Keratoconus in Children

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Keratoconus typically has its onset at puberty and progresses until the third to fourth decade of life, when it usually stabilizes [1]. Although it is a relatively rare disease at the age of 10 years, in pediatric patients keratoconus is often more advanced at diagnosis [2] and its progression may be more frequent and more rapid with a sevenfold higher risk of requiring corneal grafting [3]. Childhood onset cases have a more aggressive progression than those of later onset [4]; therefore, detection of progressive keratoconus in early stages of the disease is necessary to prevent severe visual impairment [5, 6].

Some authors report that young age is associated with more severe forms of keratoconus and faster progression, with an inverse correlation between age and severity [7, 8]. After congenital corneal opacities, keratoconus represents one of the most common causes of pediatric corneal transplantation causing about 15–20 % of all corneal transplants in children [9, 10]. A retrospective monocentric study confirms that at diagnosis keratoconus is more severe in children than in adults, and the age of the youngest child included in the study was 6 years [5]. The diagnosis of pediatric keratoconus is often made late. It depends on the scarcity of functional complaints in children, especially before the age of 8. Furthermore, it is supposed that progression of keratoconus is "explosive" in these patients (Fig. 5.1), with a short time between the onset of functional symptoms and the development of a severe form of keratoconus [11]. The late diagnosis predisposes children to serious complications including corneal perforation, microbial keratitis, glaucoma, and amblyopia.

As reported in the literature keratoconus can be associated with systemic and ocular diseases [12, 13]. In children these associations are typical and include Down's syndrome, atopy, Ehlers–Danlos syndrome, Marfan syndrome, mitral valve prolapse, Arterial Tortuosity Syndrome, Laurence–Moon–Biedl Syndrome, Costello Syndrome, Intellectual Disability. Ocular conditions include vernal keratoconjunctivitis (VKC), Leber congenital amaurosis (LCA), retinitis pigmentosa, aniridia, iridocorneal endothelial syndrome, blue sclera, corneal dystrophies such as granular and macular dystrophy, posterior polymorphous dystrophy, fleck dystrophy, Fuchs endothelial dystrophy, and lattice-granular dystrophy.

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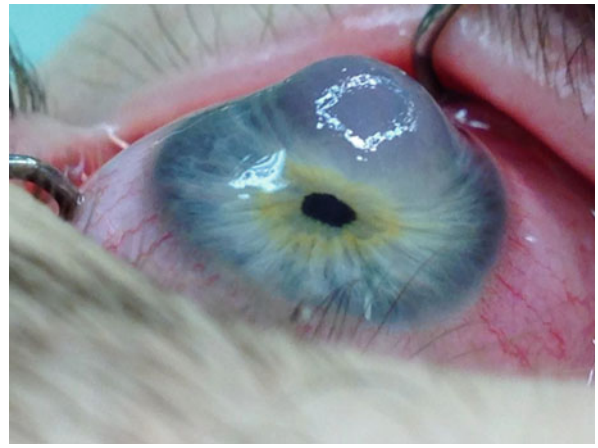

Fig. 5.1 Acute keratoconus in a 13-year-old patient

The incidence of keratoconus in patients with Down's syndrome has been reported in up to 15 % [1]. The eye rubbing, frequently observed in patients with Down's syndrome, represents one of the main pathogenetic hypothesis of keratoconus [14, 15].

Howard et al. [16] described a case of hyperthyroidism and acute hydrop secondary to underlying keratoconus in a child with trisomy 21, and they hypothesized that thyroid gland dysfunction may be associated with the development of keratoconus.

Many studies have discussed on the probably association of atopy with keratoconus [17, 18]. Copman and Gasset reported that the prevalence of eczema and asthma was higher in keratoconus patients than in control group [19, 20].

In children with keratoconus, percentage of patients with VKC ranged from 8.8 to 36 % [21]. The literature has reported that changes in corneal topography are more severe and faster in pediatric patients with keratoconus and VKC than keratoconus alone, and the progression of keratoconus in atopy takes place more rapidly [18, 22, 23]. It is of note that allergic keratoconjunctivitis with eye rubbing may increase the incidence of corneal hydrops in children with keratoconus.

In children with keratoconus the association with LCA has been documented in some reports. The incidence of keratoconus has been noted in 29 % of children with LCA and 2 % of all children with blindness. Keratoconus in patients with LCA occurred in 2 % of 0- to 14-year-olds and it is absent prior to 9 years of age and its incidence increases with increasing age [24]. There is no definitive consensus about the origin of keratoconus in patients with LCA. A working hypothesis suggests that keratoconus could result from the repetitive trauma to the cornea secondary to the characteristic extraocular sign of Franceschetti's oculodigital sign in LCA patients, comprising three components: eye poking, pressing, and rubbing [25].

