Essentials in Ophthalmology
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Kathryn Colby *Editor*

Corneal Diseases in Children

Challenges and Controversies

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Essentials in Ophthalmology

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Preface

In my second year of residency at the Massachusetts Eye and Ear Infirmary in Boston, I found myself torn between the subspecialties of pediatric ophthalmology and cornea. I sought consultation with Dr. Claes Dohlman to help make my decision. Corneal specialists will need no introduction to Dr. Dohlman, whom many credit as the founder of the subspecialty of cornea. His tireless work on his beloved Boston keratoprosthesis has created a device that has restored vision to thousands of corneal-blind patients for whom a standard corneal transplant will not succeed. Claes started the first formal corneal fellowship approximately 50 years ago, served as chair of the Harvard Department of Ophthalmology for 15 years, and trained generations of corneal specialists, including scores of department chairs. And, on top of all that, he continues to innovate at the tender age of 94. He is a true legend in our field and a role model for all of us.

Claes listened attentively as I extolled what I perceived to be the benefits of pediatric ophthalmology. When I finally stopped talking, he said, in his characteristic Swedish accent, "Yes, yes, that is all very true, but your patients… they are children." Therein lies the first challenge in pediatric cornea, and of course, one of its greatest joys. One must fundamentally enjoy working with children (and their parents) in spite of the challenges if one is to be successful in a subspecialty within pediatric ophthalmology. Certainly children can be cranky and uncooperative, but they also have a joie de vivre that is refreshing and inspiring. In the end, I chose cornea, but I never forgot my love of pediatric ophthalmology. After about a decade as a busy corneal surgeon at Mass Eye and Ear, I approached Dr. David Hunter, the chief of ophthalmology at the Boston Children's Hospital, about setting up a pediatric cornea service there. Thus, I was finally able to combine my two loves! When I left Boston to take the chairmanship at the University of Chicago, the farewells with my pediatric patients were some of the hardest for me.

This volume will cover most of the major corneal diseases that affect children—infectious, allergic, congenital, ocular surface, and ectatic. The introductory chapter presents a general approach to children with corneal disease, as well as a differential diagnosis for children with red eyes. Diagnostic tools, including imaging modalities, and therapeutic modalities, including contact lenses, are also featured. A chapter on pediatric corneal surgery is a highlight. Finally, the critically important topic of amblyopia management is covered by my esteemed pediatric ophthalmology colleague,

Dr. Melanie Kazlas. I am grateful to all those who contributed to this effort, many of whom are rising stars in the field of pediatric cornea. It is my hope that this volume will improve the corneal care of our youngest patients and perhaps inspire some of the next generation to take an interest in this important ophthalmic discipline.

Chicago, IL, USA Kathryn Colby, MD, PhD

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Approach to the Child with a Corneal Condition

1

Kathryn Colby

Corneal Examination in Children

Caring for an ill child is challenging in any circumstance. There are, however, specific issues and approaches when a child has a corneal problem that can cause distressing symptoms like eye pain and light sensitivity. This chapter will review strategies to examine and diagnose corneal conditions in children.

Different strategies are needed depending upon the age of the patient, but first and foremost, one must understand the different developmental stages of childhood and tailor the approach accordingly. Examination of an infant is generally facilitated by feeding immediately before or during the exam. A pacifier may be a useful tool as well. Swaddling an infant and placing a lid speculum may induce crying, but typically allows for an adequate examination. Toddlers (age 18–36 months) are generally the most challenging group to engage, since they are too big to swaddle and too young to understand reason. A variety of colorful toys with sounds or motion may help. One needs a selection because typically the "one toy, one look" rule applies. Favorite movies playing at the end of the exam room can also act a distraction. Simple giveaways such as stickers can often facilitate cooperation. For preschoolers (ages 3 and above), the same distraction techniques apply, but one can begin to engage preschool children by asking simple questions, for example, regarding siblings or pets. Even the most shy child will talk about a beloved pet, and a wise provider will use this time to observe the child—is their eye red, are they closing their eyelids, are they comfortable in a lit exam room, are they rubbing their eyes? It is even helpful to observe the child in the waiting room before calling them into be examined—are they playing with toys or a handheld device without difficulty? Are they sitting with their eyes closed or their head down?

Things become easier with school-age children. A more detailed conversation regarding the child's interests or hobbies can take place. It helps to have at least some knowledge of popular children's books, movies or TV shows, sports, or video games. Documenting in the chart or electronic record of any information gathered can facilitate the conversation at subsequent visits. For example, a simple phrase such as "has a bulldog named Spot and loves to read" will remind the provider to ask about these things at the next visit, thus promoting the development of a therapeutic relationship. Teenagers have their own challenges, but a sensitivity regarding the issues children in this age group face will aid the provider.

Despite these approaches, occasionally even the most experienced provider will not be able to obtain enough of an exam. At this point, management depends upon the history and the differential diagnosis. For a self-limited condition,

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such as presumed viral conjunctivitis, one can use the history of a concurrent upper respiratory infection and a "pink eye" outbreak at preschool to arrive at the likely diagnosis and send the child on their way with supportive therapy. In the setting of potentially more serious conditions like a corneal ulcer or uveitis, the child should be brought back in the next day or two for another attempt at an office exam. If this is not possible, or if the provider is very concerned based upon the severity and intensity of symptoms, an exam under anesthesia may be needed.

Most history will come from the parents or other caregivers; however, one should also ask even a young child if they have anything to add to what the parents have said. Since many corneal conditions (corneal dystrophies, keratoconus) have a hereditary component, one should perform a quick slit lamp examination of parents and cooperative siblings who accompany the patient.

Observing the child during the history-taking will provide information before the corneal exam is attempted. I generally start with a penlight exam to evaluate the status of the conjunctiva and the quality of the corneal light reflex. This is almost always possible, even in the most uncooperative child.

Performing a slit lamp exam in a child is different than examining an adult, and different strategies will be useful. While in adults, we generally start with the examination of the right eye, in children, I generally start with the affected eye in a unilateral process. Often you only get one good look and it is better for it to be at the affected eye. It is important to make sure that the slit lamp is at the correct height for the child. This may involve sitting on a parent's lap or kneeling. I try to make a game of this, encouraging the child to hold on to the handles of the slit lamp and "ride the motorcycle." An adult in the room may help by stabilizing the child's head against the bar of the slit lamp. It is prudent to start with a low light intensity and gradually increase the illumination as needed for the exam and as tolerated by the child. The provider should carry on a conversation during the exam, coaching the child as to the progress and duration of the exam. With younger children, silly comments, such as "can you find Mickey Mouse in the light?", can help with cooperation. You will never get a very detailed slit lamp exam with a young child and it therefore important to know what you are looking for prior to starting. Multiple exams, for example to teach medical students, residents, and fellows, can be challenging for the pediatric patient. Again, if the exam is insufficient, options include a rapid follow-up visit to try again or an exam under anesthesia. For conditions that require multiple office visits (for example, management of vernal keratoconjunctivitis) one should make a note of what works for a particular child and plan accordingly. Some children are more cooperative in the morning, others better after a nap. Limiting wait time prior to seeing the provider is also helpful in optimizing cooperation.

Diagnosis of the Red Eye in Children

The remaining chapters in this book will cover important causes of red eye in children (infections, allergic eye disease, ocular surface disease) in detail. For the provider faced with a child with an acute red eye, the most important decision is whether an examination by an ophthalmologist is needed, as well as the timing of such a visit. Certain symptoms (e.g., severe pain or loss of vision) or history (including eye trauma or use of contact lenses) should almost always trigger an ophthalmology referral due to the potential for vision-threatening conditions like corneal ulceration or laceration. Milder symptoms such as eye redness and watery discharge in the setting of an upper respiratory infection or ocular itching with the onset of the spring pollen season can often be effectively managed by a pediatrician or advanced care provider. When in doubt, it is always safer to refer a child with a worrisome history, suspicious exam, or recurrent or recalcitrant symptoms to an ophthalmologist.

Table 1.1 details common causes of unilateral and bilateral eye redness in children. Interested readers are referred to specific chapters for a discussion of treatment options for these conditions.

Table 1.1 Common causes of unilateral and bilateral eye redness in children

Unilateral red eye	Bilateral red eye
1. **Corneal abrasion or foreign body** (Gerstenblith and Rabinowitz 2012; Pavan-Langston 2008) (May have a history of trauma, abrasion may be visible as disruption of the corneal light reflex, foreign body may be visible. Typically acute onset of symptoms. Often associated with pain, tearing and light sensitivity. Abrasions may be managed with topical ophthalmic antibiotics to prevent infection during healing, foreign bodies require referral for removal)	1. **Infectious conjunctivitis** (Koo and Colby 2017) (Watery discharge, pre-auricular lymphadenopathy, concurrent URI common with adenoviral conjunctivitis. Mucopurulent discharge more commonly bacterial conjunctivitis. Can often be managed with topical antibiotics by the pediatrician. Referral indicated if lack of improvement or atypical history)
2. **Contact lens keratitis** (Koo and Colby 2017) (History of contact lens use, white spot may be visible on exam. Can be acute or subacute onset. Same symptoms as abrasion/foreign body. Requires urgent referral for cultures and antimicrobial treatment)	2. **Allergic eye diseases** (Cruzat and Colby 2017) (Often associated systemic atopy, symptoms typically seasonal, itching is a predominant symptom, findings on exam may be less impressive than symptoms. Mild cases can be managed with over the counter allergy drops. Referral for more serious or nonresponsive symptoms)
3. **Herpetic keratitis or conjunctivitis** (Koo and Colby 2017) (Very common in children, can be associated with a history of oral cold sores, can occasionally be bilateral in children. Requires referral)	3. **Blepharitis/dry eye syndrome** (Trief and Colby 2017) (Typically underdiagnosed in children, symptoms include an intermittent dry or gritty feeling, may be associated with recurrent eyelid styes, parents may show signs of facial rosacea. Trial of artificial tears to improve symptoms. If no improvement, consider referral)
4. **Subconjunctival hemorrhage** (Gerstenblith and Rabinowitz 2012; Pavan-Langston 2008) (Bright red spot visible with a penlight, can be associated with history of trauma or eye rubbing, must make sure there is no severe injury to the eyeball)	4. **Contact lens issues** (Jacobs and Barrett 2017) (May be due to poor lens fit, lens overwear, or overnight use of lenses. Symptoms include discomfort when wearing lenses, foreign body sensation, reduced vision with lenses. Treatment is cessation of lens use and a lens refit by the eye care provider)
5. **Eye trauma** (Gerstenblith and Rabinowitz 2012; Pavan-Langston 2008) (Often history of injury, although not always. Irregular pupil, soft eye pressure are signs of open globe injury. Blood in the anterior chamber (hyphema) may be visible. Requires referral)	
6. **Scleritis/uveitis** (Gerstenblith and Rabinowitz 2012; Pavan-Langston 2008) (Can be associated with systemic diseases like juvenile idiopathic arthritis or Crohn's disease; severe pain common with scleritis; light sensitivity common with uveitis. Requires referral)	

Compliance with Ethical Requirements Kathryn Colby declares that she has no conflict of interest. No human studies were carried out by the author for this chapter.

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Corneal Diseases in Children: Imaging

2

Christina Rapp Prescott, Lois J. Hart and Kathryn Colby

Introduction

Pediatric cornea patients present unique challenges in terms of both diagnosis and management. Obtaining an accurate and complete history and examination is especially challenging with younger patients. Fortunately, an ever-increasing array of ophthalmic imaging tools can assist in making correct diagnoses, explaining pathology to both patient and family members, and managing many corneal conditions. This chapter will discuss when to consider various ophthalmic imaging modalities, including photography, specular or confocal microscopy, anterior segment optical coherence tomography, ultrasound, ultrasound biomicroscopy (UBM), topography, and keratometry.

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Photography

When to use: Detailed slit lamp examination is critical for the diagnosis and management of most corneal pathology This can be especially challenging in pediatric patients, who may not be able to position appropriately or remain still (Figs. 2.1a and 2.2a). High-resolution photographs, which are useful to document findings and monitor progression, are especially useful in pediatric patients, though they are not always possible. A length standard can be included in the image to facilitate corneal diameter measurements, which is especially useful in patients with small (microcornea or microphthalmos) or large (megalocornea or congenital glaucoma) corneas (Puvanachandra and Lyons 2009). To provide the highest quality images, the examiner should select a camera based on both patient characteristics (age, level of cooperation, and degree of photophobia) and level of detail needed.

Options available: Slit lamp cameras can be used with cooperative children who are able to sit at the slit lamp and focus at a specific location. Children as young as 3 years of age, who are cooperative, can often position at the slit lamp, as long as the chair and headrest are adjusted properly.

