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Evaluating the evidence for and against the use of IOLs in Infants and Young Children

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Summary

Congenital cataracts account for 5–20% of childhood blindness worldwide. In the US, the prevalence of visually significant infantile cataracts is anywhere from 3–4 per 10,000 live births. Infantile cataracts need to be removed early in life in order to prevent the onset of deprivation amblyopia. As a result, cataract surgery is usually performed between age 4–8 weeks depending on the laterality and severity of the cataract. Given advances in the field, pediatric cataract surgery is now a safe and effective intervention for infants, but good visual outcomes require occlusion therapy and optical correction. This review will address current perspectives on the use of intraocular lenses to optically correct infants and young children after cataract surgery, as well as novel designs for intraocular lenses and directions for future research.

Keywords

Congenital cataract; infantile cataract; primary infantile intraocular lens implantation; Infant Aphakia Treatment Study; IoL under 2 cohort study; adjustable intraocular lenses

Expert commentary

Pediatric cataract surgery is the first step in a journey towards visual rehabilitation in patients with congenital and infantile cataracts. For decades, the standard treatment for infant aphakia was aphakic spectacles. However, limitations include bulkiness, constriction of peripheral vision, and lack of suitability for treating monocular aphakia. Beginning as early as 1959, contact lenses were used to optically correct aphakic children. Their popularity increased after the introduction of silicone contact lenses that could be worn on an extended wear basis[1,2]. Although contact lens (CL) wear has been shown to be safe and associated with good visual outcomes, it has the disadvantage of requiring ongoing maintenance. With the almost universal use of intraocular lenses (IOLs) in adult cataract surgery, a new interest developed in the role of IOLs to treat children of all ages after cataract surgery. However, there were significant concerns about the long-term safety of IOLs in the infantile eye and the challenges involved in selecting an appropriate IOL power given the rapid growth of infantile eyes. In a survey of members of the American

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Association for Pediatric Ophthalmology and Strabismus (AAPOS) between 1997 and 2001, Lambert and coworkers reported that although most AAPOS members still favored CL correction of aphakia after unilateral cataract surgery, fives times as many pediatric ophthalmologists had implanted an IOL in an infant in 2001 compared to 1997[3]. Subsequently, it was decided to conduct a randomized clinical trial in the US to compare the two treatments for infants less than 6 months of age with unilateral cataracts. A similar approach was taken in the UK with the goal of studying the role of IOLs in children under 2 years of age with either unilateral or bilateral cataracts. This review will touch on the salient points of these two studies, provide the authors' opinion on the use of IOLs in infants and young children, and outline a five year view of the future of the field.

The Infant Aphakia Treatment Study (IATS) was designed as a multicenter, randomized trial conducted at 12 clinical sites across the United States. It enrolled 114 infants with unilateral congenital cataracts who underwent cataract surgery between age 1 and 6 months. Equal numbers of patients were randomized to the two arms, with 57 randomized to aphakic correction with contact lenses and 57 to IOL implantation with spectacle correction of residual refractive error. From IATS, significant data from the one year and five year endpoints compared IOL correction with CL correction for aphakia after infantile cataract surgery. Benefits of the study included its randomized nature; strict protocols for surgical intervention, postoperative eye drop regimens, and patching; and data collection of primary and secondary outcomes, including grating visual acuity, motility, biometry, stereopsis, microscopy, tonometry, and keratometry[4].

At one year, no statistically significant difference was found in the grating acuity between the two groups, although there was an increased rate of adverse events and additional intraocular surgeries in the IOL group compared to the CL group (77% vs 25%, $p < 0.0001$, and 63% vs 12%, $p < 0.001$ respectively)[5,6]. The most common adverse events were lens reproliferation, pupillary membranes, and corectopia, which all occurred more often in the IOL group compared to the CL group. The number of non-visual axis related adverse events was similar between both groups. Importantly, when the visual acuity in the subset of patients requiring additional intraocular surgeries to clear visual axis opacities was compared between the two groups, visual outcomes were equal[6]. As a result of these adverse events at one year, there was a corresponding increase in additional intraocular surgeries performed on children randomized to the IOL group. Specifically, 18% of those in the IOL group had 2 or more additional intraocular surgeries compared to only 4% in the CL group ($p<0.001$), and the most common procedure in the IOL group was clearing of the visual axis. There was also an increased occurrence of intraoperative complications (IOL 28% vs 11% CLs, $p=0.03$), though the difference was primarily a greater incidence of iris prolapse attributed to larger wounds necessary for IOL insertion[6].