5.1 Treatment

Corneal cross-linking (CXL) is actually the standard, low-invasive, safe treatment for patients affected by keratoconus [26, 27], with documented clinical progression or perceived risk of progression. Since younger patients usually show a fast progression of keratoconus [5], cross-linking in children and adolescents is actually indicated as soon as the diagnosis has been made [6].

Few authors reported clinical outcomes after CXL in pediatric patients affected by keratoconus. Caporossi et al. [4] published the largest study on pediatric CXL. This prospective study of 152 eyes of 77 patients 18 years old and under (range 10–18 years) treated by Epi-off CXL, at 36 month follow-up showed improvement in best corrected visual acuity (BCVA), *K* readings, asymmetry index values, and coma values. The authors then suggested that riboflavin-UVA-induced cross-linking stabilized

the progression of keratoconus in all cases and led to functional improvement in 80 % of cases, with statistically significant results.

However, some are the considerations related to Epi-off technique in children: the severe pain induced by epithelial debridement and the consequent temporary visual loss that usually make postoperative management more complicated, the risk of postoperative complications (stromal haze [28] and infections [29]), and the variable period of visual recovery (2–6 months) [26, 30, 31].

Therefore, CXL performed without epithelial removal and by shortening the surgical time could represent a great advantage in children, providing local anesthesia and making the cross-linking treatment and its follow-up management more comfortable. In fact the preservation of the epithelial layer could avoid postoperative pain and visual impairment, as well as all complications related to epithelial debridement.

Recently, it has been proposed a new transepithelial CXL technique in which a iontophoresis system provides riboflavin delivery in corneal stroma [30, 31]. Iontophoresis is a noninvasive delivery system designed to enhance the penetration of molecules as well as riboflavin into tissue using a small electric current.

We published the first clinical study on transepithelial CXL by iontophoresis of riboflavin in pediatric patients [32]. We evaluated visual acuity, and refractive and corneal aberrometric changes through 15-month follow-up in 14 eyes of 14 pediatric patients (mean age 13 ± 2.4 [SD] years; range, 10–18 years) affected by keratoconus (stage 1 or 2 according to Amsler-Krumeich classification). In opposite to previous reports on transepithelial technique in pediatric eyes [33, 34], we did not report keratoconus progression over 15 months; furthermore, we did not observe an improvement in refractive, topographic, and aberrometric parameters, excepting for BCVA.

Our unpublished data at 24-month follow-up, recorded in 27 eyes of 17 patients (mean age 14 ± 2.5), seem to confirm the same "trend" (Tables 5.1 and 5.2).

These early findings suggest that iontophoresis-assisted transepithelial CXL performed by means of riboflavin delivery could halt the keratoconus progression in pediatric patients up to 24 months. For sure longest follow-ups need to indicate if this technique could really become an alternative to Epi-off one, currently still considered the "gold standard."

Table 5.1 Corrected distance visual acuity, manifest spherical equivalent, and refractive astigmatism measured preoperatively and 24 months after cross-linking (27 eyes, 17 patients, mean age 14 ± 2.5)

	Preoperative	24 months postoperative
CDVA	7.5 ± 1.8	8.1 ± 2.1 (P = 0.1)
Spherical equivalent (D)	−1.5 ± 1.6	−1.7 ± 2.0 (P = 0.5)
Refractive astigmatism (D)	−1.4 ± 1.9	−1.3 ± 1.3 (P = 0.8)

CDVA corrected distance visual acuity, *D* diopters

Table 5.2 Topographic and tomographic data measured preoperatively and 24 months after cross-linking

	Preoperative	24 months postoperative
K_{max} (D)	47.9 ± 3.2	48.6 ± 3.6 (P = 0.06)
K_{min} (D)	43.1 ± 9.0	43.6 ± 9.2 (P = 0.07)
K_{avg} (D)	44.5 ± 9.2	47.0 ± 9.3 (P = 0.2)
Posterior elevation map (μ)	17.96 ± 28.5	16.81 ± 21.5 (P = 0.77)