A video capture technique, which will tolerate a degree of motion greater than is acceptable for standard flash-based slit lamp imaging systems, can be useful in children who are unable to maintain focus (Mireskandari et al. 2011). The video capture technique can also be used to image

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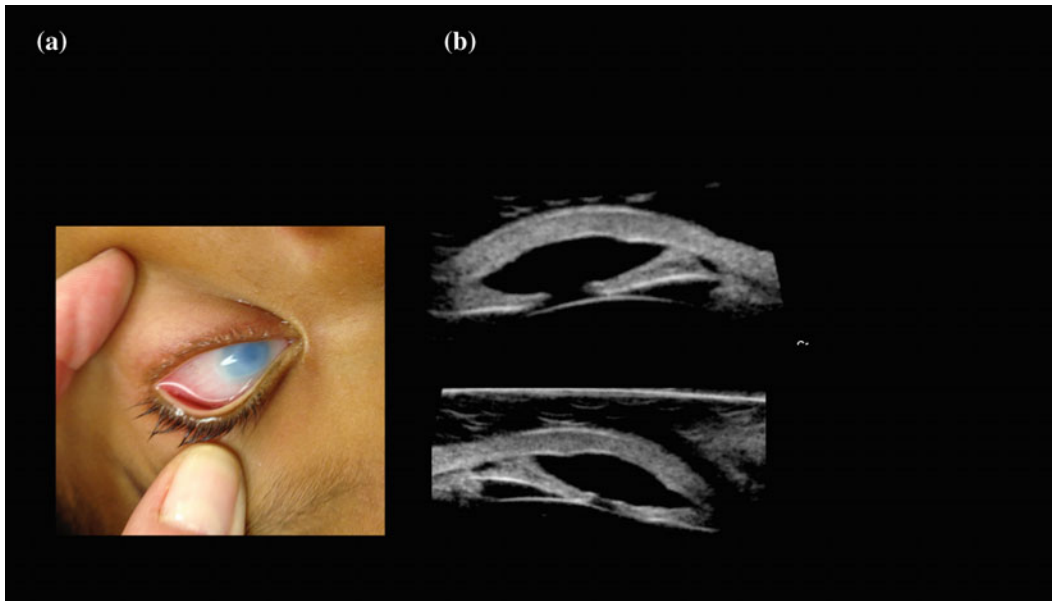


Fig. 2.1 A 1-week-old boy presented with a cloudy left cornea (**a**), noted at birth. On exam, the left cornea was opacified, the intraocular pressure was 9 in the right eye and 10 in the left eye, and the vision was blink to light in both eyes. At age 10 months, an exam under anesthesia with ultrasound biomicrocopy was performed to determine the extent of the pathology. The ultrasound biomicroscopy showed a thickened cornea, extensive iridocorneal adhesions without any lenticular corneal adhesions and an atrophic ciliary body consistent with Peter's anomaly (**b**). The decision was made not to proceed with corneal surgery

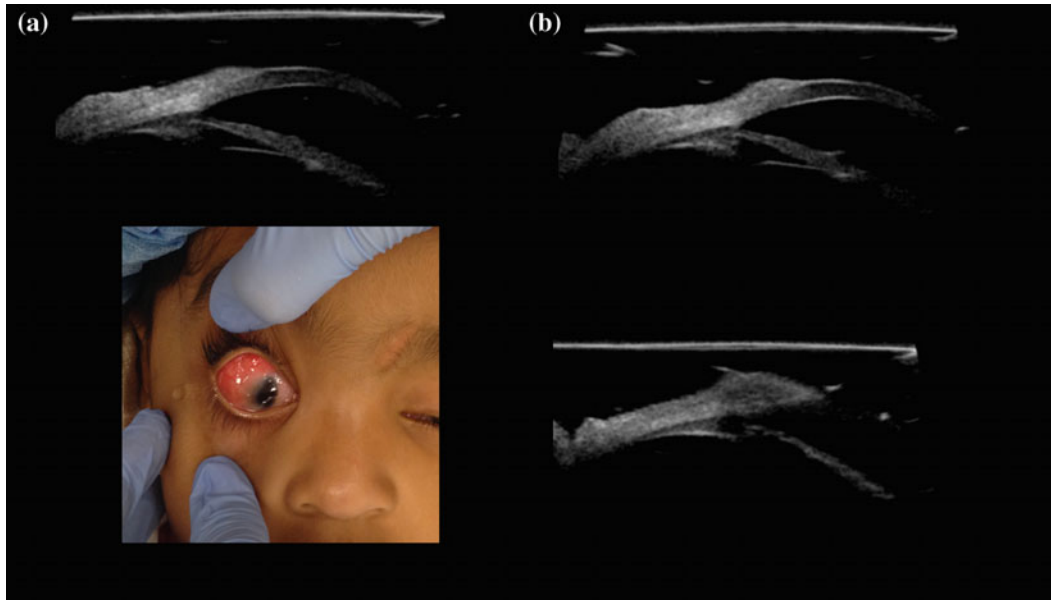


Fig. 2.2 A 4-year-old boy presented with a diffuse dome shaped lesion, covering part of the left cornea (**a**). A UBM was performed, which revealed a diffuse dome-shaped elevation of the corneal/scleral interface measuring approximately 0.97 mm. There appeared to be a demarcation line identified but the lesion did appear to extend into the corneal interface (**b**). The lesion was removed and the pathology report came back as "conjunctiva lining dense connective tissue with hair follicles, adipose tissue, and nerves, consistent with a dermoid"

dynamic phenomenon such as Seidel tests, phacodonesis, and subtle eye movement anomalies.

Children who are photophobic and unable to tolerate the minimum light requirement associated with slit lamp photography can sometimes be imaged using simple digital single-lens reflex cameras with medium telephoto macro lenses with a ring flash setting to minimize shadows (Mireskandari et al. 2011).

An increasing number of adaptors are now available for various smartphones, most specifically the iPhone® and these can be used to obtain ophthalmic images. Some of these adapters are specifically designed for use in conjunction with the slit lamp, the indirect ophthalmoscope, or the direct ophthalmoscope, but others allow the smartphone itself to be used as the primary device, often with a relatively low level of light (Myung et al. 2014). These are especially useful in children since many children feel more comfortable with a smartphone than with traditional ophthalmic imaging systems.

When used to image the anterior segment, fundus cameras lead to images with peripheral distortion, so their usefulness is limited in this setting. However, in patients with posterior segment pathology, the convenience of imaging both the anterior segment and the posterior segment with a single device may be worth sacrificing some peripheral details.

Microscopy

When to use: Confocal and specular microscopy can be used both to establish an initial diagnosis and to monitor patients over time. This high-resolution imaging modality is indicated when there is need for detailed imaging of a specific cell type, most commonly the endothelial cells. Specular microscopy can be used to assess endothelial cell counts both pre- and postoperatively.

This is especially useful in cases of congenital hereditary endothelial dystrophy (CHED). Patients with CHED have traditionally been treated with penetrating keratoplasty (PKP) for replacement of damaged endothelium, a technique associated with multiple long-term complications, including need for suture removal (often under anesthesia in children), risk of neovascularization, rejection, and loss of structural integrity of the cornea. However, Descemet's stripping endothelial keratoplasty (DSEK) is becoming an accepted treatment for CHED and may lead to lower complications, relative to PKP, in pediatric cases (Busin et al. 2011). As DSEK becomes more commonly performed in children, long term studies comparing the complication rates and endothelial cell loss between these two techniques will be critical to help determine the best surgical choice for these patients. Specular microscopy is critical to follow the endothelial cell count and morphology in these patients pre and post operatively.

Confocal microscopy provides extremely high-resolution imaging of specific regions of the cornea and is a useful tool in management of complex corneal infections, especially fungal and acanthamoeba infections. Though the gold standard for diagnosis of corneal ulcers, especially fungal and acanthamoeba, remains microbial culture, there is debate over the ideal culture medium for specific microorganisms (Boggild et al. 2009). Additionally, not all ophthalmic offices are equipped with onsite microbiology laboratories, so turn around time for these cultures can be significant. Therefore, in centers where confocal testing is available, it can provide a useful adjunct to microbial cultures. It can also be used to follow patients over time, and is especially useful when the infection is located in the deeper layers of the cornea (which often occurs with both fungal and acanthamoeba infections) (Oldenburg et al. 2011; Keay et al. 2011).

Confocal microscopy can also be used to assess morphological changes in the epithelium and stroma following corneal cross-linking in patients with keratoconus (Mazzotta et al. 2001). As corneal cross-linking becomes more widely performed, this will become increasingly relevant. Also, as this treatment modality is relatively new, data regarding the long term (greater than 10 years) effects on the morphology as well as the topography of the cornea will be critical to access the safety as well as the efficacy of the treatment.

Options available: Though only available in large, primarily academic centers, the confocal microscope allows the clinician to examine and image individual cells in all layers of the cornea. The specular microscope, is more readily available and allows for a similar level of high-resolution imaging, but is limited to the endothelium. Endothelial cell counts can be followed using specular microscopy in children who are able to maintain position in camera chinrest and who are able to focus. Though the confocal microscope is able to image a wider range of cell types and cell layers, it is much more challenging to use in children. The scan times are significantly longer for confocal microscopy versus specular microscopy and many models require the use of a coupling gel, which further limits tolerability in children.

Anterior Segment Optical Coherence Tomography (OCT) Ultrasound Biomicroscopy (UBM) and Posterior Segment Ultrasound

When to use: Both anterior segment OCT and UBM are useful for imaging the structures of the anterior segment, including all layers of the cornea, the iris, and the morphology of the angle. Therefore, they are useful in imaging patients with both congenital and acquired anomalies of the anterior segment, including tumors (Fig. 2.2b), Peter's anomaly (Fig. 2.1b), ICE syndrome, congenital glaucoma, and following ocular trauma (Cauduro et al. 2012). Both anterior segment OCT and UBM can be useful in the pre and postoperative management of patients (Nesi et al. 2012). Vengayil et al. reported the use of OCT to enable visualization of a retained host Descemet membrane following PKP for CHED, before and after surgical removal (2008).

Though the structures imaged by the UBM and anterior segment OCT are similar, there are some differences between the two modalities. The primary difference is that OCT requires a relatively clear cornea and media, since it relies on light for imaging. This precludes its use in patients with opaque corneas. Since ultrasound relies on sound waves, this imaging modality is especially useful when corneal opacities limit the view to the anterior and posterior segments. In complex diagnostic cases with co-existing anterior segment dysgenesis, the UBM can be used to assess the need for additional procedures and surgical approach prior to corneal transplantation, including cataract extraction, intraocular lens implantation, iris reconstruction, and glaucoma procedures. UBM is also helpful in planning tumor excision. For anterior segment tumors, the UBM offers overall better anatomic resolution, especially of posterior tumor margins. The anterior segment OCT, however, demonstrates better resolution of anterior tumor margins (Bianciotto et al. 2011).

The contact B-scan is used to scan the posterior segment of the globe to identify pathology. Examples of this would be vitreous debris or various types of choroidal lesions, excavation of the optic nerve head, and orbital pathology. In pediatric patients, B-scan often visualizes the superior ophthalmic vein within the intraconal space.

Options available: Anterior segment OCT is a noncontact device and can thus be more readily employed when examining children, provided they are able to position and fixate. Anterior segment OCT uses a superluminescent light-emitting diode with a wavelength of 1310 nm to image the cornea (Izatt et al. 1994). The anterior segment OCT can penetrate 3–4 mm and has a resolution of 18 μm.

UBM is a high-frequency, 20–50 MHz, and has an axial resolution of approximately 30 microns depending on the frequency. Higher frequency ultrasound leads to shallower penetration of the ultrasound wave and better resolution of the image. There are a number of commercially available UBM systems with transducer ranges between 20 and 50 MHz.

There are two UBM scanning techniques, both require contact to the eye either with saline use as a standoff or gel as a contact medium.

The Immersion Method

To perform an immersion scan, the eye is anesthetized, a scleral shield is placed securely under

eyelids. The shield is then filled with a coupling solution, usually sterile saline. Since this is an open system the transducer can be moved closer or further away from the eye, allowing the area of interest to be kept within the focal zone. For safety reasons it is important the immersion technique only be performed during an examination under anesthesia (EUA) for the pediatric population.

The Contact Method

Standoff caps are available in 4 depths, the most common is the 3.5–4.5 mm. The standoff cap is inserted over the transducer, filled with saline/distilled water, then covered with a thin barrier such as Tegaderm (3 M). Tegaderm is a sterile transparent dressing which is waterproof and a viral barrier used often as over IV sites. A generous amount of coupling agent such as Genteal gel® is then used between the probe cover and the cornea. There is no contact of the transducer to the cornea since the transducer is on the surface of the gel.

The ClearScan Probe cover system (ESI, Inc) is a similar technique, in which the sterile probe cover is filled with saline/distilled water and the transducer is placed into the probe cover. A coupling agent such is then used between the probe cover and the cornea. However, there is direct contact to the cornea with this technique.

Images through closed lids can be obtained with the contact methods, with limited diagnostic information.

The primary difference between UBM and conventional B-scan technology is the frequency of the ultrasound. B-scan uses 10–12.5 MHz frequency, which is primarily used for imaging of the posterior segment due to its deeper penetration and lower resolution. However, B-scan systems can be modified with a standoff to allow anterior segment scanning. The focal zone of the B-scan transducer typically starts approximately 15 mm from the scanning surface. Therefore, it is important that the area to be examined be within the focal zone.

Topography

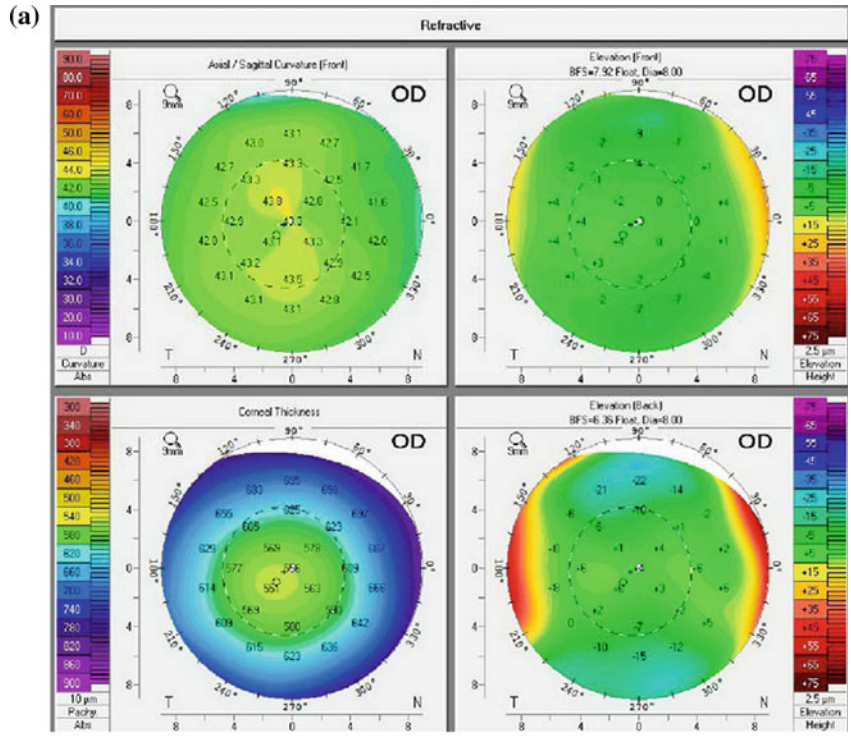
When to use: Corneal topography is especially important for preoperative assessment and for postoperative management of pediatric patients undergoing corneal surgery. Children with keratoconus require serial topography for assessment of progression (Fig. 2.3a, b). Though collagen cross-linking is not yet FDA approved in the United States, several clinical trials evaluating its use are underway, and inclusion criteria are based largely on topographical parameters (Kankariya et al. 2013). Patients between the ages of 12 and 35 years with keratoconus may be candidates for one of these trials based on their corneal topography. Enrollment varies depending on the trial, but generally requires a minimum corneal thickness of at least 400 μm and a maximal keratometry of less than 60 diopters, as well as the absence of additional corneal pathology, including infection and visually significant scarring (Keating et al. 2010).