Visual acuity was tested at age 4.5 years by a traveling examiner using HOTV optotypes, and again, the visual outcomes were not statistically different between the two treatment groups. However, more than twice as many treated eyes in the CL group had visual acuity > 20/32 as compared to the IOL group[7]. Secondary analyses of baseline characteristics that were most predictive of visual outcome at the five year endpoint found weak associations between age at cataract surgery and vision when analyzed as a continuous variable, but

statistically significant improvements in median visual acuity when age was compared as a categorical variable (28–48 days, versus 49–120 days, p = 0.046)[8]. Baseline characteristics were grouped into three categories: physiological (age at surgery, gestational age, birth weight, sex, and race), characteristics of the eye (type of cataract, corneal diameter, average corneal power, axial length, intraocular pressure, pupillary diameter), or sociologic (type of insurance, primary caregiver, and highest education level of mother or father). Private insurance was the only variable isolated in a multivariate analysis that was associated with a significantly better median visual acuity (p=0.0004), but it only accounted for 12% of the difference in visual acuity, confirming that "considerable unexplained variation in visual acuity remains"[8].

At five years, more patients in the IOL group had at least 1 adverse event, (81% versus 56%, p = 0.008), which was again most often lens reproliferation, pupillary membranes and corectopia[7]. In line with other published reports, the occurrence of lens reproliferation occurred 10 times more often in the IOL versus the CL group. This has been attributed to the fact that the fused anterior and posterior lens capsules in aphakic patients prevents lens material from extending from the Sommerring ring into the pupillary axis, while in pseudophakic patients, the presence of the IOL prevents fusion of the anterior and posterior capsule, thereby facilitating the egress of reproliferating lens material into the visual axis[6, 7]. Given the importance of patching and continued refractive correction, it is notable that adherence to patching therapy between groups was not statistically different, and patients in the contact lens group had excellent adherence to daily contact lens wear. Despite the higher rate of complications in the IOL group at both the one and five year mark, it is also relevant to mention that CL use was not without risks: 10 patients (18%) had CL related adverse events - 2 corneal ulcers, 2 corneal abrasions, 5 transient corneal opacities or episodes of punctate keratopathy, and 1 broken contact lens on the eye. None of the CLs associated adverse events resulted in central corneal scars that permanently affected visual acuity. Of note, there were more severe adverse events in the contact lens group (1 case of endophthalmitis and 2 retinal detachments (one which resulted in phthisis bulbi), although the difference between treatment groups was not statistically significant using the Fisher exact test[6, 7, 9]. Compared to the first year in which there were 110 adverse events (22 in the contact lens group and 88 in the IOL group), the five year analysis showed only 54 total adverse events in years 2–5 (33 in the contact lens group and 21 in the IOL group)[10]. The total comparisons still indicated a greater rate of adverse events at age 5 years in the IOL group compared to the CL group, but the number of patients with adverse events in the CL group increased in years 2–5, while decreasing in the IOL group. After the first year, the percentage of patients having surgery did not differ significantly between the groups, although over the entire follow-up period, a lower percentage of patients in the CL group had additional intraocular surgeries. However, the two groups at the one year and five year marks are not equivalent with regard to likely future surgeries, since many patients in the CL group will likely choose secondary IOL implantation in the future, thereby potentially increasing the number of additional surgeries that will be performed on children in the contact lens group.

In addition to visual acuity and intraoperative and postoperative complication rates, the IATS also addressed the risk of glaucoma, the development of stereopsis, and the relative costs of

the two treatment arms. At one year, a total of 9% (n=10) of eyes developed glaucoma (defined as IOP greater than 21mmHg with corresponding anatomical changes in corneal diameter, axial length, cup-to-disc ratio, and/or progressive myopia), and 4% (n=4) were labeled glaucoma suspect due to increased IOP alone[11]. There was no difference in the subgroup analysis of patients with glaucoma and glaucoma suspect between the IOL and CL group. However, a relationship was established between certain preoperative characteristics that predisposed to a higher risk of glaucoma. Persistent fetal vasculature (PFV) conferred a 3.1 times higher risk of glaucoma, and for every month younger in age at the time of surgery, a patient's risk for glaucoma increased by 1.6 times[11]. No difference was found in the risk for glaucoma between those who had an IOL implanted in the bag versus the sulcus. Although gonioscopy was not part of the protocol, 90% of eyes were judged to have open angle glaucoma and only one eye was noted to have iris bombe/angle closure. Of the eyes diagnosed with glaucoma, 60% underwent surgical intervention to control IOP, (trabeculotomy or Baerveldt implant), but no statistical significance between the IOL and CL groups was found in the likelihood of needing glaucoma surgery. Of note, visual acuity was worse in eyes that developed glaucoma or suspected glaucoma one year after cataract surgery, but this difference was not statistically significant ($p = 0.15$)[11]. The 5-year postoperative risk of developing glaucoma was 17%, while the risk of being identified as a glaucoma suspect was 31%[12]. Data analysis confirmed that both younger age at surgery and smaller corneal diameters increased risk for both glaucoma and glaucoma suspect. However, there was no statistically significant difference in risk between patients in the CL and IOL groups. Four new cases of glaucoma were diagnosed between the one year follow-up and five year follow-up, and 6 of the eyes that were glaucoma suspects at 1 year developed glaucoma by five years of age, for a total of 10 additional cases of glaucoma reported at the five year point. Of these 10 additional cases, only one required glaucoma surgery. Thirteen additional glaucoma suspects were identified in years 2 through 5. Interestingly, although PFV conferred a 3.1 times higher risk of glaucoma at the one year analysis, neither PFV nor IOP at time of surgery were found to be associated with either glaucoma or glaucoma suspect at the five year time point[12]. Similar to the one year analysis, visual acuity at the five year follow up showed no statistically significant difference in visual acuity between eyes with and without glaucoma, although this finding was attributed to the small sample size.