D diopters, μ micron

Intracorneal ring segments (ICRS) have been demonstrated to be effective in improving visual acuity and reducing the refractive error and the mean keratometry in selected cases of keratoconic eyes of adult patients [35, 36]. However, up to now poor is the experience about ICRS implantation in pediatric patients. Estrada et al. [37] reported the outcomes of ICRS in the surgical correction of different levels of severity of keratoconus obtained in a large multicenter series of cases: 611 consecutive keratoconic eyes of 357 patients ranging in age from 10 to 73 years (mean age: 35.15 ± 11.62 years), but they did not separately analyze pediatric patients. Generally, ICRS are not preferred in the pediatric patients for aggressive nature of keratoconus, tendency of

eye rubbing, and noncompliance. Kankariya et al. [38] observed that although the option of ICRS (less invasive) is not commonly utilized in pediatric eyes, in adolescent patients with end-stage keratoconus and imminent keratoplasty (more invasive), this option may be worth considering.

Pediatric keratoplasty still represents a very challenging surgery, generally performed when corneal opacification induces a visual deprivation [39]. The Penetrating Keratoplasty (PK), actually the "gold standard" in pediatric keratoplasty, has shown a prognosis for graft survival of approximately 50–60 % [40, 41], mainly because of endothelial rejection [42, 43]. Deep anterior lamellar keratoplasty (DALK) diffusion is currently limited in pediatric patients and few papers report outcomes after big-bubble DALK in children. Harding et al. [44] treated 13 eyes of 9 pediatric patients affected by partial thickness corneal scarring and mucopolysaccharidoses performing DALK with manual dissection, except for one eye that underwent big-bubble DALK with conversion to PK because of an intraoperative inadvertent perforation. Ashar et al. [45] observed that DALK is a feasible option in children with stromal corneal pathology. The authors evaluated 26 eyes: three underwent big-bubble procedure, while 23 layer-by-layer dissection.

Recently, the femtosecond solid-state laser was successfully used in several corneal surgical procedures and Buzzonetti et al. [46] proposed a standardized big-bubble technique in DALK assisted by femtosecond laser called Intrabubble. The laser provides a pre-Descemet's plane lamellar dissection to a predefined corneal depth and the creation of a stromal channel, 50 μm above the thinnest corneal point, into which a smooth cannula for air injection can be introduced. The Intrabubble can be considered a standardized procedure: the femtosecond laser is accurate in achieving the desired corneal depth and the big-bubble, and provides good refractive outcomes for the good alignment of donor and recipient configuration. We successfully applied this technique also to pediatric patients [47] in an attempt to decrease the rejection percentage, to improve the refractive outcome, and thus provide an anti-amblyopic effect.

We are using the IntraLase femtosecond laser (IntraLase FS Laser, Abbott Medical Optics, Inc.) that works by applying the applanation lens after obtaining a proper vacuum seal using a 10 mm diameter suction ring. However, this size can result too big to perform the treatment in smallest eyes. Thus, we experimented docking without suction ring by fixing the ocular bulb by four silk conjunctival stitches sutured over the skin (Fig. 5.2). This technique effectively provides a safe and effective applanation (Fig. 5.3).

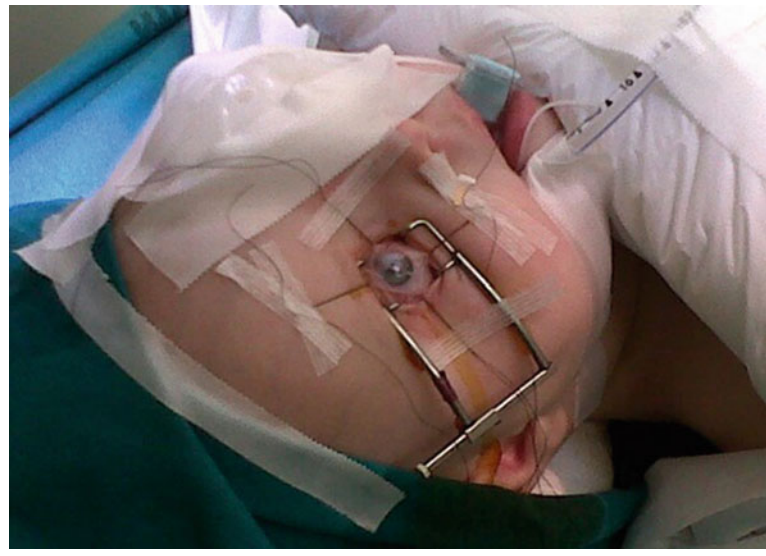

Fig. 5.2 To perform docking without suction ring we fixed the ocular bulb by four silk conjunctival stitches sutured over the skin