Among patients with irregular or opacified corneas, autokeratometers may be inaccurate and topography may therefore be a more reliable option for intraocular lens calculations, when indicated. Finally, topographic analysis of pediatric patients is important following corneal transplantation, to direct suture removal and assist in contact lens fitting when needed.

Options available: Optical, placido disc, or Scheimpflug topography can be used to access corneal steepening across multiple areas of the cornea and are widely available.

Keratometry

When to use: Keratometry is necessary to calculate optimal lens power and is thus essential prior to intraocular lens implantation, which is becoming a more accepted part of pediatric cataract surgery (The Infant Aphakia Treatment Study Group 2014). In rare instances, pediatric patients with anisometropic amblyopia who are unable to tolerate correction with glasses or contact lenses can be considered for refractive


(a)
Refractive
Axial / Sagittal Curvature (Front)
OD
Elevation (Front)
BFS=7.92 Float, Dia=8.00
OD
Corneal Thickness
OD
Elevation (Back)
BFS=6.36 Float, Dia=8.00
OD

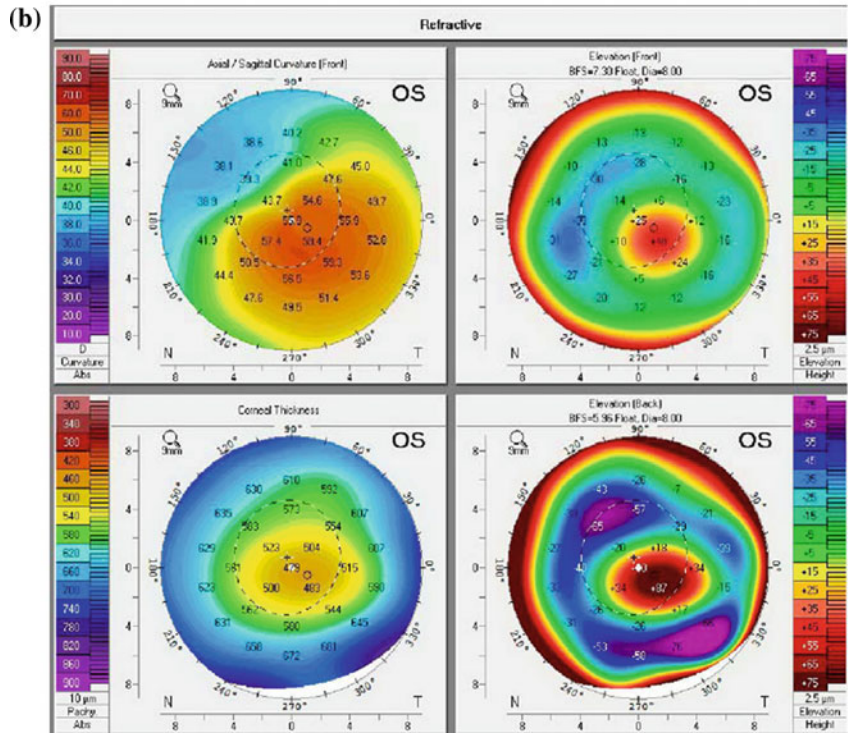

(b)
Refractive
Axial / Sagittal Curvature (Front)
OS
Elevation (Front)
BFS=7.30 Float, Dia=8.00
OS
Corneal Thickness
OS
Elevation (Back)
BFS=5.96 Float, Dia=8.00
OS

Fig. 2.3 A 14-year-old boy presented with blurry vision in his left eye, progressing over approximately 2 years. His vision was 20/20 in his right eye (**a**) without correction and counting fingers in his left eye without correction, and with a refraction of −4.25 − 5.25 × 146. One year prior to our exam, he was seen by an outside optometrist and per those records, he was 20/20 in the right eye and 20/50 in the left eye without correction. At that time, the vision in his left eye had corrected to 20/20 with +0.50 − 1.50 × 115. Tomographic imaging showed inferior paracentral steepening and associated thinning, typical of keratoconus, in the left eye only (**b**). Based on his topography, the rapid decrease in his vision, and his relatively young age, the decision was made to enroll him in a corneal cross-linking clinical trial

surgery, in the form of phakic anterior chamber intraocular lens implantation, refractive lens exchange, or corneal refractive laser ablations (Pirouzian 2011). Though refractive surgery for children remains controversial and is not FDA approved, it is an area of growing interest that will require accurate keratometry measurements.

Options available: Keratometry can be performed as part of a complete exam under anesthesia using a handheld autokeratometer (Capozzi et al. 2008). Older children who are able to sit at the slit lamp and focus may be able to have ocular biometry measurements performed using the IOLMaster (Carl Zeiss Meditec, Jena, Germany) or Lenstar LS 900 (Haag-Streit AG, Koeniz, Switzerland) (Sahin et al. 2011).

Discussion

Ophthalmic imaging has traditionally been used primarily to document exam findings, but as technology evolves, newer imaging modalities enable the ophthalmologist to view structures not visible on ophthalmic examination. This includes individual cells in the cornea, not visible with even the highest slit lamp magnification. Additionally, corneal opacification no longer precludes examination of anterior segment structures, as they can be imaged using UBM. Corneal topography allows quantification of corneal power and thickness, which facilitates both diagnosis and perioperative management.

For children, the appropriate use of these imaging modalities is especially important. For very young children, it is especially critical to acquire all necessary information to limit the number of examinations required since these examinations may need to be performed under anesthesia. Additionally, when surgical intervention is required in children, precise postoperative management is critical to reduce risk of amblyopia. Finally, these imaging tools can be a valuable addition to discussions with patients and family members, since an ophthalmic image can be worth more than a thousand words when explaining a complex ocular condition to a family.

Compliance with Ethical Requirements Christina Prescott, Lois Hart, and Kathryn Colby declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this article.

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Corneal Diseases in Children: Infectious Keratitis

3

Eubee B. Koo and Kathryn Colby

Infectious keratitis is a serious, potentially vision-threatening condition that represents one of the most common causes of ocular morbidity worldwide (Whitcher et al. 2001). While it is considered an uncommon event among pediatric populations, estimated to be between 9 and 13% of all cases (Ormerod et al. 1986, 1987; Srinivasan et al. 1997; Parmar et al. 2006a; Hsiao et al. 2007), the timely diagnosis and treatment of these infections is particularly important as younger patients are susceptible to developing not only blindness from corneal disease, but also secondary amblyopia (Singh et al. 2006). Thus, any suspicion of an infectious etiology should be thoroughly investigated, with special attention to the history of infectious exposure, epidemiological trends, and clinical clues—including ocular findings and patterns of corneal inflammation and systemic signs and symptoms that may be specific to a certain pathogen. While corneal scraping and laboratory culture may aid in making the correct diagnosis and in guiding the therapeutic approach, it should be noted that culture positivity has been shown to range anywhere between 34 and 87% in children with presumed microbial keratitis (Ormerod et al. 1986; Cruz et al. 1993; Clinch and Palmon 1994; Kunimoto et al. 1998; Vajpayee et al. 1999; Parmar et al. 2006a; Hsiao et al. 2007; Al Otaibi et al. 2012; Chirinos-Saldaña et al. 2013); therefore, knowledge of the epidemiological and clinical features of the most likely pathogens is crucial in prompt diagnosis, treatment, and, ultimately, the prevention of poor outcomes.

Nonviral Microbial Keratitis

Worldwide, nonviral microbial keratitis, which refers mostly to bacterial and fungal keratitis, is a very common cause of corneal opacification and legal blindness—second only to cataracts—in study populations encompassing both adult and pediatric patients (Al-Mujaini et al. 2009). Overall, there are fewer studies observing pediatric populations versus adult populations. However, the available retrospective case analyses have revealed that (1) boys appear to have a higher rate of microbial keratitis than girls (Jhanji et al. 2011), which may be attributed to higher rates of trauma among boys (Luff et al. 1993; Thompson et al. 2002), and (2) trauma is almost unanimously the most common predisposing factor to developing microbial keratitis in children (Ormerod et al. 1986; Cruz et al. 1993; Clinch and Palmon 1994; Kunimoto et al. 1998; Vajpayee et al. 1999; Singh et al. 2006; Al-Otaibi 2012; Chirinos-Saldaña et al. 2013). These studies have also revealed that the incidence and types of bacterial infections, in general, vary with

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region and differ especially amongst populations in developed versus developing countries (Al-Otaibi 2012). For example, the incidence of microbial keratitis, in general, has been noted to be higher in developing countries (Erie et al. 1993; Srinivasan et al. 1997; Upadhyay et al. 2001; Al-Otaibi 2012), with reports of up to a 20-fold greater incidence of cornea-related blindness in children in tropical versus developed countries (Maurin et al. 1995).

Clinical Picture

The pediatric ophthalmologic patient is often a diagnostic challenge to even the most experienced clinician. While adults may be able to provide a complete history of possible inciting events and readily describe symptoms of infectious keratitis such as pain, redness, photophobia, discharge, and hazy vision, pediatric patients are often unable and one must rely on their parents' observations, which may or may not be completely accurate. Further, pediatric patients may not be able or willing to cooperate with ophthalmologic exams, which are often considered intimidating even to new adult patients. Regardless, a thorough and careful exam must be attempted to help determine the likely etiology.

Distinguishing between bacterial and fungal keratitis can be very difficult, especially as one can masquerade as the other; for example, yeast ulcers that are plaque-like and slightly more defined may be confused with bacterial ulcers, while some bacteria may present with satellite lesions mimicking a fungal ulcer (Al-Mujaini et al. 2009). However, there are some distinct features that make one diagnosis more likely than the other. For example, the onset of symptoms is typically more rapid in bacterial keratitis versus the gradual onset that is often described with fungal infections. In bacterial keratitis, slit-lamp exam of the cornea may reveal well-demarcated white infiltrates in the central or paracentral cornea; in comparison, fungal keratitis is more likely with poorly demarcated grayish-white infiltrates with feathery borders and satellite lesions. Stromal edema, corneal thinning, epithelial defects, endothelial inflammatory plaques, and Descemet's folds, as well as other signs including mucopurulent discharge, inflammatory cells in the anterior chamber, hypopyon, and lid edema can be found in varying degrees in both types of bacterial and fungal keratitis.

Risk Factors

In the healthy eye, bacterial infection of the cornea is a rare event as the protective mechanisms of the eye, including the blink reflex and the antimicrobial properties of tear film, impede bacterial adherence and invasion of corneal epithelium and stroma (Akpek and Gottsch 2003). With any disruption of these natural barriers, however, the cornea becomes susceptible to pathogenic bacteria that are able to adhere to epithelial defects and invade further into healthy tissues (Al-Mujaini et al. 2009). The various risk factors that have been identified in microbial keratitis, such as trauma, contact lens wear, and ocular and systemic disease, all involve corneal compromise.

Several studies have shown that trauma is associated with microbial keratitis in up to 80% of presumed cases (Song et al. 2012; Ormerod et al. 1986; Cruz et al. 1993; Clinch and Palmon 1994; Kunimoto et al. 1998; Vajpayee et al. 1999; Singh et al. 2006; Hsiao et al. 2007; Al-Otaibi 2012; Chirinos-Saldaña et al. 2013; Young et al. 2013), making it, by far, the most common associated finding in pediatric microbial keratitis. These traumatic events, caused by plants, metals, plastics, fireworks, and pencils, for example, are thought to occur more frequently in the pediatric group secondary to a poor understanding of hazardous objects and their proper handling (Parmar et al. 2006a).

Two studies in the current literature did not find trauma to be the most commonly associated finding; both of these studies, conducted in Asia where overnight orthokeratology is commonly implemented to reduce myopic refractive error, reported contact lens wear as the most common predisposing risk factor (Hsiao et al. 2007; Young et al. 2013). While contact lens wear is

less common in the pediatric population and even less so in the pediatric population of the developing world, it remains an important risk factor in causing infectious keratitis (Cruz et al. 1993; Clinch and Palmon 1994; Singh et al. 2006; Chirinos-Saldaña et al. 2013). The association between corneal infection and use of contact lenses is well known (Dart 1988). Studies have revealed that contact lenses induce hypoxia, increase corneal temperature, and decrease tear flow over the corneal surface, effectively disrupting the innate protective mechanisms (Evans and Fleiszig 2013). Further, contact lenses encumber the exchange of fluids between the contact lens–cornea interface, creating a stagnant pool of debris and cellular material that may play a role in causing inflammation (McNamara et al. 1999; Paugh et al. 2001; Maki and Ross 2014). Orthokeratology lenses have been shown to be worse in this regard, retaining more bacteria than alignment-fitted rigid gas-permeable lenses (Tseng et al. 2005; Choo et al. 2009). Additionally, contact lenses and their storage cases may foster the formation of biofilms, further encouraging bacterial growth and infection (Kang et al. 1995; Gorlin et al. 1996; McLaughlin-Borlace et al. 1998; Dart et al. 2008; Stapleton et al. 2008; Behlau and Gilmore 2008; Chirinos-Saldaña et al. 2013; Gu et al. 2013). While the increasing availability of silicone hydrogel lenses and other improvements in contact lens design and storage solutions have helped ameliorate some of the risks of contact lens use (Sweeney 2013), contact lens-related infections continue to pose a risk to users, especially children who may not understand the necessity of regular cleaning and proper use and handling of contact lenses (Tuli et al. 2013).

Ocular disease is another commonly reported risk factor in the development of microbial keratitis, associated with up to 18% of pediatric cases (Song et al. 2012; Ormerod et al. 1986; Kunimoto et al. 1998; Hsiao et al. 2007; Chirinos-Saldaña et al. 2013; Young et al. 2013). These conditions, which include vernal keratoconjunctivitis, chronic blepharitis, ocular rosacea, trichiasis, congenital facial paralysis or corneal anesthesia, eyelid abnormalities, and prior viral infections, for example, create conditions in which epithelial defects and subsequent infection are more likely to occur.

Systemic conditions, including systemic immunodeficiencies, hypoxic encephalopathy, severe prematurity, Stevens–Johnson syndrome/toxic epidermal necrolysis, vitamin or protein energy deficiencies, and measles, have all been noted to be associated with pediatric microbial keratitis (Cruz et al. 1993; Clinch and Palmon 1994; Kunimoto et al. 1999; Vajpayee et al. 1999; Chirinos-Saldaña et al. 2013). Systemic conditions and malnutrition interfere with wound healing (Emery and Sanderson 1995), potentially slowing the resolution of epithelial defects and thus prolonging the window of opportunity for microbial infection.