We now place the above-mentioned IATS data in the context of recently published literature on the role of IOLs in children under 2 years of age. The IoL under 2 Cohort Study was a prospective, non-randomized population based cohort study conducted in the British Isles that included a total of 254 children under 2 years of age with either unilateral or bilateral cataract[13]. Complete postoperative data at 1 year was available only for 221 children (350 eyes), of whom 131 had bilateral cataracts. Approximately half of both groups of children (56/131 bilateral, and 48/90 unilateral) underwent primary IOL implantation. It was noted that those children selected for implantation were older, had larger eyes, and had a decreased likelihood of coexistent ocular abnormalities. Overall, the median age at diagnosis of cataract was 1.8 weeks, with surgery occurring at a median of 9.2 weeks. This early recognition rate is attributed to The Newborn and Infant Physical Examination program in the United Kingdom that resulted in half of all children in the study being diagnosed within the first fortnight of life. Intraoperative complications were more frequent in the IOL group,

with the most common complication being iris prolapse. However, IOL implantation was independently associated with increased odds of better vision in the bilateral cataract group but not the unilateral cataract group. Factors that were correlated with better visual acuity in the unilateral group included good concordance with occlusion therapy and the absence of postoperative glaucoma. Younger age at surgery was identified as an independent risk factor for glaucoma in the bilateral cataract group ($p<0.01$), while microphthalmos was the only independent predictor of glaucoma in unilateral disease ($p =0.01$). IOL implantation increased the odds of postoperative intervention, primarily for visual axis opacification, with the median time for reoperation being 3.9 months. However, there was an increased odds ratio of reoperation in the unilateral versus bilateral disease groups. Limitations of the study include the observational cohort nature of the study, which can introduce bias and confounding variables. In summary, the authors propose that IOLs should be reconsidered in children under age 2, especially in children with bilateral disease.

With regard to stereopsis evaluated in the IATS at 4.5 years, 25% of patients had a positive response to at least 1 stereopsis test (Stereotest, Randot test, or Titmus Fly test), without a significant difference between the two treatment groups. However, median age at cataract surgery was younger for patients with stereopsis compared to those without stereopsis ($p=0.002$), and the visual acuity for patients with stereopsis was better than those without stereopsis (20/40 vs 20/250, $p=0.0003$)[14].

IATS and the IoLunder 2 Cohort Study illustrate the complexities of the decision to perform cataract surgery and place IOLs in infants and young children, especially given the proinflammatory eye and the period of critical growth and development. Theoretical advantages of primary IOL implantation during infancy include having a constant, albeit partial, optical correction during the early years of visual development, the ability to place the IOL within the capsular bag, and the avoidance of the expense and difficulties associated with contact lens use. Advantages of leaving the baby aphakic and visually rehabilitating the eye with a contact lens include the ability to change the contact lens power as needed to keep up with the changing refractive error, and not subjecting the baby to the increased rate of complications and subsequent need for additional intraocular surgeries associated with IOL implantation. The conundrum we face is the desire to achieve maximum visual acuity, which requires early surgery, balanced against the increased risk of glaucoma or glaucoma suspect associated with younger age at time of surgery. As for IOL implantation versus CL correction, concerns regarding the risk of increased intra- and post-operative complications and additional intraocular surgery must be balanced with cost and ease of follow up care.

