postoperative period) in a pediatric patient of VKC with keratoconus showing early suture loosening (a) [(note that differential wound healing had necessitated prior removal of few sutures (b)); a different case of DALK in pediatric keratoconus with loose sutures (c)]

Postoperative management for monitoring and repeated examinations to assess wound healing, intraocular pressure, posterior segment, and to manage suture related concerns needs general anaesthesia in children. Traumatic graft dehiscence, immune graft rejection [Fig. 7], secondary glaucoma, or cataract due to long term steroid use, are also expected to have a higher occurrence in pediatric cases. Topical steroids are needed to control inflammatory reaction, which are to be tapered and replaced with low potency steroids by 3-6 months. Steroid sparing immune-modulators like cyclosporine A 2%, are ideal for long term use to address immune graft rejection. Early suture removal and refractive correction is also needed to achieve optimum visual rehabilitation. Teaching the children as well as parents or caretakers to strictly follow the postoperative regimen, follow-up visits, and to use protective eye gears are imperative.^[79-82,88]

Patel *et al.* noted a significant visual improvement with BCVA equal to or better than 0.3 Log MAR in 86.4% of their PK cases of mean age 10.6 years \pm 4.3 years (range: 2 weeks to 14 years) in 65 pediatric patients, at the final examination.^[89] McClellan *et al.* also reported visual acuity better than 6/12 at the last follow-up in pediatric KC eyes that underwent PK.^[90] In their comparison of big bubble (BB) DALK to pd-DALK, though Feizi *et al.*^[82] noted postoperative BCVA was better in the BB-DALK subgroup, the difference was not found to be significant. In cases where big bubble is not achievable after several air injections, the surgical technique conversion to pd-DALK will be safe given the comparable postoperative visual and refractive outcomes.^[90,91] Ashar *et al.*^[81] reported that 75% of their DALK grafts performed for keratoconus were clear in with a visual acuity of > 20/80 which is comparable to PK for KC in children.

Buzzonetti *et al.* compared refractive outcome at 2 years follow-up post DALK by mechanical trephine and femtosecond laser assisted procedure in KC children (mean age 11.2 \pm 2.2 years; range: 8-16 years), with standardized suturing technique and suture removal protocol.^[92] The corrected distance visual acuity and manifest astigmatism were comparable in both groups, whereas spherical equivalent was statistically less in laser-assisted DALK. Better host-donor matching and interlocking in fs-DALK perhaps enable superior refractive outcome in DALK cases.^[92]

VKC, despite being quiescent at the time of keratoplasty, can complicate the postoperative course by causing graft epithelial problems, vascularization, graft opacification, and rejection leading to graft failure.^[85] Feizi *et al.* have reported graft epitheliopathy and superficial punctate keratitis in 3 out of 44 eyes in their series.^[85] Arora *et al.* observed reactivation of

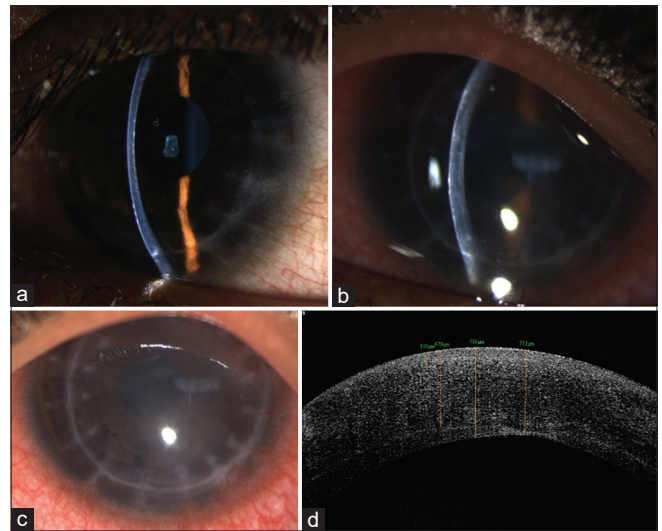


Figure 7: Slit lamp photograph of DALK of a case of pediatric keratoconus (a) showing increased stromal edema (b), corneal haze (c) due to stromal graft rejection; (d) ASOCT picture of the same eye showing the increased stromal thickness due to edema as a result of immune rejection

VKC and appearance of shield ulcers in two of their patients resulting in subsequent graft opacification.^[87] This importance of optimal medical management of VKC before surgery and prompt initiation of treatment of any inflammation after surgery needs to be greatly emphasized in pediatric KC.