Finally, iatrogenic causes such as corneal surgery (Cruz et al. 1993; Chirinos-Saldaña et al. 2013), which compromise the ocular surface by direct manipulation of tissues as well as the introduction of foreign materials (e.g., sutures) that act as bacterial substrate, are also a commonly cited association. Topical steroids (Chirinos-Saldaña et al. 2013), which are frequently used in various eye diseases and act to decrease inflammation by directly downregulating host defense mechanisms, unsurprisingly, are also associated with microbial keratitis.

Host Response

While a healthy immune system is crucial for overcoming infection, in avascular tissues such as the cornea, a florid inflammatory response as might be seen in pediatric patients may further worsen the integrity of corneal tissues, contributing to poor outcomes in infectious keratitis. For example, the action of polymorphonuclear neutrophils, or PMNs, a key player in host defenses against infection, is associated with corneal damage. To kill bacteria, PMNs degranulate to release bactericidal host enzymes and toxins, which, while successfully destroying unwanted bacteria, often destroy corneal tissue as well. The detrimental effects of such inflammatory responses can lead to scarring and even

perforation (Matsumoto et al. 1992; Al-Mujaini et al. 2009).

Further, the destruction of bacteria also results in the release of endotoxins, proteases, collagenases, coagulases, lipases, and fibrinolysins, which further damage the cornea (AlonsoDeVelasco et al. 1995; Al-Mujaini et al. 2009). In fact, the formation of corneal ring infiltrates, which can be found in infectious keratitis of various types, may be due to the chemotactic response of PMNs to endotoxins, such as lipopolysaccharide (LPS), which is found in Gram-negative bacteria (Mondino et al. 1977).

Common Pathogens and Pathogenesis

In children, bacterial keratitis is more prevalent than fungal keratitis, and infections with parasites and amoebae, such as *Acanthamoeba*, are rare. Here, we describe the most common microorganisms associated with pediatric microbial keratitis.

Bacteria

The ocular surface is by no means sterile, populated by bacteria during birth or rapidly thereafter, with both aerobic and anaerobic species. Aerobic species include coagulase-negative *Staphylococcus*, *Corynebacterium*, *Streptococcus*, *Enterococcus*, and *Escherichia*, while common anaerobic species are *Propionibacterium* and *Bifidobacterium* (Brook et al. 1979; Isenberg et al. 1988; Kowalski and Roat 2006). A few days after birth, other species, including *Moraxella catarrhalis* can be found (Isenberg et al. 1988). The microbiome of the ocular surface continues to change with age and environmental exposures (Singer et al. 1988; Al-Otaibi 2012). Although most of the bacteria found on the conjunctiva do not cause pathology in the healthy eye, given the opportunity—namely, an epithelial defect on which to adhere—certain bacteria can invade and proliferate within the cornea and quickly become destructive. In pediatric patients with presumed microbial keratitis, *Staphylococcus epidermidis*, *Streptococcus pneumonia*, *Staphlyococcus aureus*, and *Pseudomonas aeruginosa* are the most commonly isolated organisms in culture-positive specimens (Song et al. 2012; Ormerod et al. 1986; Cruz et al. 1993; Clinch and Palmon 1994; Kunimoto et al. 1998; Vajpayee et al. 1999; Parmar et al. 2006a; Singh et al. 2006; Hsiao et al. 2007; Al-Otaibi 2012; Hong et al. 2012; Chirinos-Saldaña et al. 2013; Young et al. 2013; Chaurasia et al. 2014). These common bacteria, as well as other Gram-positive, Gram-negative, and spirochete species are discussed in this section.

Gram-Positive Bacteria

Staphylococcus epidermidis

S. epidermidis is a coagulase-negative staphylococcus that is found in abundance on human skin and mucous membranes, including that of the eye (e.g., lid margins, conjunctiva) (Bannerman et al. 1997). It is an example of an opportunistic pathogen, capable of infecting only susceptible individuals such as those with immune deficiencies or other serious illnesses and, in ophthalmology, those with compromised corneal epithelium. In pediatric cases of microbial keratitis, *S. epidermidis* has been frequently found to be the most commonly isolated pathogen in corneal scrapings (Song et al. 2012; Clinch and Palmon 1994; Kunimoto et al. 1998; Vajpayee et al. 1999; Hong et al. 2012; Chirinos-Saldaña et al. 2013); in one study, it was found to be associated with more than one-third of culture-positive cases (Song et al. 2012).

Relative to other staphylococcal species like *S. aureus*, *S. epidermidis* is considered to be less virulent; nevertheless, in its possession are various characteristics that allow it to successfully adhere to and survive within the cornea. Like all Gram-positive bacteria, *S. epidermidis* contains the polysaccharide teichoic acid within its cell wall. Based mostly on in vitro studies, it has been hypothesized that teichoic acid is the main compound that allows for attachment of Gram-positive bacteria to exposed epithelial

receptors (Aly and Levit 1987; Ofek et al. 1975; Nealon and Mattingly 1984; Reichert and Stern 1984; Panjwani et al. 1990), thus initiating the pathogenic process of infection. Surface proteins have also been identified on the bacteria that bind to collagen, fibrinogen, elastin, and other matrix proteins (Otto 2009). After initial adherence to the epithelium, *S. epidermidis* aggregates to form a biofilm, effectively protecting itself from the insults of host immunity while it continues to invade and replicate within the corneal stroma (Otto 2009). In addition to these virulence factors, *S. epidermidis* has other mechanisms that allow it to evade the immune system. For example, it produces exopolymers that interfere with neutrophil phagocytosis, complement deposition, and the innate protective effects of high osmolar environments (Otto 2009).

Streptococcus pneumoniae

Like *S. epidermidis*, *S. pneumoniae*, a Gram-positive diplococcus, is commonly found in the human body—namely, the upper respiratory tract—without causing pathology; however, in susceptible individuals, infection with *S. pneumoniae* can have devastating effects on the body without proper treatment. In the eye, pneumococcal keratitis typically presents with a central yellow to gray-white ulcer with pronounced inflammatory signs including infiltrates and hypopyon (Parmar et al. 2003). One of the key distinguishing features of *S. pneumoniae* is its serpiginous pattern of spread, with an undermined leading edge (Mascarenhas et al. 2012). Unchecked, *S. pneumoniae* can cause significant damage to the cornea in a relatively short period of time (Mascarenhas et al. 2012). Although cases of pneumococcal keratitis continue to decline globally (Parmar et al. 2003), it remains a significant problem in the pediatric population. Among the commonly isolated Gram-positive bacteria, *S. pneumonia* represents up to 20% of all culture-positive specimens (Ormerod et al. 1987; Clinch and Palmon 1994; Kunimoto et al. 1998; Singh et al. 2006; Hsiao et al. 2007; Hong et al. 2012; Chirinos-Saldaña et al. 2013; Chaurasia et al. 2014).

Although teichoic acid in the cell wall may aid in initial attachment of *S. pneumoniae* to exposed corneal epithelial receptors, the most important virulence factor is likely its polysaccharide capsule, which has been shown to interfere with opsonization by complement and subsequent phagocytosis by host neutrophils (Al-Mujaini et al. 2009; Norcross et al. 2011). Other surface proteins such as pneumococcal surface protein A and complement factor H-binding component have also been found to serve a similar function, inhibiting complement activation (AlonsoDeVelasco et al. 1995). However, one study (Reed et al. 2005) of *S. pneumoniae* keratitis in a rabbit model showed that even strains lacking capsules were just as virulent as strains with capsules, implying that other characteristics may play an even larger role in corneal infection than previously thought. Indeed, *S. pneumoniae* has been found to possess various toxins that may enhance its ability to infect and destroy tissues. Pneumolysin, for example, has been revealed as a major contributor to corneal ulceration, via the formation of porous structures in host cell membranes, which lead to osmotic dysregulation and, eventually, cell death (Taylor et al. 2013).

Staphylococcus aureus

S. aureus is yet another Gram-positive opportunistic pathogen that is present on the eyelids in up to 15% of people (Al-Mujaini et al. 2009). In the pediatric population, it is a rarer cause of keratitis relative to the other aforementioned Gram-positive bacteria; however, the current literature reports an incidence ranging from 2.6% up to 20% of culture-positive cases (Song et al. 2012; Ormerod et al. 1986; Cruz et al. 1993; Clinch and Palmon 1994; Kunimoto et al. 1998; Singh et al. 2006; Hsiao et al. 2007; Hong et al. 2012; Chirinos-Saldaña et al. 2013). *S. aureus* is a more virulent bacterial species than *S. epidermidis* and is typically associated with more severe corneal infiltration, which left untreated, may require invasive interventions.

The precise mechanisms of virulence factors of *S. aureus* in the cornea, like those of other

bacteria, remain poorly understood. In vitro and animal model investigations suggest that *S. aureus* achieves initial adherence to host epithelium via proteins on its surface that can bind fibronectin and collagen (Rhem et al. 2000; Jett and Gilmore 2002; Marquart and O'Callaghan 2013). Once bound, bacteria are able to rapidly penetrate the corneal epithelium to reach the corneal stroma (Marquart and O'Callaghan 2013). The most important virulence factors in *S. aureus* keratitis, however, are thought to be its exotoxins. Near ubiquitous to all *S. aureus* strains (O'Callaghan et al. 1997) and, presumably the most important of the exotoxins, is alpha-toxin, a lytic cytotoxin that has been shown—even in very small quantities—to be capable of causing extensive edema and damage to the corneal epithelium in animal models (Callegan et al. 1994; Moreau et al. 1997). Gamma-toxin is another example of a hemolytic protein that can cause substantial damage to the corneal epithelium; in studies investigating alpha-toxin deficient *S. aureus* strains, those bacteria with gamma-toxin were still able to mediate corneal ulceration (Dajcs et al. 2002). Other toxins, such as beta-toxin may also contribute to corneal pathology, but to a lesser degree than alpha- and gamma-toxins (O'Callaghan et al. 1997).

S. aureus also possesses a variety of other virulence factors that allow it to evade the immune system and persist within the cornea. These virulence factors include bacterial enzymes such as leukocidin, kinases, and hyaluronidase that help it spread within host tissues; a capsule with associated surface proteins, like Protein A, that interfere with innate immunity and phagocytosis (Foster et al. 2014); and an exceptional ability to develop resistance to various antibiotics (Zecconi and Scali 2013). While their specific roles in corneal infection have not been studied, it is thought that these factors may contribute to *S. aureus*' resilience in and its damaging effects on corneal tissue.

Less Common Gram-Positive Bacteria

Other bacterial pathogens thought to be capable of causing keratitis have been reported, although the pathogenesis of these organisms has yet to be fully elucidated. In rare pediatric cases, cultures of corneal ulcers have grown *Corynebacteria* (Hong et al. 2012; Young et al. 2013). It is still highly debated whether *Corynebacterium*, which is part of the normal conjunctival flora, is virulent enough to cause keratitis; nevertheless, in the adult population, few cases of suture-related biofilm formation and *Corynebacteria* keratitis (Mihara et al. 2004; Suzuki et al. 2007) and *Corynebacteria* keratitis following refractive surgery (Garg et al. 2010) have been reported.

Overall, keratitis caused by *Bacillus* is an uncommon event in both adult and pediatric populations; however, *Bacillus* may be implicated in up to approximately 1–2% of bacterial keratitis in some parts of the developing world (Choudhuri et al. 2000). Like other bacterial keratitides, *Bacillus* keratitis is often preceded by injury to the eye—either traumatic or surgical and contact lens wear (Pinna et al. 2001; Ramos-Esteban et al. 2006). Exposure to dust and mud—where *Bacillus* is found—is also commonly associated; however, *Bacillus* species have been found to reside in healthy hosts without causing pathology, suggesting that preexisting tissue damage may be prerequisite for infection with *Bacillus* (van Bijsterveld and Richards 1965). *Bacillus* is considered a highly virulent species, likely due to the various phospholipases, proteases, and hemolysins they possess, and infection in a susceptible host can cause a variety of nonspecific sequelae including stromal infiltrate, abscesses, and ulceration (Olitsky et al. 1932; van Bijsterveld and Richards 1965; Choudhuri et al. 2000; Pinna et al. 2001).

Nocardia-associated keratitis is even more rare. In combined adult and pediatric studies, *Nocardia* has been reported to have been cultured from corneal ulcers, though often in conjunction with other bacteria (Choudhuri et al. 2000). The most common predisposing factors identified were the same as those for *Bacillus* (Choudhuri et al. 2000; Pinna et al. 2001; Garg et al. 2010; Basak et al. 2012). Ulcers caused by *Nocardia* are often indolent and may even be asymptomatic for some time. Clinically, infection caused by *Nocardia* may be readily

identified by the appearance of tiny yellow-white infiltrates in a wreath-like arrangement.

Gram-Negative Bacteria

Pseudomonas aeruginosa

The most common Gram-negative bacteria associated with microbial keratitis among both adult and pediatric patients is the aerobic Gram-negative rod, *Pseudomonas aeruginosa*. This species is pervasive throughout nature, growing most favorably in moist environments, such as soil and water (Tümmler et al. 2014); not only is it ubiquitous in nature, *Pseudomonas* has been commonly found to contaminate aqueous solutions such as those used to clean and store contact lenses, as well as contact lens cases (Stern and Schultz 2006). Not surprisingly, contact lens wear is the most commonly identified predisposing factor in *P. aeruginosa* keratitis. In the pediatric literature, Pseudomonas was found in 62.5 and 44.7% of culture-positive specimens in Hong Kong (Young et al. 2013) and Taiwan (Hsiao et al. 2007), respectively, where there is a high prevalence of high myopia and consequent contact lens and orthokeratology use; these studies largely reflected an older pediatric population, however. On the other end of the spectrum, prematurity and prolonged neonatal intensive care appeared to be an important predisposing factor in cases of *Pseudomonas* keratitis in neonates (Chaurasia et al. 2014). As *Pseudomonas* is an opportunistic pathogen, all infections appear to be associated with compromised corneal tissue, whether it be in the setting of extended contact lens wear, prematurity, or trauma.

While *Pseudomonas* is unlikely to infect healthy, intact corneal tissue, in the presence of even partial-thickness defects in the corneal epithelium, *Pseudomonas* is quick to adhere and begin its pathologic processes (Klotz et al. 1989). Left untreated, perforation can occur within as little as 72 h (Al-Mujaini et al. 2009). Pseudomonas virulence factors assist in bacterial adhesion and evasion of host immune response, and include surface structures, such as glycocalyx, pili, and flagella; endo- and exotoxins; and bacterial enzymes (Hahn 1997; Källström et al. 1998; Scheuerpflug et al. 1999).