A cost analysis at age 1 year in the IATS revealed that the mean cost of surgery and any additional surgeries, examinations and supplies used during the first year was $14,752 for the IOL group compared to $10,726 for the CL group[15]. Accordingly, IOL implantation was 37.5% more expensive than CL correction, equal to approximately $4000. At the five year endpoint, however, treatment costs began to approach each other, and in the IOL group were $27,090 versus $25,331 for the CL group[16]. The total cost of supplies was $3,204 in the IOL group vs $7,728 in the CL group, with the average number of lenses required annually in the CL group starting at 10 in the first year and subsequently declining to 9 in year 2, 7 in year 2, and 5 in years 4 and 5. While the cost of supplies was higher in the CL group, the cost of

additional surgeries was higher in the IOL group for all years, peaking in years 3 and 4. Although the costs for the CL group increased and appeared to more closely match those of the IOL group by age 5 years, all calculated costs were direct costs only. Indirect costs should also be considered such as the time spent by caregivers fitting contact lenses, number of follow up appointments, cost of travel to and from appointments, emotional burden, and lost productivity from work-days missed[15, 16].

Interestingly, the highest cost IOL patient was $50,437, which included the cost of the cataract removal and IOL implantation, a membranectomy, glaucoma surgery, and a wound dehiscence with scleral patch graft. This is in stark comparison to the highest cost patient in the CL group at $27, 506, which included the cataract removal, a membranectomy, glaucoma surgery, and retinal detachment repair. In contrast, the lowest cost IOL patient was $9,412 compared to $8,805 in the CL group[16, 17]. The broad range in cost in both groups underscores the variability that could not be controlled for despite rigorous IATS protocols. This suggests that in the real-world, costs for both groups of patients will likely continue to fluctuate widely. Also, given that many of the supplies in the study were provided free of cost to patients, adherence will likely be different in the real-world setting, which underscores the concepts of effectiveness and efficacy.

Despite the controversies of IOL implantation in infants, the role of IOL implantation in older pediatric patients, whether primary or secondary is better accepted. Wilson et al reported a similar rate of complications and visual acuities in 33 eyes that underwent secondary IOL in the bag versus 21 eyes with sulcus lens implantation in patients who had cataract extraction in the first 4 months of life[18]. Another study of children with a unilateral cataract removed by age 8 months and secondary IOL placed prior to 6 years of age evaluated whether vision could be improved in children who may have been noncompliant with treatment regimens earlier in the postoperative period, such as follow up appointments, occlusion therapy, and optical correction[19]. The authors found that vision was better in children who underwent primary cataract removal before 4 months of age. Of those who had surgery between 1 and 4 months, 87.5% had visual acuity better than 20/150, and the one patient with 20/30 vision also had stereoacuity. The 3 children that had cataract extraction between 5 and 7 months had poor vision (< 20/250) prior to secondary IOL implantation and maintained low final acuity thereafter. They also demonstrated a clear correlation between poor visual outcomes and poor compliance with contact lens wear and patching protocols. The only two patients with 20/30 visual acuity were compliant with patching and contact lens treatment, and had cataract surgery at 1 month of age[18]. These studies concluded that secondary IOLs may be helpful in maintaining the current level of visual acuity, but should not be expected to improve final visual acuity.

Despite the advances in the field of pediatric cataract surgery, there are a number of challenges associated with biometry and postoperative eye growth that make primary IOL implantation difficult in children. It has been well established that the pediatric eye grows rapidly in the first two years of life, and then grows at a slower rate thereafter until the teenage years. The IATS demonstrated that cataractous eyes were shorter than fellow eyes by an average of 0.6mm (p= 0.0001) at the time of cataract surgery, and that eyes with IOLs grew more than aphakic eyes over the first year of life after cataract surgery (p=0.0006)[20].

Other factors that have been described as affecting infant axial elongation include optical defocus and amblyopia, both of which can confound any results investigating the role of aphakia as an independent variable. Other known variables that were intentionally excluded from the analysis included eyes affected by glaucoma or increased IOP[19]. Therefore, given these changes in axial length, it is clear that there are postoperative changes in refraction associated with a state of aphakia. However, even the immediate postoperative refractive error often differs significantly from the intended goal, that in IATS was +8D for those undergoing surgery between 4–6 weeks of age, and +6D for those over the age of 6 weeks.