Among all other indications for pediatric keratoplasty, KC carries the best prognosis for long-term graft survival. Older studies reporting results in a series of 164 pediatric PK (mean age at diagnosis - 30 months), noted a good survival rate of 80%, with grafts performed for KC being the most successful in terms of survival.^[92] Similar results with keratoplasty performed for KC showing excellent prognosis with a reported 1-year survival rate of 90% by Patel *et al.* in their series of 58 eyes (mean age 10.6 \pm 4.3 years; range 2 weeks - 14 years) from New Zealand.^[89] Gulias-Cañizo *et al.* found in their recent retrospective review of a large series of 574 pediatric keratoplasties, KC showed the best graft survival at 60-months follow-up of 85%, as compared to other indications.^[93] The Australian Registry Study on corneal transplantation in KC in all age groups observed significantly better outcomes with the first PK for KC to have a significantly better survival of 89% at 10 years in comparison to 49% at 20 years.^[92]

Graft rejection remains the most important cause for graft failure in keratoplasty for keratoconus, especially in PK. In bilateral transplants, there is no increased risk of graft rejection, when the second eye was grafted after 1 year.^[25] Long-term graft survival beyond 23 years cannot be assured and in pediatric eyes requiring surgery, there still exists the need for more than one graft in lifetime.^[94] Pediatric DALK can also experience subepithelial and stromal graft rejection. Early recognition is imperative to initiate prompt therapy in order to salvage the graft and vision in these children.

Feizi *et al.* observed subepithelial graft rejection in 5 out of 44 eyes that underwent DALK (11.36%) at a mean interval of 7.6 ± 2.5 months (range 6–12 months) in 9.1% of eyes, which was successfully treated with topical corticosteroids in 3–6 weeks.^[85] Arora *et al.* observed 1 patient who developed stromal rejection 3 months after surgery.^[87] Elbaz *et al.* noted stromal rejection in 5 eyes (9.8%) of which four eyes responded completely to topical steroids and one graft failed.^[84]

Buzzonetti *et al.*'s analysis of graft survival and difference in graft failure between PK and DALK in children below and above 5 years age observed 78% graft failure in the younger children (below 5 years of age) and 31% in the older children.^[92] Though lesser overall graft failure was seen in DALK compared to PK, there was no statistically significant difference between the younger and older children but the DALK eyes showed a statistically significant longer survival time than PK eyes (588 vs. 406 mean days).^[92,95,96]

With reported incidence of glaucoma in pediatric keratoplasties being as high as 25%,^[28] but Feizi *et al.*^[85] noted transiently elevated IOP in 18.2% post DALK for keratoconus eyes which responded well to the treatment of reduction of steroids and anti-glaucoma medications. The addition of topical cyclosporine can help reduce the long-term corticosteroid use required to alleviate graft rejection in children.^[97] The Urret-Zavalía syndrome can occur, especially after DALK, with the prolonged anterior chamber filling with a tight air bubble, as with cases of long drawn of anterior lamellar dissection as in BB-DALK^[93] or after tight pneumopexy for DM perforation.^[82] Though the exact pathogenesis is not clear, pressure-induced ischemic necrosis is postulated to cause dilated and fixed pupil, iris atrophy, and even cataract.

Children are more prone to traumatic graft host dehiscence due to their higher physical activities where, in cases of PK, the entire anterior segment can be compromised as compared to DALK. Posttraumatic graft host dehiscence was reported in 4.8% post DALK eyes by Feizi *et al.*^[85]

While keratoplasty for KC in children has become a much safer procedure than before, enabling an excellent anatomical and functional outcome in pediatric eyes, concerns do remain to be addressed for enhancing prognosis. DALK is preferable to penetrating keratoplasty because of better structural stability, preservation of host endothelium, and lesser rejection rates.

Conclusion

Pediatric keratoconus can present at an advanced stage, faster progression and associated ocular co-morbidities. Need for timely intervention to stop progression with collagen crosslinking therapy, optimal visual rehabilitation, management of associated ocular comorbidities is imperative. Optimal decision making in management of keratoconus involves a thorough knowledge of the clinical challenges that

can occur during the course of treatment of this ectactic corneal condition.

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Conflicts of interest

There are no conflicts of interest.

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