While glycocalyx may play a role in hindering complement deposition, it is most important in allowing *Pseudomonas* to adhere to injured corneal cells, which is prerequisite for successful colonization and infection of host tissue (Pollack 1984). Additionally, glycocalyx allows for the formation of attachments among bacteria, leading to the formation of a biofilm, which not only creates a favorable microenvironment for further *Pseudomonas* growth, but also protects the organisms from phagocytosis by host immune cells (Costerton et al. 1983). Additionally, biofilm allows *Pseudomonas* to colonize the surface of contact lenses and contact lens cases, for example, both of which are common bacterial reservoirs (Dart and Seal 1988).

Other surface structures, such as the flagella and pili of *Pseudomonas*, fortify bacterial attachment to host cells, by binding to the glycosphingolipid asialo ganglio-*N*-tetraoslyceramide (asialo-GM1). Asialo-GM1 may be expressed in greater amounts in injured corneal tissue, as demonstrated in animal models, which may explain the increased susceptibility of *Pseudomonas* infection in traumatized corneas (Hazlett et al. 1993).

Further facilitating *Pseudomonas* adherence are endotoxins such as LPS, which have been found to act as an important ligand for the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is expressed in the basal epithelial cells of the cornea, which, when exposed to LPS, bind, then internalize the bacteria. Safe within the intracellular space, *Pseudomonas* can replicate (Lyczak et al. 2000).

Exotoxins, such as exotoxin A, also contribute to the rapid damage caused by *Pseudomonas* infection. Exotoxin A has been demonstrated to halt protein synthesis, thereby causing quick destruction of the affected cell; in the cornea, small amounts of this toxin have been shown to result in extensive damage to the cornea with eventual ulceration in a period of less than 24 hours (O'Callaghan et al. 1996).

Like *S. aureus*, *Pseudomonas* also has enzymes such as leukocidin and various other proteases that may contribute to corneal damage in microbial keratitis. To date, however, little is known about the specific roles each plays in corneal pathology secondary to the difficulty of separating the impact of bacterial versus host proteases (Lyczak et al. 2000).

Less Common Gram-Negative Bacteria

Neisseria gonorrhoeae is a much-feared neonatal infection, best known for its role in ophthalmia neonatorum, or newborn conjunctivitis. With the implementation of better antenatal and postnatal care, however, *Neisseria* infection has become increasingly rare; in fact, most of the pediatric literature is devoid of any mention of *Neisseria* keratitis with only one study of neonatal keratitis in India (Chaurasia et al. 2014) reporting it as a keratitis-associated pathogen. Even then, it was present in only two of 20 culture-positive specimens. Despite its low incidence, clinicians should remain mindful of its virulence in the cornea, as this bacteria is capable of causing significant pathology in the absence of an epithelial defect, unlike most other bacteria, by using its proteases to penetrate intact cornea (Al-Mujaini et al. 2009).

Spirochetes

Treponema pallidum

Transmitted in utero or at birth from mother to child, infection with *Treponema*, a small bacterial spirochete, is a cause of serious morbidity and mortality. While an emphasis on antenatal care and syphilis screening has helped diminish the number of adverse pregnancy outcomes and complications from infection, congenital syphilis continues to be a global problem (Kamb et al. 2010). Most recent studies estimate the incidence of congenital syphilis to be approximately 150,000 cases per year (Newman et al. 2013).

The manifestations of congenital syphilis are many, and include skin eruptions, rhinitis, abnormal facies, bone lesions, ophthalmologic, and neurological problems that may be present at any time, including at birth; however, about two-thirds of infected neonates appear normal at birth, which may delay the diagnosis and treatment of congenital syphilis. Consequently, these individuals are at greater risk for the inflammatory complications of untreated late congenital syphilis, which includes interstitial keratitis. Interstitial keratitis—which in addition to vestibular deafness and Hutchinson's teeth, form the Hutchinson triad of congenital syphilis—can occur at any stage of the disease but is commonly a late feature of the disease process, presenting between the ages of 5 and 25 (Harcourt 1967; Orsoni et al. 2004).

Interstitial keratitis caused by congenital syphilis is a non-suppurative, non-ulcerative, immune-mediated inflammatory process driven primarily by host antibodies against treponemal antigens as opposed to actual bacteria in the cornea (Lee and Lindquist 1989; Singh and Romanowski 1999; Aldave et al. 2001; Durnian et al. 2004; Kiss et al. 2005). Syphilitic keratitis may be localized or diffused and may or may not be associated with keratic precipitates or other eye pathology. It can present either unilaterally or bilaterally, although it has been noted that in 75% of patients with congenital syphilis keratitis, both eyes are affected at one time or another (Hariprasad et al. 2002). While the pathogenesis of this process remains unclear, it is well known that without treatment, the keratitis may progress to stromal neovascularization and, ultimately, severe scarring of the cornea with significant visual impairment (Orsoni et al. 2004; Kiss et al. 2005).

While *Treponema pallidum* can also cause an active interstitial keratitis in those primarily infected, it is much less common than keratitis associated with congenital syphilis, which comprises approximately 90% of syphilitic interstitial keratitis worldwide (Khurana 2003). It presents on average 10 years after infection and tends to be unilateral, with less vascularization than is seen in congenital syphilitic interstitial keratitis. No cases describing acquired syphilitic keratitis in children have been reported in the literature, although it has been noted to occur. Of note, any child with acquired syphilis should be assumed

to have been infected via sexual abuse and clinicians should act accordingly, until it has been proven otherwise.

Fungi

Pediatric cases of fungal keratitis have been reported in various parts of the world, with rates of incidence ranging up to 49% in China (Song et al. 2012) and 38% in Southern India (Singh et al. 2006); in the United States (Ormerod et al. 1987; Clinch and Palmon 1994), Taiwan (Hsiao et al. 2007), and Mexico (Chirinos-Saldaña et al. 2013), fungal keratitis comprises a much smaller percentage of microbial keratitis. To date, few studies have attempted to characterize the species involved in pediatric keratomycoses; of the available data, *Aspergillus* appears to be the most commonly associated fungus, especially in areas of warmer, tropical climate (Panda et al. 1997). Other cases reported to have been isolated from pediatric cases include *Fusarium*, *Alternaria*, *Curvularia*, *Microsporum*, *Penicillium*, *Mucor*, and *Candida* (Panda et al. 1997; Chirinos-Saldaña et al. 2013; Chaurasia et al. 2014). The diagnosis of fungal keratitis can be assisted by Gram stain which might show hyphal elements in approximately half of cases and wet-mount preparation which are positive in approximately 90% of cases (Panda et al. 1997).

Like most bacterial causes of microbial keratitis, fungi lack the ability to penetrate intact corneal epithelium, relying primarily on traumatic injuries to establish themselves on the cornea. In fact, the most commonly associated risk factor reported was trauma, typically with plant or vegetable matter (Panda et al. 1997). Once inoculated on compromised host tissue, however, fungi prove to be virulent organisms that can cause substantial morbidity. In contrast to most bacteria, fungi do not release chemotactic substances; this effectively delays the response of host innate immunity and allows the pathogen more time to adhere and establish itself within corneal tissues. Additionally, fungi have the added advantage of size as neutrophils and macrophages cannot fully ingest these large pathogens. Finally, fungi possess exotoxins, hemolysins, and proteases that facilitate the destruction of corneal tissue (Jones 2006).

Protozoa

Acanthamoeba

Acanthamoeba is a protozoan ubiquitous in nature; while it is found predominantly in soil and fresh water, it has also been isolated from the nares of up to 50% of normal adults (Mathers 2004). It can exist in one of two forms including an active, infective trophozoite and a dormant resilient double-walled cyst. There have been identified eight different species of acanthamoeba implicated in keratitis; of these, *A. castellani* and *A. polyphagaare* are the most common (Wang et al. 2014). Overall, acanthamoeba keratitis is very rare and estimated to occur at a rate of less than two cases per million adults per year (Ibrahim et al. 2009). While the literature reports individual cases of pediatric acanthamoeba keratitis, there is no report of cumulative pediatric incidence. Studies of combined adult and pediatric populations have estimated the average age of affected individuals to be approximately 32 years (Ibrahim et al. 2009).

As aforementioned, reports of pediatric cases of acanthamoeba are rarer than adult cases, which is likely due to a lower rate of contact lens wear—the main predisposing factor identified for acanthamoeba keratitis (Ibrahim et al. 2009). Still, studies of both adult and pediatric populations have shown that acanthamoeba keratitis comprises only 2% of lens-related infectious keratitis (Ibrahim et al. 2009); of these cases, however, approximately one quarter were found to occur in patients between the ages of 12 and 17 years old (Verani et al. 2009). These younger patients are less likely to understand the importance of proper contact lens care, and may be more prone to high-infectious risk behaviors such as washing lenses in tap water, failing to properly disinfect lenses, and swimming with lenses (Radford et al. 1995; Seal et al. 1999; Radford 2002; Robertson et al. 2007; Verani et al. 2009). It was previously thought that in

addition to these behaviors, certain lens materials made a user more susceptible to microbial keratitis; however, this remains to be determined (Beattie et al. 2003).

Like contact lenses, overnight orthokeratology use is also a commonly identified risk factor for acanthamoeba keratitis, especially in Asia, where it is often employed in pediatric patients as young as 8 years old (Watt and Swarbrick 2007; Wong et al. 2007).

While most cases of acanthamoeba keratitis appear to be associated with contact lens wear, noncontact lens-related cases have also been reported. In one study of both adult and pediatric patients, approximately 10% of cases were in individuals without contact lenses (Verani et al. 2009). Of the noncontact lens-related incidences, ocular trauma and preexisting ocular surface disease were the most common risk factors (Erdem et al. 2014). These conditions, in addition to contact lens wear, may disturb the normal production and/or circulation of tear fluid, which contains factors protective against acanthamoeba (Panjwani et al. 1990).

Acanthamoeba derives its virulence primarily from its ability as a trophozoite to adhere to corneal epithelial cells using mannose- and laminin-binding proteins on its cell membrane (Hurt et al. 2003; Panjwani 2010). After adhering, an exuberant cytopathic response is triggered in which substantial cell death and degradation of the epithelial basement membrane and stromal matrix occur (Panjwani 2010). Additionally, release of virulence proteins that digest collagen and protein further exacerbates damage to the cornea directly and indirectly via host cytopathic responses (Khan et al. 2000; Hurt et al. 2003; Alizadeh et al. 2005). Without prompt treatment, acanthamoeba keratitis may lead to loss of visual acuity and even eventual blindness.

Clinically, symptoms of acanthamoeba are highly nonspecific (e.g., eye pain, light sensitivity, eye redness, and tearing) (Verani et al. 2009). Infection is usually restricted to one eye, although up to 15% of patients may have either simultaneous or sequential involvement of the second eye (Bacon et al. 1993; Radford et al. 1998; Hargrave et al. 1999; Wilhelmus et al. 2008). The pain associated with acanthamoeba keratitis is often disproportionate to the clinical appearance (Sun et al. 2006; Clarke and Niederkorn 2006; Wilhelmus et al. 2008); however, while "pain out of proportion to the exam" is often considered pathognomonic for acanthamoeba keratitis, it should be noted that (1) there may be a complete absence of pain (Shukla Kent et al. 2012) and (2) in younger children, a correct assessment of pain may be difficult and, thus, an unreliable symptom on which to base diagnosis (Srinivasan et al. 1997). As such, it is imperative that with any suspicion of acanthamoeba keratitis a thorough investigation be conducted.

On exam, the most frequently documented signs of acanthamoeba keratitis are pseudodendrites, satellite lesions, perineural infiltrates, and ring infiltrates (Bacon et al. 1993; Dart et al. 2009; Mascarenhas et al. 2014). Unfortunately, these signs are not specific to acanthamoeba keratitis and often lead to the misdiagnosis and subsequent ineffective treatment of this entity. For example, ring infiltrates, found in approximately one-third of cases, are commonly reported both in fungal- and pseudomonas-associated ulcers (Klotz et al. 2000; Srinivasan 2004), though to a much lesser degree (Mascarenhas et al. 2014). Similarly, satellite lesions are reported with similar frequency in both acanthamoeba and fungal keratitis (Illingworth et al. 1995; Illingworth and Cook 1998; Hargrave et al. 1999; Mascarenhas et al. 2014). At the more advanced stages, corneal thinning and melt, uveitis, and hypopyon can be observed. Clinical findings of acanthamoeba keratitis are largely nonspecific, making clinical diagnosis very challenging.

To facilitate diagnosis of acanthamoeba keratitis, various diagnostics tests can be utilized. Microscopy of corneal scrapings may reveal cysts or trophozoites; using various stains including hematoxylin and eosin, Giemsa, or Kinyoun acid-fast stain, a positive diagnosis can be made in anywhere between 15 and 90% of cases (Boggild et al. 2009; Erdem et al. 2014).

Corneal scrapings can also be cultured on non-nutrient agar with an overlay of *E. coli* with culture positivity noted by the presence of trails left by motile trophozoites. Unfortunately, retrospective studies have shown that specimens cultured on this medium, buffered charcoal-yeast extract agar, or Trypticase soy agar containing horse or sheep blood are culture-positive in only approximately 64% of contact lens-related and 74% of noncontact lens-related cases (Bacon et al. 1993; Penland and Wilhelmus 1997; Sharma et al. 2000); additionally, cultures may be contaminated by other bacteria and yeast from the specimen making diagnosis of acanthamoeba keratitis challenging. Further, culture of corneal scrapings can be both a personnel-heavy and time-consuming process with results obtained anywhere between 24 h to several days following inoculation (Epstein et al. 1986; Bottone et al. 1992; Schuster 2002; Sun et al. 2006; Hammersmith 2006). On the other hand, drug sensitivities obtained with cultures offer valuable guidance in choosing the most efficacious treatment. Corneal scrapings can also be used for polymerase chain reaction (PCR) diagnosis, which is more sensitive, though more costly than culture diagnosis (Villani et al. 2014).