One of the challenges involved in the decision to implant an IOL in a young eye is IOL selection itself, both with regards to type and power. In the CL group from the IATS protocol, it was projected that had a +32D lens been dispensed based on the preoperative biometry, 44% of patients would have needed a change in contact lens power at the first postoperative refraction[21]. Another arm of the IATS trial assessed the predictability of IOL calculations using the Holladay 1 formula and early postoperative refractive outcomes. Multivariate analyses showed that there was a higher predictive error associated with short axial length (< 18mm)[22]. Overall, 45% of eyes had postoperative refractions within 1D of the targeted refraction, but 41% had a greater than 2D predictive error[21]. The decision to use the Holladay 1 formula for calculations was based on an analysis of the different available lens calculation formulas using the IATS data. Per their results, Holladay 1 and SRK/T formula showed similar clinical results[23]. Holladay 1 showed the lowest median absolute prediction error (1.2D), while SRKT had the lowest mean absolute prediction results (1.4 ± 1.1 D). Of note, eyes shorter than 18mm in axial length had the largest mean and median values regardless of formula used. Hoffer Q tended to overcorrect eyes, with less residual hyperopia than expected, while SRKII tended to undercorrect eyes, with more residual hyperopia than expected[21, 22]. Given the strict protocols involved with IATS, common underlying reasons for postoperative refractive surprise, such as surgical technique, type of IOL, and IOL position, were less likely to be responsible for prediction errors. Another study evaluating postoperative refractions in over 200 patients reported a prediction error of 1.08 D ± 0.93, with those aged less than 2 years of age with the most unreliable refractive changes[24].

Authors' Expert Opinion

Despite the evidence that exists for and against the use of IOLs in the infantile and toddler eye, much of the modern-day surgeon's practice is based upon a combination of this evidence with personal experience. With regard to baseline characteristics of patients selected for IOL implantation, we prefer to leave infants with a unilateral cataract who are 3 months of age or younger aphakic and to optically correct them with contact lenses. Infants older than 3 months of age appear to be less prone to develop visual axis opacities than younger infants. We do not implant IOLs in infants with bilateral cataracts until they are at least 7 months of age because they can be optically corrected with contact lenses, and aphakic glasses if contact lenses are poorly tolerated.

Our standard approach for cataract surgery involves two incisions—a scleral tunnel and a side port. An infusion cannula is inserted through the side port and a vitrector through a stab

incision in the center of the scleral tunnel. The elasticity of the infant capsule underlies its tendency to tear outwards during a manual capsulorhexis. Thus, we perform a vitrector-capsulorhexis in infants because it allows for creation of a controlled, well-centered, adequately sized anterior capsulotomy. During lens aspiration, we recommend switching the vitrector to the side port incision as often as needed to aspirate subincisional cortex. We aim to completely remove lens cortex to minimize postoperative anterior chamber inflammation. The posterior capsulotomy is then usually created with the vitrector, followed by a thorough anterior vitrectomy. If the child is to be left aphakic, the posterior capsulotomy is made the same size as the anterior capsulotomy, approximately 5–6 mm in diameter. If there is a plan to implant an IOL, the posterior capsulotomy is sized 1 mm smaller than the anterior capsulotomy, and Healon GV (Abbott Medical Optics, Santa Ana, CA) is used to separate the anterior and posterior capsular leaflets to facilitate in-the-bag placement of the IOL. Our IOL of choice is a one-piece acrylic IOL (AcrySof SN60WF, Alcon Labs, Fort Worth, TX) in the capsular bag, and care is taken to guide the inferior haptic into the capsular bag so that it does not prolapse through the posterior capsulotomy into the vitreous. The superior haptic can then be positioned into the capsular bag with an IOL pusher. If an IOL cannot be safely placed in the capsular bag, a 3-piece acrylic IOL (AcrySof MA60AC, Alcon Labs, Fort Worth, TX) is placed in the ciliary sulcus.

We generally wait to implant a secondary IOL until the refractive error in an aphakic eye has been stable for one year or longer. In most cases, this occurs by the time a child is 4 to 5 years of age. However, in those children who tolerate contact lenses remarkably well, we defer secondary IOL implantation until the child is a teenager or young adult since the chance of a myopic shift is significantly reduced.

Contact lenses are not a viable option for children in many countries because of their cost, poor availability, or the environment. In the Middle East, the arid climate and frequent sand storms make it difficult for children to successfully wear contact lenses. In developing countries, the cost of contact lenses and the challenges of maintaining good contact lens hygiene are significant barriers to their wide spread use. Although Silsoft contact lenses (Bausch + Lomb, Rochester, NY) are the most commonly used soft contact lens for aphakic children in the United States, they are not currently available in many countries. As a result, infants with bilateral cataracts in developing countries are often left aphakic after cataract surgery and optically corrected with aphakic spectacles. For infants with a unilateral cataract in developing countries, cataract surgery is often deferred until children are 3 to 6 months of age when IOL implantation can be safely performed since aphakic glasses are not a viable option for these children. Obviously, this practice portends poorer visual outcomes due to the onset of deprivation amblyopia in the affected eye, and is a problem that still requires a long-term solution in the developing world.