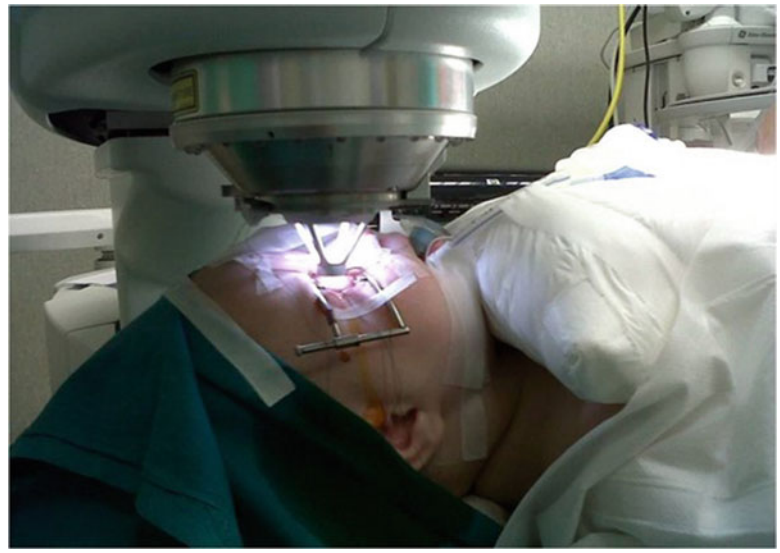

Fig. 5.3 The docking without suction ring effectively provides a safe and effective applanation

Few authors investigated the application of femtosecond laser in pediatric keratoplasty [47–49], but long-term follow-up after big-bubble DALK has not yet been reported. In a comparison between pediatric patients that underwent big-bubble DALK using mechanical trephine (seven patients, mean age 11.4 ± 3.0; Group 1) or femtosecond laser (seven patients, mean age 11.6 ± 4.2; Group 2), 2 year after surgery (at least 16 months after complete suture removal) we observed that (unpublished data), respectively, BCVA was 0.7 ± 0.1D and 0.7 ± 0.2D ($P = 0.3$), spherical equivalent −4.5 ± 0.7D and −2.4 ± 1. ($P = 0.09$), and refractive astigmatism 4.8 ± 2.2D and 3.3 ± 1.3D ($P = 0.2$).

We did not record statistically significant differences, but our findings suggest that femtosecond laser could decrease spherical equivalent and refractive astigmatism amount. If these data will be confirmed, they will can be added to all the other typical advantages of DALK: immune rejection of corneal endothelium cannot occur, surgical procedure is extraocular, topical corticosteroids can usually be discontinued earlier, and lower is loss of endothelial cell density; compared with PK, DALK may have superior resistance to rupture of the globe after blunt trauma and sutures can be removed earlier [50].

In conclusion, keratoconus in children needs a prompt diagnosis in order to plan the most appropriate therapeutic strategy. Since the high frequency of association with systemic diseases, a best cooperation between pediatricians and ophthalmologists could improve the treatment of these young patients.

Compliance with Ethical Requirements *Conflict of Interest*. Luca Buzzonetti, Paola Valente, and Gianni Petrocelli declare that they have no conflict of interest.

Informed Consent. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. No animal studies were performed by the authors for this chapter.

References

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42:297–319.
2. McAnena L, O'Keefe M. Corneal collagen crosslinking in children with keratoconus. J AAPOS. 2015;19:228–32.
3. Leoni-Mesplie S, Mortemosque B, Touboul D, et al. Scalability and severity of keratoconus in children. Am J Ophthalmol. 2012;154:156–62.
4. Caporossi A, Mazzotta C, Baiocchi S, et al. Riboflavin UVA-induced corneal collagen cross-linking in pediatric patients. Cornea. 2012;31:227–31.
5. Reeves SW, Stinnett S, Adelman RA, et al. Risk factors for progression to penetrating keratoplasty in patients with keratoconus. Am J Ophthalmol. 2005;140:607–11.
6. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric (corrected) corneal collagen cross-linking in children and adolescents. J Refract Surg. 2012;28:753–8.