Corneal biopsies, which are most helpful for deeper ulcers, can also be used for histologic diagnosis with fluorescent stains that help identify organisms (Wang et al. 2014). Transmission electron microscopy, while, perhaps, less readily available for clinical use, can readily detect cysts and trophozoites within corneal buttons (Mathers 2004). Recently, in vivo confocal microscopy (IVCM) has emerged as a diagnostic tool for diseases of the ocular surface. With IVCM, acanthamoeba can be diagnosed with the presence of double-walled cyst structures in the corneal epithelium and stroma. With skilled users, IVCM has been reported to have a sensitivity and specificity of up to 100% (Nakano et al. 2004; Villani et al. 2014). With less experienced users, IVCM may only have a sensitivity and specificity of up to 56 and 84%, respectively (Hau et al. 2010). These various diagnostic tests, however, may have limited utility in uncooperative patients, such as those of the pediatric population, and exam under anesthesia may have to be performed for both clinical examination and diagnostic testing.

Viral Keratitis

Globally, viral keratitis is a significant cause of ocular morbidity due to both inflammatory and infectious components and is a leading cause of infection-related loss of vision, especially in developed countries (Farooq and Shukla 2012).

Herpesviridae

The most common viruses to cause infectious keratitis come from the virus family Herpesviridae, which include herpes simplex virus-1 and 2, varicella zoster virus, and Ebstein–Barr virus.

Herpes Simplex Virus

Herpes simplex virus (HSV) infections are ubiquitous in humans, which are the only known reservoirs for this virus. HSV is responsible for oral (generally HSV-1) and genital herpes (generally HSV-2). In children, HSV-1 is contracted via contact of the virus with the mucosal surfaces of the oropharynx, while HSV-2 is predominantly transmitted from mother to child in the neonatal period. Notably, most children are infected with HSV-1 by the time they reach the age of five (Kimberlin 2004). Most studies report an average age of onset or first documented episode of HSV keratitis to be around 5–6 years, although it has been reported to occur as young as 6 weeks (Beneish et al. 1987; Colin et al. 1982; Beigi et al. 1994; Schwartz and Holland 2000; Chong et al. 2004; Hsiao et al. 2009; Liu et al. 2012).

HSV is an obligate intracellular pathogen that requires healthy, intact host cells to undergo its lytic replication cycle. To begin this cycle of infection, HSV must first adhere to the host cell via viral envelope glycoproteins, after which fusion of viral envelope and host plasma membrane allows for nucleocaspid entry.

The nonenveloped nucleocapsid then traverses the cell to empty its viral DNA into the host nucleus, where the synthesis of viral progeny can begin. Because viral DNA replication interrupts host protein synthesis, the host cell cannot survive, eventually undergoing cell lysis. This appears to be the main process by which corneal tissue sustains damage during active HSV infection (Dix 2006). While both simplex viruses are capable of causing infectious keratitis, HSV-1 is the more common pathogen.

HSV can also establish latency in the sensory nerves of trigeminal ganglia, from which reactivated virus may be released at a later time to cause a recurrence of ocular infection. The detrimental effects of HSV result primarily from these recurrent attacks rather than the initial episode, which may present as a self-limiting blepharoconjunctivitis with or without nonspecific systemic symptoms such as malaise, fever, and lymphadenopathy. Oftentimes, initial herpetic infection is subclinical; in fact, primary herpes infections are often misdiagnosed and resolve without intervention (McGill and Scott 1985).

Recurrences have been noted to occur more frequently in the pediatric population, with up to 80% of pediatric patients experiencing recurrences within as little as 15 months of the first episode (Chong et al. 2004; Liu et al. 2012). These recurrences are the most concerning feature and clinically significant aspect of HSV infection as the repeat infectious and inflammatory insults to the cornea, especially corneal stroma, are what eventually lead to corneal opacification and blindness (McGill and Scott 1985; Remeijer et al. 2009).

HSV keratitis is diagnosed primarily from clinical findings; various tests such as Tzank preps, viral culture, and PCR can be used to confirm, though not exclude, diagnosis due to the high rate of false negatives. Additionally, confocal microscopy, bacterial and fungal cultures, and other tests can be used to rule out other causal agents of microbial keratitis.

Depending on the time of presentation and primary site of involvement within the cornea, the clinical manifestations of recurrent HSV keratitis can vary significantly. Based primarily on the pathophysiology and the corneal layer involved, HSV keratitis is commonly classified into the four broad categories of (1) epithelial keratitis, (2) stromal keratitis without ulceration, (3) stromal keratitis with ulceration, and (4) endothelial keratitis. Importantly, aspects of all four types may be present at once and it may be difficult to clinically differentiate the specific types.

Epithelial keratitis refers to HSV-induced pathology localized to the corneal epithelium. Lesions range from corneal vesicles, superficial punctate lesions, stellate erosions, to dendritic or geographic ulcers. They are all caused by lysis of host cells by replicating virus (Farooq and Shukla 2012) and likely exacerbated by the host response to infection. When examined histologically, edematous epithelial cells are present at the margin with necrotic and inflammatory cells in the ulcer bed (Léger et al. 2001).

Epithelial keratitis is typically accompanied by complaints of foreign-body sensation, photophobia, tearing, redness, and blurry vision. The degree to which patients are affected varies with the location of lesions as well as the number of prior recurrences; with more frequent recurrences, for example, patients are likely to have hypoesthesia or even complete corneal anesthesia, and consequently less corneal irritation. On exam, a dendritic ulcer with terminal bulbs, which is the most common type identified in recurrent HSV epithelial keratitis, may be visualized anywhere on the cornea; however, the earliest signs may not be so pathognomonic, and lesions may resemble opaque plaques of varying shapes. Fluorescein dye accentuates herpetic ulcers, while Rose Bengal staining highlights the heaped up, edematous and scalloped ulcer margins consisting of devitalized corneal cells in which HSV cells have undergone replication. Superficial scarring, or "anterior stromal footprints," and neovascularization of the cornea act as evidence of prior episodes and may assist in making the correct diagnosis.

Any epithelial damage can affect the integrity of the more posterior layers of the cornea; when there is stromal involvement, the entity is known

as herpes stromal keratitis (HSK). HSK may be the primary manifestation of herpes keratitis or may result from progression of epithelial keratitis (Knickelbein et al. 2009). In adults, stromal keratitis is less common than epithelial keratitis, but in children, stromal keratitis is a common feature of cases of HSV keratitis, especially in recurrences (Beigi et al. 1994; Kaye and Choudhary 2006). In general, the pathology involved in stromal keratitis is driven by the inflammatory response of the host, which leads to considerable edema and infiltration by inflammatory cells. This stromal involvement substantially threatens corneal transparency by causing edema, neovascularization, and scarring, which is a common complication in pediatric patients with HSK (Chong et al. 2004).

Patients with stromal keratitis present similarly to those with epithelial keratitis and complain of redness, photophobia, and blurry vision. On clinical examination, HSK can be further differentiated by the presence (i.e., necrotizing keratitis) or absence of ulceration (also referred to as non-necrotizing keratitis, interstitial keratitis, and immune stromal keratitis). Of the two, HSK with ulceration is much more severe and is characterized by the presence of actively replicating virus coupled with a robust immune response that, together, is thought to drive stromal necrosis (Liesegang 1999). Stromal opacities with overlying defects are indicative of necrotizing HSK; these areas are particularly susceptible to corneal thinning and perforation (Kaye and Choudhary 2006). In contrast, HSK without ulceration is characterized by the absence of active viral particles and is thought to be primarily immune response driven (Rowe et al. 2013); it typically presents as stromal opacification without epithelial defects. Both forms may exhibit other signs of inflammation, including stromal edema, indicated by a thickened, ground-glass appearance, and anterior chamber cell and flare (Hill et al. 2014). Signs of more chronic or recurrent pathology include stromal scars, areas of thinning, lipid deposits, and stromal neovascularization.

HSV endothelial keratitis is a rare manifestation of recurrent HSV keratitis. Infection of corneal endothelium disrupts pump and barrier function, resulting in corneal edema and compromising corneal transparency (Suzuki et al. 2007). Similar to patients with epithelial keratitis, those with endothelial involvement may complain of symptoms such as redness, pain, photophobia, and blurry vision. On exam, most endothelial keratitis presents with round central or paracentral opacification of the endothelium and deep stroma; this represents the most common morphology of endothelial keratitis and is referred to as disciform keratitis. Two other patterns, which include diffuse and linear, may occur as well, although these are rare in comparison to disciform endotheliitis. Associated signs include secondary stromal edema, anterior chamber cell and flare, keratic precipitates, and elevated intraocular pressure (Hill et al. 2014). The presence of stromal edema often makes it difficult to distinguish endothelial from stromal keratitis; however, the former is not associated with stromal infiltrate (Ritterband and Friedberg 1998).

Another complication of herpes keratitis is neurotrophic keratopathy (NK). Overall, NK associated with herpes keratitis is estimated to have a prevalence of approximately 0.01% (Sacchetti and Lambiase 2014); however, in pediatric populations, decreased corneal sensation has been reported in up to 64% of cases (Liu et al. 2012). As corneal hypoesthesia is the main feature, patients typically do not complain of ocular symptoms. NK is commonly graded in severity by a three-stage scale developed by Mackie (1995). In stage I, clinical findings consist of epithelial hyperplasia or irregularity, Gaule spots, superficial punctate keratopathy, Rose Bengal staining of the inferior conjunctiva, increased viscosity of tear mucus, decreased tear breakup time, superficial neurovascularization, stromal scarring, and dellen. Stage II is characterized by persistent epithelial defects with smooth, rolled edges, Descemet's folds and stromal edema, and anterior chamber inflammation. Stage III of NK encompasses corneal ulceration, perforation, and stromal melt. All of these findings are thought to occur, at least in part, secondary to the disruption of corneal

neurotransmission and blink reflexes as well as aberrant epithelial turnover caused by recurrent insults to the sensory nerves of the cornea and epithelial basement membrane by infection and host inflammatory response (Ritterband and Friedberg 1998; Hamrah et al. 2012).

Varicella Zoster Virus

Overall, pediatric cases of keratitis associated with varicella zoster virus (VZV) are rare; more commonly, VZV ocular infection manifests solely with a rash that involves the periocular skin. When keratitis does occur, it is anywhere between one to 10 weeks following the appearance of classic chicken pox exanthema (Wilhelmus et al. 1991; Fernández de Castro et al. 2006). Corneal lesions, usually found in the peripheral cornea, may resemble those of HSV keratitis with morphologies ranging from dendritic to disciform. These findings may be associated with or without overlying epithelial defects and can ultimately lead to the formation of corneal opacities with significant visual impairment (Loewenstein 1940; Nesburn et al. 1974; Uchida et al. 1980; de Freitas et al. 1992; Power et al. 1997; Fernández de Castro et al. 2006; Matoba et al. 2014). Other associated findings that have been reported include avascular, stromal opacities with diffuse borders in the central cornea (Krall and Kubal 2014). Fluorescein staining often reveals an appearance of branching lesions similar to those seen in HSV keratitis; however, in comparison, fluorescein staining is often minimal and the branching lesions are found to lack terminal end bulbs. Lesions are not likely to stain with Rose Bengal (Magone et al. 2005).

The pathogenesis of primary varicella keratitis has yet to be fully discerned, although it is thought that, as with herpes simplex keratitis, greatest corneal injury occurs in the process of active viral replication, which can occur shortly after primary inoculation or following a period of latency. After initial infection, VZV remains latent within the sensory dorsal root ganglia. Reactivation causes a vesicular rash associated with severe nerve pain in a dermatomal distribution. On the skin, this entity is termed shingles, or herpes zoster, while reactivation in the V1 branch of the trigeminal nerve is called herpes zoster ophthalmicus (HZO). With more widespread varicella vaccination in children, primary infection and subsequent reactivation of VZV are likely to become even more rare in the future; however, the live-attenuated varicella vaccine itself has been reported to be associated with the occurrence of HZO (Krall and Kubal 2014).

Adenovirus

There are several adenovirus serotypes that have been implicated in ocular infection and conjunctivitis (i.e., epidemic keratoconjunctivitis, EKC); however, only serotypes 8, 13, 19, and 37 of subgroup D have been shown to be capable of significantly affecting the cornea (i.e., keratoconjunctivitis) (Butt and Chodosh 2006). Remarkably, these adenovirus serotypes comprise the vast majority of all keratoconjunctivitis in both adult and pediatric patients (Mueller and Klauss 1993; Klauss et al. 2002). Overall, however, in contrast to adults, corneal involvement is much less common in children with adenoviral infections and, when present, is typically transient and resolves without any permanent sequela. Only one report of monocular corneal scarring in association with prior EKC resulting in amblyopia has been published to date (Gu et al. 2011). Overall, the course of EKC in children is less severe than adults, although they are more likely to have—in addition to the nonspecific eye symptoms of unilateral eyelid edema, pruritus, tearing, and discharge with sequential involvement of the second eye—nonspecific systemic flu-like symptoms and pre-auricular lymphadenopathy (Ghebremedhin 2014).

On slit-lamp exam, features and complications of adenoviral infection are largely the same as that found in adults, including follicular conjunctivitis, pseudomembrane formation, and punctal occlusion. As aforementioned, children are less likely to have subepithelial findings,

which, when present are evidenced by no more than faint epithelial keratopathy. Due to the nonspecific nature of the findings, adenoviral infection in children is especially difficult to differentiate from other causes of conjunctivitis.

While EKC is largely a clinical diagnosis, various methods have been used to help expedite correct diagnosis and avoid mistreatment with antimicrobials. In the past, cell culture with immunofluorescence (CC-IFA) and serological tests were the predominant diagnostic tests (Pihos 2013); today, PCR is the gold standard for diagnosis due to both high specificity and sensitivity. However, PCR may not be readily accessible to clinicians due to a lack of facilities and/or resources. Newer methods, such as the Rapid Pathogen Screening (RPS) Adeno Detector, are being developed with the aim of making diagnosis both expedient, readily accessible, and affordable for clinicians. The RPS system reports a sensitivity and specificity of 88 and 91%, respectively, relative to the historic gold standard of CC-IFA (Sambursky et al. 2006).

EKC is a highly contagious entity, communicable for a large part of the disease. Even before signs and symptoms can manifest, approximately one week after inoculation, EKC begins shedding viral particles that render an individual infectious until up to 2 weeks following disease onset (Ghebremedhin 2014). Transmission occurs when an individual comes into contact with shed virus, either directly from the infected individual's secretions or by contact with inert fomites with viral particles; as such, when EKC is suspected, precautions should be taken to minimize the risk of spreading infection. For example, patients should avoid returning to school for approximately 14 days after symptom onset. Additionally, patients should be advised to practice careful hand hygiene, disinfect possible fomites, avoid sharing towels or cosmetics, and dispose of contact lenses and contact lens paraphernalia and discontinue their use until the infection is cleared. Similarly, the clinician should take care to disinfect all equipment in the office prior to seeing other patients; commonly recommended is the use of isopropyl alcohol tissues consisting of 30% alcohol solution or sodium hypochlorite (i.e., bleach) solution (Lakkis et al. 2007).