Five-year view

Over the course of the last 50 years, the field of pediatric ophthalmology has made significant strides in achieving good visual outcomes in patients with unilateral and bilateral congenital cataracts. In 1957, Costenbader and Albert unequivocally recommended against surgical intervention for unilateral congenital cataracts[7,25]. Then, Hubel and Wiesel[26,27] and

Wiesel and Hubel[28,29] established the importance of deprivation amblyopia, leading to earlier surgical intervention for children with congenital cataracts, and part-time patching of the unaffected or preferred eye. However, concerns regarding the safety of IOL implantation in infant eyes persist, as do challenges surrounding the management of post-operative refractive error, risk of glaucoma, and the cost effectiveness of this treatment. The above discussion highlights potential directions for future research, including methods to minimize the risks of intra- and post-operative complications in the IOL group that are directly related to the increased incidence of additional surgeries, and better ways to manage postoperative eye growth and concordant change in refractive error.

As mentioned in both IATS and the IoLunder2 Cohort Study, the most common complication was visual axis opacification requiring additional surgery to clear the visual axis. A variety of techniques have been described that address postoperative visual axis opacification, including optic capture and the bag-in-the-lens technique. Optic capture was first described in the 1990s by Dr. Gimbel as a technique to prevent secondary membrane formation after pediatric cataract removal. By positioning the haptics of the lens in the bag, and pushing the optic through the posterior capsulotomy, proponents suggest this technique ensures centration of the lens and may decrease the need for anterior vitrectomy, while reducing formation of visual axis opacification. Subsequent studies by Koch et al in 20 eyes of 15 children reported a retrospective review of rates of posterior capsular opacification using different methods of managing the posterior capsule and anterior vitreous[30]. Five of the twenty eyes had an IOL implanted in the bag with an intact posterior capsule. 100% of these eyes developed visually significant secondary cataract. Of the 15 eyes that underwent a posterior continuous curvilinear capsulorhexis, 6 underwent concomitant anterior vitrectomy, of whom half had an in the bag lens and half underwent optic capture. None of these eyes developed secondary membranes. In the 9 eyes that underwent posterior capsulotomy without anterior vitrectomy, 5 underwent optic capture and 4/5 developed visual axis opacification within 6 months. Of the 4 eyes that had posterior capsulotomy without anterior vitrectomy and an in the bag lens, 100% developed secondary membranes. Accordingly, the authors concluded that anterior vitrectomy was the critical step in preventing or delaying secondary cataract formation. This report was followed by a prospective study of 40 eyes in 28 children evaluating the role of optic capture in congenital cataract removal with anterior vitrectomy and IOL implantation[31]. Both groups maintained a clear visual axis. Authors reported a greater incidence of posterior synechiae and IOL deposits in the optic-capture group with improved IOL centration compared to the non-optic capture group. As the largest study to date on the use of optic capture, they concluded that the technique resulted in better IOL centration but predisposed the eye to an increased inflammatory response. Importantly, successful completion of this technique requires a perfectly sized posterior capsulotomy.

A newer approach that has been recently published and is gaining ground in the field is the “bag-in-the-lens” technique. In a long-term study of 46 eyes of 31 children, Tassignon et al showed that the technique allowed for maintenance of a clear visual axis in 91.3% of cases over 5 years[32]. Successful completion of this technique requires positioning of a specially designed IOL with a circumferential interhaptic groove in the anterior and posterior capusulotomy, allowing the leaflets of the anterior and posterior capsule to rest in the

groove. This also requires a perfectly sized anterior and posterior capsulotomy. Recent work in the application of the femtosecond laser to infantile cataract surgery suggest that the precision of the laser may allow for the safe creation of well-centered and perfectly sized anterior and posterior capsulotomies[33]. We posit that the ability to create such anterior and posterior capsulotomies may make surgical techniques such as optic capture and bag-in-the-lens a routine part of future pediatric cataract surgical methods. Moreover, the use of femtosecond lasers may facilitate placement of an IOL in an eye that may not have otherwise been able to have one placed, such as in an eye with an abnormal anterior capsule, like Peter's type II with keratolenticular adhesions.

With regard to the spectrum of adjustable IOLs currently in development, Ford et al published a recent extensive review capturing the newest novel designs[34]. The categorization of adjustable IOL technologies is divided into those that are adjusted using secondary surgical procedures such as multicomponent IOLs, mechanically adjustable, and repeatedly adjustable IOLs, and those that are adjusted noninvasively, like the magnetically adjustable IOL, liquid crystal IOL with wireless control, femtosecond or 2-photon adjusted IOLs, and light adjustable lenses (LAL).