7. Al Suhaiba Al Suhaibani AH, Al-Rajhi AA, Al-Motowa S, Wagoner MD. Inverse relationship between age and severity and sequelae of acute corneal hydrops associated with keratoconus. Br J Ophthalmol. 2007;91(7):984–5.
8. Ertan A, Muftuoglu O. Keratoconus clinical findings according to different age and gender groups. Cornea. 2008;27(10):1109–13.
9. Gabrić N, Dekaris I, Vojniković B, Karaman Z, Mravicić I, Katusić J. Corneal transplantation in children. Coll Antropol. 2001;25(Suppl):17–22.
10. Beltaief O, Farah H, Kamoun R, Ben Said A, Ouertani A. Penetrating keratoplasty in children. Tunis Med. 2003;81(7):477–81.
11. Slim EA, Jarade EF, Charanek BM, Antoun JS, Hemade AI, Awada SH, Fakhoury HW, Cherfan CG. Acute corneal hydrops mimicking infectious keratitis as initial presentation of keratoconus in a 10-year-old child. Case Rep Ophthalmol Med. 2015;2015:308348.
12. Javadi MA, Rafee'i AB, Kamalian N, Karimian F, Ja'farinasab MR, Yazdani S. Concomitant keratoconus and macular corneal dystrophy. Cornea. 2004;23(5): 508–12.
13. Cremona FA, Ghosheh FR, Rapuano CJ, Eagle Jr RC, Hammersmith KM, Laibson PR, Ayres BD, Cohen EJ. Keratoconus associated with other corneal dystrophies. Cornea. 2009;28(2):127–35.
14. Courage ML, Adams RJ, Reyno S, Kwa PG. Visual acuity in infants and children with Down syndrome. Dev Med Child Neurol. 1994;36:586–93.
15. Watt T, Robertson K, Jacobs RJ. Refractive error, binocular vision and accommodation of children with Down syndrome. Clin Exp Optom. 2015;98(1):3–11.
16. Howard S, Raine J, Dattani M. Corneal rupture in a child with Down syndrome and hyperthyroidism. BMJ Case Rep. 2009; 2009. pii: bcr08.2008.0842. doi: 10.1136/bcr.08.2008.0842. Epub 2009 Mar 5.
17. Lowell FC, Carroll JM. A study of the occurrence of atopic traits in patients with keratoconus. J Allergy Clin Immunol. 1970;46:32–9.
18. Kaya V, Karakaya M, Utine CA, Albayrak S, Oge OF, Yilmaz OF. Evaluation of the corneal topographic characteristics of keratoconus with orbscan II in patients with and without atopy. Cornea. 2007;26(8):945–8.
19. Copeman PWM. Eczema and keratoconus. BMJ. 1965;2:977–9.
20. Gasset AR, Hinson WA, Frias JL. Keratoconus and atopic disease. Ann Ophthalmol. 1978;10:991–4.
21. Kok YO, Tan GF, Loon SC. Review: keratoconus in Asia. Cornea. 2012;31(5):581–93.
22. Lapid-Gortzak R, Rosen S, Weitzman S, et al. Videokeratography findings in children with vernal keratoconjunctivitis versus those of healthy children. Ophthalmology. 2002;109:2018–23.
23. Rehany U, Rumelt S. Corneal hydrops associated with vernal conjunctivitis as a presenting sign of keratoconus in children. Ophthalmology. 1995;102(12):2046–9.
24. Dharmaraj S, Leroy BP, Sohocki MM, Koenekoop RK, Perrault I, Anwar K, Khaliq S, Devi RS, Birch DG, De Pool E, Izquierdo N, Van Maldergem L, Ismail M, Payne AM, Holder GE, Bhattacharya SS, Bird AC, Kaplan J, Maumenee IH. The phenotype of Leber congenital amaurosis in patients with AIPL1 mutations. Arch Ophthalmol. 2004;122(7):1029–37.
25. Weleber RG, Francis PJ, Trzupek KM, Beattie C.Leber Congenital Amaurosis. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors.GeneReviews®[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. 2004 Jul 7 [updated 2013 May 2].
26. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. Am J Ophthalmol. 2010;149:585–93.
27. Gomes JAP, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34:359–69.
28. Mazzotta C, Balestrazzi A, Baiocchi S, Traversi C, Caporossi A. Stromal haze after combined riboflavin-UVA corneal collagen cross-linking in keratoconus: in vivo confocal microscopic evaluation. Clin Exp Ophthalmol. 2007;35:580–2.
29. Zamora KV, Males JJ. Polymicrobial keratitis after a collagen cross-linking procedure with postoperative use of a contact lens: a case report. Cornea. 2009;28(4):474–6.
30. Bikbova G, Bikbov M. Transepithelial corneal cross-linking by iontophoresis of riboflavin. Acta Ophthalmol. 2013;92:e30–4.
31. Mastropasqua L, Nubile M, Calienno R, Mattei PA, Pedrotti E, Salgari N, Mastropasqua R, Lanzini M. Corneal cross-linking: intrastromal riboflavin concentration in iontophoresis-assisted imbibitions versus traditional and transepithelial techniques. Am J Ophthalmol. 2014;157:623–30.
32. Buzzonetti L, Petrocelli G, Valente P, et al. Iontophoretic transepithelial cross-linking to halt keratoconus in pediatric cases: 15 month follow-up. Cornea. 2015;34:512–5.
33. Koppen C, Wouters K, Mathysen D, Rozema J, Tassignon MJ. Refractive and topographic results of benzalkonium chloride-assisted transepithelial cross-linking. J Cataract Refract Surg. 2012;38:1000–5.
34. Buzzonetti L, Petrocelli G. Transepithelial corneal cross linking in children. Early results. J Refract Surg. 2012;28:763–7.
35. Colin J. European clinical evaluation: use of Intacs for the treatment of keratoconus. J Cataract Refract Surg. 2006;32:747–55.
36. Zare MA, Hashemi H, Salari MR. Intracorneal ring segment implantation for the management of keratoconus: safety and efficacy. J Cataract Refract Surg. 2007;33:1886–91.
37. Vega-Estrada A, Alio JL, Brenner LF, Javaloy J, Plaza Puche AB, Barraquer RI, Teus MA, Murta J, Henriques J, Uceda-Montanes A. Outcome analysis of intracorneal ring segments for the treatment of keratoconus based on visual, refractive, and aberrometric impairment. Am J Ophthalmol. 2013;155: 575–84.