Treatment of Infectious Keratitis

Because of the severe morbidity with corneal scarring secondary to keratitis in the pediatric population, corneal cultures may be necessary to ascertain the most appropriate and effective therapy, especially since the outcome of microbial keratitis largely depends on how rapidly it is diagnosed and treated (Al Otaibi et al. 2012). Because there is often considerable lag between clinical presentation and availability of specific microbial data, the initial choice of treatment typically depends on clinical suspicion, knowledge of the most likely corneal pathogen, as well as regional data on patterns of drug resistance.

Treatment of Bacterial Keratitis

When bacterial keratitis is suspected, empiric therapy should be begun, covering all possible etiologies, and then narrowed, based on clinical response and culture results (McLeod et al. 1995). Current recommendations suggest beginning empiric treatment with aminoglycoside-cephalosporin combinations, which offer antibacterial coverage against both Gram-negative and Gram-positive organisms. A combination of gentamicin (14 mg/mL) or tobramycin (14 mg/mL) and cefazolin (50 mg/mL), administered every 15–30 min, is frequently employed in the pediatric population (Al Otaibi et al. 2012). A loading dose of a drop every 5 min for the first 30 min may be employed for the treatment of severe ulcers. With clinical improvement, drop frequency may be reduced.

Alternatively, a broad-spectrum fluoroquinolone instilled hourly may be used to begin empiric treatment (Parks et al. 1993; Gangopadhyay et al. 2000); clinicians should remain mindful of geographic variation in antibacterial susceptibility, however. For example, strains of

S. aureus and *Pseudomonas* found on the Indian subcontinent have been noted to have greater resistance to early generation fluoroquinolones (Willcox 2011; Oldenburg et al. 2013). For this reason, fourth-generation fluoroquinolones, such as moxifloxacin and gatifloxacin, may be preferred, having been shown to have greater in vitro activity against certain Gram-positive organisms (Parmar et al. 2006b; Al-Otaibi 2012). The dosing schedule is similar to that of fortified drops.

Fortified drops are more costly, require compounding and refrigeration, have a shorter shelf-life, are more likely to cause ocular discomfort, and are more toxic to the cornea causing delays in corneal epithelialization (Nelson et al. 1990; Lin and Boehnke 2000; McDonald et al. 2014). Regardless, they remain the most reliable option in treating bacterial keratitis and preventing the complications (e.g., corneal perforation) of severe infection. Additionally, they are less likely to cause white corneal precipitates than drugs such as ciprofloxacin (McDonald et al. 2014).

As pediatrics patients can be difficult to treat and may cry causing dilution of medication, weekly subconjunctival antibiotics have been recommended in the past (Baum and Barza 1983; Ormerod et al. 1986). However, these injections require sedation, can cause pain and redness, and have a higher risk of injury to the eye without providing enhanced efficacy in fighting infection (Gokhale 2008). Consequently, subconjunctival injections are no longer recommended.

Finally, oral or parenteral antibiotics have been shown to have no benefit in simple bacterial keratitis although they may be indicated in patients with perforation, extensive infection involving the sclera, or endophthalmitis (Davis et al. 1979; Gokhale 2008). However, any gonococcal infections of the eye should be treated with systemic ceftriaxone.

Corticosteroids are often contemplated for adjunctive use with antibiotics for the treatment of infection-related inflammation. Unfortunately, in reducing host inflammatory responses, they inevitably reduce the ability for host defenses to effectively fight and eradicate infection. In addition to hampering the host immune system, corticosteroid eye drops also have potential side effects including raising intraocular pressure and accelerating the formation of cataract; because of these disadvantages, the use of corticosteroids in the setting of infectious keratitis has long been debated. After adequate control of infection, however, corticosteroids may play a role in reducing corneal neovascularization and scarring.

Adjunctive use of corticosteroids in the setting of bacterial keratitis has been studied the most extensively—albeit primarily in adult patients. The Steroids for Corneal Ulcers Trial (SCUT) remains the largest trial to date investigating their utility in adult patients with bacterial ulcers. Overall, researchers demonstrated no statistical differences in best-corrected visual acuity, infiltrate and scar size, or adverse events at 3 months when antibiotics were compared with antibiotics plus prednisolone sodium phosphate (1.0%). However, subgroup analyses showed that patients who had the worst visual acuity at initial presentation and patients who had central ulcers attained greater improvements on corticosteroid drops (Srinivasan et al. 2012). Other studies have found similar results. Thus, with bacterial corneal ulcers, there may be some role for adjunct corticosteroid therapy.

Treatment of Fungal Keratitis

In contrast to antibacterial medications, topical antifungal therapies are less effective due to poor corneal penetration and predominantly static versus cidal mechanism of action. Nevertheless, a few topical antifungals, including natamycin, various azoles (e.g., fluconazole, miconazole, ketoconazole, itraconazole, voriconazole), and amphotericin B, have been identified as being effective in treating fungal keratitis. Notably, all of the aforementioned treatments, except natamycin, must be compounded.

When hyphae are visualized on stains or confocal microscopy, topical natamycin 5% is the most appropriate first-line therapy; alternatively, amophotericin B or voriconazole can also be used. For certain filamentous fungal species,

such as *Fusarium*, voriconazole should not be used as a first-line treatment. In the Mycotic Ulcers Treatment Trials, natamycin demonstrated superiority in achieving better visual acuity at 3 months and was associated with a lower rate of perforation than that of voriconazole-treated cases (Prajna et al. 2013).

In contrast, when yeast or pseudohyphae are detected, amphotericin B is preferred to natamycin as the first-line treatment—although the latter may also be used effectively. Fluconazole or voriconazole can also be used to treat yeast. All drops should be applied hourly until clinical improvement is seen. Additionally, surface debridement can enhance drug delivery by removing debris and fungi; even so, it may take up to 8 weeks of treatment to successfully treat fungal keratitis.

While fungal keratitis might elicit a pronounced inflammatory response and may even contribute to the pathology of keratitis, corticosteroids are contraindicated in fungal keratitis (Stern and Buttross 1991; Gokhale 2008; Herretes et al. 2014).

Primary treatment (i.e., natamycin 5%) failure has been reported in up to 30% of cases, with larger ulcer size and Aspergillus infection associated with poorer prognosis (Lalitha et al. 2006); ulcers refractory to medical management may require further debridement, keratectomy, or therapeutic penetrating keratoplasty (Thomas and Kaliamurthy 2013).

Treatment of Acanthamoeba Keratitis

For Acanthamoeba infection, current recommendations include hourly application of 0.02% polyhexamethylne biguanide or chlorhexidine—both of which act by inhibiting proper membrane function of Acanthamoeba—for at least the first two days. These drugs, while effective against both trophozoites and cysts, can also be damaging to the corneal epithelium and should be reduced thereafter to minimize epithelial injury (Hay et al. 1994; Gokhale 2008; Baig et al. 2014); however, as acanthamoeba cysts can be especially resistant, treatment should continue for several months at a reduced dosing schedule (Clarke et al. 2012).

Several other drugs have been investigated for use in the treatment of Acanthamoeba keratitis, including triazoles, such as voriconazole 1% (Bang et al. 2010; Sunada et al. 2014). Few studies have reported success with using antifungals in addition to the aforementioned standard treatment. While there may be a role for antifungals in enhancing response to medical treatment, evidence remains insubstantial and too meager for the routine implementation of antifungals in Acanthamoeba keratitis.

The use of corticosteroids in Acanthamoeba keratitis has been controversial in the past. To date, there continues to be no consensus on the therapeutic approach to Acanthamoeba keratitis; however, it is now believed that topical steroids may be used safely after treatment with antiamoebal drugs and, perhaps, even at the earliest stages of infection (Clarke et al. 2012). Regardless, steroids should be used judiciously, as dampening host immune response may also allow the persistence of infectious organisms.

Viral Keratitis Treatment

HSV

For infectious epithelial disease, due to challenges in administration of topical medication in children, oral agents are often preferred or used in conjunction with other medical therapies, which vary with the age of the child. In young children and infants, a weight-based dose of oral acyclovir suspension is often used at a thrice daily dose of 200 mg/5 ml (see Table 3.1). Older children that can tolerate pills can be treated with acyclovir 400 mg thrice daily, valacyclovir 500 mg twice daily, or famciclovir 250 mg twice daily (Liu et al. 2012). Oral acyclovir is generally well tolerated in children, although the suspension may cause diarrhea and the capsules other gastrointestinal disturbances as both formulations contain the inactive ingredients of carboxymethylcellulose and lactose monohydrate, respectively. For children with lactose

intolerance, a simple remedy of lactase can be implemented (Revere and Davidson 2013).

Topical steroids are contraindicated with active epithelial infection.

For stromal keratitis, the herpetic eye disease study (HEDS), which studied adult patients with herpetic infections, recommends using topical steroids (Barron et al. 1994); however, pediatric stromal keratitis, endotheliitis, and iridocyclitis are commonly treated with oral antivirals in combination with topical steroids (Hsiao et al. 2009; Liu et al. 2012). In children, adequate control of inflammation is crucial as persistent herpes-related inflammation can lead to corneal scarring and considerable visual impairment (Knickelbein et al. 2009). However, steroids, in addition to having numerous side effects, have been suggested to promote the development of resistant HSV strains (Revere and Davidson 2013). Newer targeted therapies have been studied in animal models to avoid the issues associated with steroids. Gene therapy utilizing plasmid and naked DNA encoding VEGF antagonists and inflammatory mediators, such as interleukin-18, have been studied in reducing HSV-associated neovascularization, for example (Stechschulte et al. 2001; Kim et al. 2005; Elbadawy et al. 2012). Anti-HSV IgG fab fragments have also been investigated and have been shown to be more effective than placebo in reducing viral titers and disease burden in mice (Berdugo et al. 2012). While these therapies are only in their most early stages of development, they may eventually come to play a large role in greatly reducing and, perhaps, curing herpetic eye disease.

For epithelial neurotrophic ulceration, topical antivirals are not indicated, and topical steroids and other anti-inflammatory medications should only be used with great caution in the presence of stromal inflammation. These patients are best managed with preservative-free lubrication. For refractory or severe cases, several nonmedical options can be tried including bandage contact lenses, amniotic membrane grafts, tarsorrhaphy, or conjunctival flaps.

For children with recurrent HSV prophylactic oral acyclovir may be recommended; kidney and liver function should be monitored with chronic use of systemic acyclovir (Liu et al. 2012; Revere and Davidson 2013). The recommended pediatric doses for prophylactic acyclovir are noted in Table 3.1.

EKC

Currently, treatment of adenoviral infections is mainly supportive as there are no therapies definitively proven to be effective in preventing or shortening the duration of the disease. Various drugs have been developed, however, that work primarily by interfering with human adenovirus replication; these drugs include zalcitabine, sanilbudine, cidofovir, ganciclovir, interferon beta, and anitosteopontine peptide, and *N*-chlorotaurine (Ghebremedhin 2014). While current literature suggests beneficial effects, randomized clinical trials are few.

When there are subepithelial infiltrates or pseudomembrane formation, topical corticosteroids can be employed to quiet the host response to infection with the understanding that steroids prolong viral replication and shedding. After infiltrates have cleared, steroids should be tapered very slowly as sudden withdrawal can cause subepithelial infiltrates to recur. In cases refractory to corticosteroids, topical cyclosporine A has been used.

Table 3.1 Treatment and prophylactic dosages for acyclovir in children (from Liu et al. 2012)

Age	Treatment dose thrice daily	Prophylactic dose twice daily
Infants (up to 18 months)	100 mg (2.5 ml)	100 mg (2.5 ml)
Toddlers (18 months–3 years)	200 mg (5 ml)	200 mg (5 ml)
Young children (3–5 years)	300 mg (7.5 ml)	300 mg (7.5 ml)
Older children (6 years and older)	400 mg (10 ml)	400 mg (10 ml)

Surgery and Other Nonmedical Interventions

When treated appropriately with antibiotics and/or steroids, less than one-fifth of children go on to require surgery (Al-Otaibi 2012). However, in rare cases of refractory or inadequately treated keratitis, surgical interventions may be necessary to help clear the infection, manage severe ulceration or perforation, or to remove corneal opacities that may obscure vision and cause secondary amblyopia. These interventions range from simple debridement—commonly used with fungal keratitis, HSK, and AK—to using cyanoacrylate tissue adhesive with bandage contact lenses for corneal thinning. Deep lamellar keratoplasty and therapeutic penetrating keratoplasty may be required for extensive ulceration or perforation. Surgery is best delayed until after medical treatment has cleared the infection and inflammation has quieted.

Most recently, several groups have demonstrated the efficacy of photo-activated chromophore for keratitis cross-linking, or PACK-CXL, in the treatment of microbial keratitis. PACK-CXL is thought to exert its therapeutic effects by multiple mechanisms that inhibit pathogen replication and prevent further destruction of host tissues (Hafezi and Randleman 2014). Despite its promise, PACK-CXL remains largely experimental while scientists work to optimize treatment parameters.

Additional Therapies and Follow-Up

To help relieve discomfort associated with infectious keratitis, patients should initially be instructed to apply refrigerated preservative-free tears, which can be liberally used with little worry for negative repercussions. However, patients should be reminded not to touch the applicator tip to the eyes, as they could transmit infection from one eye to the other. Patients whose discomfort cannot be adequately controlled with this simple measure can be prescribed cycloplegics and analgesics; for example, topical atropine, an anticholinergic that causes ciliary muscle paralysis, can be used for photophobia (Baig et al. 2014).

All pediatric patients who present with keratitis should be closely monitored for signs of improvement, as a failure to respond to appropriate therapy or further progression of disease could place patients at greater risk for significant visual impairment and secondary amblyopia. They should be carefully examined for full resolution of corneal infection, since even with apparent clinical improvement, pediatric patients may not be able to appropriately vocalize any residual symptoms which might be caused by astigmatism or corneal opacities.

Table 3.2 lists strategies for the management of infectious keratitis in children.