Basic tenets of adjustable IOLs include biocompatibility with intraocular tissues, a refractive error correction range of 2.0D, correction to within 0.25D of a given target, stability of refraction, safety, and noninvasive adjustment, if possible. However, given the need for long-term correction of a large refractive range in the infantile eye, many of the options in development currently do not apply to the pediatric population. The first proponent of an adjustable lens was Dr. Werblin in 1996, who envisioned a multicomponent IOL with a base, front lens, and a cap lens. The premise of this type of lens allowed for implantation of the base of the lens into the capsular bag at the time of surgery, with insertion of the optic in a second step. The optic is then removable without disturbing the base, allowing for repeatable exchanges of the lens optic as needed. It is this type of lens that has the most promising role in pediatric cataract surgery. A study of the role of multicomponent adjustable IOLs in pediatric cataract surgery was undertaken by Portaliou et al, and followed 6 patients who had received this lens type over 2 years. At the two year endpoint, authors found good rotational stability, and no posterior capsular opacification (PCO) or interlenticular fibrosis[35]. Modifications to this original lens design have resulted in the newest generation of multicomponent IOLs, including the Harmoni lens currently designed by ClarVista Medical.

The Harmoni lens was studied in 6 New Zealand white rabbit eyes who underwent bilateral phacoemulsification, with implantation of the Harmoni test lens, a hydrophobic acrylic IOL, in the left eye and a single piece hydrophobic acrylic control IOL in the right eye (SA60AT). Of note, this rabbit has been studied as a validated accelerated model for the study of capsular bag proliferation. A six week postoperative endpoint to assess PCO is approximately equivalent to two years in a human eye. Results of this small trial demonstrated stability of the test lens in rabbit eyes, with a decreased incidence of PCO compared to the control lens. Creators of the design attribute the decreased rate of PCO to the lens's long loops, and peripheral anterior and posterior square edges. Accordingly, the company is moving forward with phase I and II trials, studying its safety and efficacy in 30 human eyes[29,36]. The benefits of such an exchangeable lens are obvious in the pediatric

population, given their changing refractive needs throughout the early years of life, but the downside includes the need for additional surgeries in order to accomplish this goal, and the risk for other complications associated with multiple IOL exchanges.

Other adjustable IOL models that are currently under investigation include a mechanically adjustable PMMA IOL that consists of a 5.5mm optic and two 1.0mm high cylinders at the optic-haptic junction. Surgeons can alter the refractive power by moving the piston and cylinder relative to each other, resulting in 1.5D of refractive change for each millimeter of adjustment. Advantages include the ability to perform adjustments several times through a paracentesis, for a total range of adjustment between 2.0 and 2.5D in an average eye[29]. The model has been tested in both animal models and the human eye, with results demonstrating safe adjustment 2 weeks after the initial surgery, and stable refractions up to 18 months post-insertion. However, published results studying the AcriTec mechanically adjustable IOL in a longer study did report a higher incidence of PCO (18/35 eyes), although all were successfully treated with YAG capsulotomy[37,38]. A similar but distinct concept for an adjustable IOL requires manipulation of a PMMA optic that screws anteriorly or posteriorly into an outer ring with J-loop haptics[29]. Such manipulation requires intraoperative adjustment with a Sinskey hook or similarly shaped instrument such that two notches on the edge of the optic can be rotated. Limitations for use of these types of IOLs in the infant and pediatric population lie primarily in the small range of dioptric adjustment afforded by these lenses. Additionally, similar to the multicomponent IOL, mechanically adjustable IOLs require additional surgery, which may be undesirable in this vulnerable population. Interest in creating an adjustable IOL that did not require intraoperative adjustments led to the creation of a generation of non-invasively adjustable IOLs.

Matthews et al describe an IOL that is embedded with magnetic spindles, which can then be controlled using an external magnetic source which allows for rotation of the IOL in the forward or reverse direction, supporting precision to within 0.04D for a 26.0D lens, or 0.01D for a 16.0D lens[39]. The authors were able to show stability of the IOL without leaching of the magnetic materials over a 1 month period, but they are still addressing concerns of long-term safety, compatibility with imaging modalities such as MRI, and human testing. Other non-invasively adjustable IOLs include liquid crystal IOLs with wireless control, and an autofocal accommodating liquid crystal intraocular lens. The design of these lenses is based on the fact that liquid crystal flows like a liquid but contains molecules that are oriented like a solid. Accordingly, in the nematic phase, they have no specific positional order but line up roughly along a parallel axis which can be manipulated with a magnet or electric field[29,40]. The latest wave of interest in noninvasively adjustable lenses entails using the femtosecond laser or two-photon chemistry to allow for postoperative non-invasive adjustments of refractive error.