38. Kankariya VP, Kymionis GD, Diakonis VF, Yoo SH. Management of pediatric keratoconus—evolving role of corneal collagen cross-linking: an update. Indian J Ophthalmol. 2013;61:435–40.
39. Colby K. Changing times for pediatric keratoplasty. J APPOS. 2008;12:223–4.
40. Hovlykke M, Hjortdal J, Ehlers N, Nielsen K. Clinical results of 40 years of pediatric keratoplasty in a single university eye clinic. Acta Ophthalmol. 2013. doi:10.1111/aos.12198x.
41. Huang C, O'Hara M, Mannis MJ. Primary pediatric keratoplasty: indications and outcomes. Cornea. 2009;28:1003–8.
42. Aasuri MK, Garg P, Gokhle N, Gupta S. Penetrating keratoplasty in children. Cornea. 2000;19:140–4.
43. Vanathi M, Panda A, Vengayil S, Chaudhuri Z, Dada T. Pediatric keratoplasty. Surv Ophthalmol. 2009;54:245–71.
44. Harding SA, Nishal KK, Upponi-Patil A, Fowler DJ. Indications and outcomes of deep anterior lamellar keratoplasty in children. Ophthalmology. 2010;117:2191–5.
45. Ashar JN, Pahuja S, Ramappa M, Vaddavalli PK, Chaurasia S, Garg P. Deep anterior lamellar keratoplasty in children. Am J Ophthalmol. 2013;155:570–4.
46. Buzzonetti L, Laborante A, Petrocelli G. Standardized big-bubble technique in deep anterior lamellar keratoplasty assisted by femtosecond laser. J Cataract Refract Surg. 2010;36:1631.6.
47. Buzzonetti L, Petrocelli G, Valente P. Big-bubble deep anterior lamellar keratoplasty assisted by femtosecond laser in children. Cornea. 2012;31:1083–6.
48. Agarwal A, Brubaker JW, Mamalis N, Kumar DA, Jacob S, Chinnamuthu S, Nair V, Prakash G, Meduri A, Agarwal A. Femtosecond-assisted lamellar keratoplasty in atypical Avellino corneal dystrophy of Indian origin. Eye Contact Lens. 2009;35(5):272–4. doi:10.1097/ICL.0b013e3181b3859c.
49. Buzzonetti L, Petrocelli G, Laborante A. Anterior lamellar keratoplasty assisted by IntraLase femtosecond laser in pediatric patient. Two years follow up. J Pediatr Ophthalmol Strabismus. 2010. doi:10.3928/01913913-20100507-01.
50. Reinhart WJ, Musch DC, Jacobs DS, Lee WB, Kaufman SC, Shtein RM. Deep anterior lamellar keratoplasty as an alternative to penetrating keratoplasty. Ophthalmology. 2011;118:209–18.