Two companies (Alcon and Perfect Lens LLC) are exploring the role of the femtosecond laser to facilitate these adjustments. The prototype design consists of an optic with two concentric rings and localized areas of heat-absorbing material where the laser is directed. A principle known as intra-tissue refractive index shaping describes application of a high-repetition, low-pulse energy femtosecond laser onto small gratings in a biologic tissue, which induces significant and persistent changes in refractive index with low scattering loss.

When this principle is combined with the idea of phase wrapping, a process in which the surface of the IOL is divided into concentric diffractive zones, each capable of a maximum dioptric correction, we have a noninvasively adjustable lens that is potentially capable of 20D of post-operative adjustment. Tightening of the diffractive zones along an x-axis and changing the relative heights and profiles of the different diffractive zones can create astigmatic and aspheric corrections in 20–60 seconds[29]. Two-photon chemistry is a similar concept using 2 photons of identical or different frequencies to excite a polymer from the ground state to a higher state, resulting in a change in refractive index and thereby focal length. With this concept, proponents claim adjustments are reversible by using a different wavelength, though this has yet to be tested via scientifically rigorous trials. All of these lenses however continue to have limited applicability to the pediatric population due to their narrow range of refractive correction and their limited number of potential adjustments.

The lens that has advanced the farthest in a short amount of time is the light adjustable 3-piece foldable lens created by Calhoun Vision, Inc, which uses UV light to polymerize a macromere upon exposure. A 100um UV-light enhanced layer on the posterior aspect of the lens protects the retina and ensures lock-in, and the lens can provide up to 2.0D of correction of hyperopia, myopia and astigmatism. Typical use plans for adjustments 2–4 weeks postoperatively, and an average of 1–2 UV light adjustment procedures, each taking less than 2 minutes prior to the lock-in treatment, which is performed the following day after the final adjustment. Advantages of this technology in children would be the ability to adjust the refractive power multiple times, as each adjustment consumes only 10–20% of the macromere and each adjustment can provide up to 2.0 D of correction. However, once it is locked in, it is permanent. Multiple trials have established the safety of this lens in humans, with long-term postoperative stability and low rate of complications, as well as the lack of harm on the cornea and retina in animal models exposed to the UV light adjustment[41, 42,43, 44,45]. As a result, the light adjustable lens is currently undergoing phase 3 FDA trials in the US, and is already available in Europe and Mexico. However, one of the main challenges of applying this technology in children is the necessity of full-time sunglass wear prior to final lock-in treatment, as aberrant UV exposure can cause untoward refractive surprises. Important considerations in using this technology will include the need for a light delivery device to administer the treatment. Calhoun Vision is collaborating with Carl Zeiss Meditec AG to develop this digital light delivery device.

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Key issues

- IOL implantation and CL correction are equivalent in terms of visual outcomes at one and five years for patients undergoing unilateral cataract surgery between the ages of 1 and 6 months
- IOL implantation may have a benefit on visual acuity in children with bilateral cataracts in children under 2 years of age
- There is an increased risk of early intraoperative and postoperative complications, as well as an increased number of additional surgeries in infants undergoing IOL implantation, which decreases in subsequent years of follow up and is matched by a relative increase in complications in the CL group
- The direct costs of IOL implantation exceed CL treatment in the first year, but by five years, the direct costs are nearly the same in both groups. However, the cost of supplies are higher in the CLs arm.
- Risk of glaucoma increases with younger age at time of surgery, which must be balanced with a better visual acuity and potential for stereopsis with younger age at time of surgery
- Techniques to prevent postoperative visual axis opacification in patients with IOL implantation, such as optic capture and bag-in-the-lens approach may allow for wider spread implantation of IOLs in the infantile eye
- With the advent of adjustable IOLs, especially the multicomponent IOL, new strategies are on the horizon for managing the postoperative refractive changes in infantile eyes

Table 1

The Infant Aphakia Treatment Study

Randomized, multicenter (12 sites) clinical trial
114 infants with a unilateral congenital cataract randomized to cataract surgery with or without primary IOL implantation
Primary outcome: HOTV acuity at age 4.5 years tested by traveling examiner
Main inclusion criteria:
• Visually significant congenital cataract
• Age 1–6 months at time of cataract surgery
Main exclusion criteria:
• Persistent fetal vasculature with stretching of the ciliary processes
• Corneal diameter <9mm
• Medical condition that would interfere with visual acuity testing
• Premature birth (<36 gestational weeks)