Illustrative Cases

Case 1:

A healthy 16-year-old girl with a history of overnight use of contact lenses presented with the acute onset of pain, redness and reduced vision of the right eye. On exam, an ulcer with a small hypopyon was seen (Fig. 3.1). Corneal smear and cultures were performed. Fortified cefazolin and tobramycin drops were started hourly. The Gram stain showed Gram-negative rods and the corneal cultures grew abundant Pseudomonas aeruginosa. The cefazolin was discontinued and ciprofloxacin ointment was

Table 3.2 Strategies for management of infectious keratitis is children

1. A thorough history (timing/duration/previous treatment/risky behaviors with contact lens use/trauma) will aid in the differential diagnosis
2. Detection of any unusual features of the infiltrate (e.g., multi-focality, feathery edges, perineuritis) will aid in narrowing the diagnosis
3. Definitive diagnosis requires corneal cultures and smears. An exam under anesthesia may be needed, especially in very young children
4. Corneal imaging may be a useful diagnostic adjunct, depending upon the age and cooperation of the child
5. Initial therapy should include frequent administration of broad-spectrum antibiotics to cover both gram positive and gram negative organisms. Antibiotic

(continued)

Table 3.2 (continued)

coverage can be tailored once the causative agent is identified
6. Treatment with anti-fungal or anti-Acanthamoeba therapy is typically delayed until there is confirmation of the diagnosis by a positive smear or culture, or a suggestive imaging study
7. Close follow-up is essential to ensure that the ulcer is responding to therapy. Often the first sign that the infection is being successfully treated is a reduction in the density of the infiltrate (rather than the size). Medications should be tapered according to clinical response
8. Herpes simplex should always be kept in mind, especially when there is recurrent infection

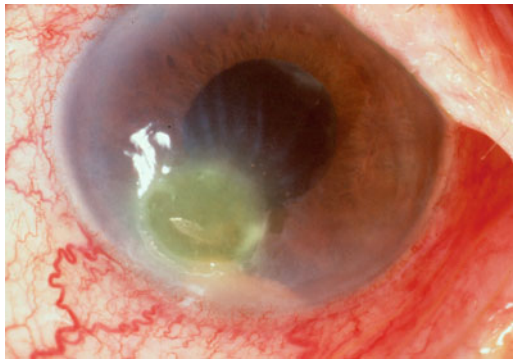

Fig. 3.1 *Pseudomonas aeruginosa* keratitis (Case 1)

added at bedtime. The tobramycin was continued, at a gradually reduced dose as the ulcer improved. The ulcer healed over 2 weeks, leaving a minimal scar and mild corneal thinning. Spectacle best-corrected vision returned to 20/25.

Case 2:

A healthy 10-year-old girl presented with a history of recurrent redness and reduced vision of her right eye. On exam, vision was reduced to 20/50. Mild conjunctival injection and a ring infiltrate were present (Fig. 3.2). Corneal sensation was reduced. A presumptive diagnosis of herpes simplex stromal keratitis was made. Oral acyclovir was begun at a dosage of 400 mg three times daily. Two days later, her symptoms had improved and the ring had resolved, although central corneal edema was present (disciform edema). Loteprednol 0.5% drops were added

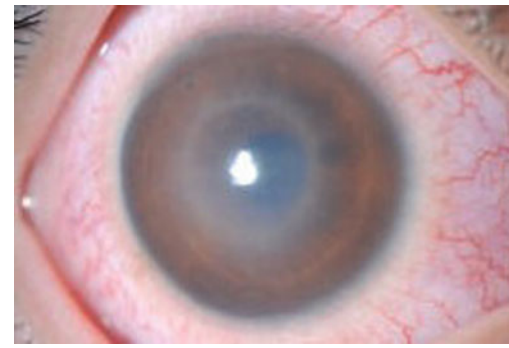

Fig. 3.2 Herpes simplex stromal keratitis (Case 2)

three times daily. Uncorrected vision returned to 20/20 over one month. The topical steroid was gradually tapered and eventually discontinued. Oral acyclovir was reduced to twice daily. She continued this prophylactic dose of acyclovir for one year, at which point it was discontinued. No further episodes occurred.

Compliance with Ethical Requirements .

Conflict of Interest Eubee B. Koo and Kathryn Colby declare that they have no conflict of interest.

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Corneal Diseases in Children: Allergic Diseases

4

Andrea Cruzat and Kathryn Colby

Allergic Conjunctivitis: Seasonal and Perennial

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most common form of ocular allergies, affecting about 15–20% of the population (Wong et al. 2014). SAC is more prevalent than PAC. The onset of symptoms is seasonally related to specific circulating aeroallergens. The difference between seasonal and perennial allergic conjunctivitis is the specific allergens to which the patient is allergic. SAC is caused by airborne pollens during spring and summer (most commonly ragweed and grass pollen) while PAC is caused by perennial allergens such as animal dander, dust mites, mold, air pollutants, and feathers. Despite this difference, 79% of children with perennial allergic conjunctivitis commonly experience seasonal exacerbations of symptoms (Bielory 2000; Abelson and Granet 2006).

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Symptoms and Signs

The cardinal symptom of allergic conjunctivitis is ocular pruritus. Watery discharge and milky or pale pink conjunctiva with vascular congestion (mild to moderate hyperemia) that may progress to swelling and conjunctival follicles may also occur. A white exudate may form during the acute state that becomes stringy in the chronic form. Palpebral edema can be mild to moderate, accompanied by venous congestion that gives it a dark appearance known as allergic dark circles. A lower lid crease (the so-called Dennie–Morgan line) may develop. Corneal involvement is rare (Friedlaender 2011). Acute chemosis (an excessive edema of the bulbar conjunctiva) may occasionally occur. In some cases a fine conjunctival follicular reaction or papillary hypertrophy along the tarsal conjunctival surface may also be seen.

Proper diagnosis is usually made clinically based on history and physical examination, with ocular itching the most common and important symptom. Most patients also have history of atopy with symptoms of allergic rhinitis (65–70%) (Takamura et al. 2011). Other frequent co-morbidities are asthma and eczema (Gradman and Wolthers 2006).

Pathogenesis

Seasonal and perennial allergic conjunctivitis are type 1 hypersensitivity reactions. Allergic conjunctivitis is caused by an allergen-induced

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inflammatory response in which allergens interact with IgE antibodies bound to the surface of sensitized conjunctival mast cells. Degranulation of mast cells induces enhanced tear levels of histamine, tryptase, prostaglandins, and leukotrienes that induce the symptoms of allergic conjunctivitis. This immediate or *early response* lasts clinically 20–30 min (La Rosa et al. 2013). Mediators released during mast cell degranulation initiate the recruitment of inflammatory cells including neutrophils, basophils, eosinophils, and T lymphocytes in the conjunctival mucosa. This leads to the ocular *late phase reaction* that occurs 4–6 h later and the release of T helper 2 type cytokines (interleukin (IL)-4, IL-5, IL-6 and IL-13) (Leonardi et al. 2007). The presence of specific IgE antibodies to seasonal or perennial allergens can be documented in almost all cases, and this test can be used for a definite diagnosis if in doubt (Bonini 2004). Tear fluid from SAC patients has been found to contain a small amount of eosinophils and histamine but elevated levels of IgE (Bielory 2000). Interestingly, 78% of PAC patients had demonstrated tear-specific IgE for house dust, whereas no SAC patients had measurable levels of IgE specific for house dust in tears (Bielory 2000). Histamine sensitivity has been noted to be different between normal subjects and atopic patients. Atopic patients require lower doses of histamine to cause symptoms than normal subjects (Bielory 2000). Allergic conjunctivitis is characterized histologically by infiltration of the conjunctiva with inflammatory cells, including neutrophils, eosinophils, lymphocytes, and macrophages (Bielory 2000).

Atopic Keratoconjunctivitis (AKC)

AKC is a bilateral chronic inflammatory disorder that involves recurrent episodes of severe inflammation of the conjunctiva and eyelids, which can secondarily affect the cornea. More than 95% of AKC patients also have eczema and 87% have history of asthma (Bielory 2000). AKC typically begins in the late teens and may persist until the fourth or fifth decade of life (Bielory 2000).

Symptoms and Signs

AKC patients tend to be older than children with SAC and present with disabling symptoms most commonly involving the lower tarsal conjunctiva. Symptoms include ocular itching year round, blepharospasm, blurred vision, burning, tearing, photophobia, eye pain, and early-morning mucous discharge. Seasonal exacerbations have been reported to be more marked in the winter or summer months and after exposure to animal dander, dust, and certain foods (Foster and Calonge 1990).

Clinical exam may reveal eyelid eczema with scaling dermatitis with a fine sandpaper-like texture, loss of eyelashes or eyebrows (madarosis), and lateral canthus ulceration. The eczema around the eyes involves the periorbital skin and cheeks. Erythema, dry scales, Dennie–Morgan lines, and allergic shiners (darkness and swelling underneath the eyes) may occur. Secondary staphylococcal blepharitis is common. Corneal findings such as punctate epithelial keratopathy (Fig. 4.1), Horner's points or Trantas dots may also be present. Mild or severe conjunctival injection or chemosis and lower tarsal follicles or papillae may be seen (Abelson and Granet 2006; Bielory and Bielory 2010). The conjunctiva is edematous and may eventually manifest subepithelial fibrosis, fornix shortening, scarring, or symblepharon.

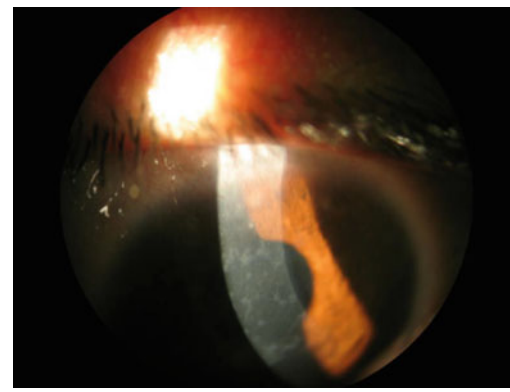

Fig. 4.1 Epithelial keratopathy in atopic keratoconjunctivitis

Complications can be severe and vision-threatening including corneal epithelial defects, keratitis, corneal scarring, and keratoconus. Atopic cataracts that are typically anterior and shield-like, but may be nuclear, cortical and even posterior subcapsular develop in 8–12% of affected patients (Bielory 2000). The use of corticosteroid therapy may also contribute to cataract development. Lichenification of the eyelid skin may cause cicatricial ectropion and lagophthalmos (Abelson and Granet 2006). Eczematous lesions may be found not only on the eyelids but also in any place of the body. Skin lesions are red and elevated in the antecubital or popliteal regions and are itchy. Physical exam findings are similar or overlap between vernal and atopic keratoconjunctivitis; however, VKC usually resolves by age 20 years, whereas AKC can persist throughout life and involves the eyelids (Friedlaender 2011). Approximately 45% of patients with AKC are skin test or allergosorbent test negative to common allergens (La Rosa et al. 2013). Other unusual complications include retinal detachment and a higher incidence of infections with herpes simplex keratitis and staphylococcus (Tuft et al. 1992; Bielory 2000).

AKC is a clinical diagnosis; the history of systemic atopy and the perennial nature aids in distinguishing this from other forms of allergic conjunctivitis. Testing blood levels of histamine and increased total IgE antibodies in serum and lacrimal fluid and positive results of the serum antigen specific IgE antibody can be used as confirmatory tests of suspected disease (Takamura et al. 2011).

Pathogenesis

The pathophysiology of AKC involves both a type 1 hypersensitivity response with a chronic degranulation of mast cells mediated by IgE and a hypersensitivity type 4 response mediated by Th1- and Th2-lymphocyte derived cytokines (La Rosa et al. 2013). The T cell inflammatory response is confirmed by elevated systemic levels of IL-4 and IL-5 in atopic individuals (Jenmalm et al. 2001). The histopathologic findings of AKC include a mixture of mast cell, eosinophil, and lymphocyte infiltration into the conjunctival epithelium with both Th1 and Th2 interactions (Trocme and Sra 2002; Leonardi et al. 2007). Patients with atopic dermatitis and rhinoconjunctivitis commonly have elevated IgE and histamine levels in tears (Trocme and Sra 2002).

Vernal Keratoconjunctivitis (VKC)

Vernal keratoconjunctivitis (VKC) is a rare (1–10.6:10.000) (Kumar 2009) severe usually bilateral—although sometimes asymmetrical or unilateral—seasonal allergic inflammatory disease (Awwad et al. 2006). It is characterized by an inflammation of the ocular surface usually involving the upper tarsal and/or bulbar conjunctiva. VKC is two times more common in boys than girls. Onset is generally before age 10. The disease tends to regress around puberty (Abelson and Granet 2006; Kumar 2009; De Smedt et al. 2013). VKC can develop after puberty; in this case, there is a more equal gender distribution. The initial seasonal attacks in spring and summer may turn into perennial disease after a few years, being not just limited to spring, with episodes of reactivity being quite common in the winter (Kumar 2009).

Although it is a self-limiting disease, patients with VKC may demonstrate periodic exacerbation of inflammatory symptoms with a consequent decline of the quality of life and with a risk of permanent corneal damage that can be vision-threatening. Symptoms often tend to disappear 4–10 years after onset. It occurs more frequently in children who have a history of seasonal allergy, asthma, and eczema. In a study done by Zicari et al. (2013) 46% of VKC patients were found to have a family history positive for immune dysfunction.

Although its prevalence is higher especially in hot and dry climates (Mediterranean areas, Indian subcontinent, Central and West Africa and South America), and is more common in persons of Asian or African origin, VKC has a wide geographical distribution (Kumar 2009).

VKC was first mentioned in the ophthalmic literature as conjunctiva lymphatica more than 150 years ago. Subsequently, most of the notables of ophthalmology during that period (Arlt, Dasmarres, von Graefe, Axenfeld, Trantas, and Herbert) published about this interesting disorder. Different authors, at different times, described it as spring catarrh, phlyctenula pallida, circumcorneal hypertrophy, recurrent vegetative conjunctiva, verrucosa conjunctiva, and aestivale conjunctiva, calling attention to the various aspects of this disease (Kumar 2009).

Symptoms and Signs

VKC is characterized by intense ocular itching exacerbated by exposure to wind, dust, bright light, hot weather, or sweating. Tearing, mucous discharge, conjunctival hyperemia, photophobia, blepharospasm, eye pain, foreign body sensation, and sometimes ptosis may be seen.

There are two forms of the disease: limbal or palpebral, depending on which portion of the conjunctiva is predominantly affected. Clinical examination may reveal a thin, copious milk-white fibrinous secretion (composed of epithelial cells, eosinophils and Charcot–Leyden crystals). *Palpebral involvement* may include conjunctival hyperemia and edema with papillae (filled with inflammatory cells) on the superior tarsal conjunctiva (Fig. 4.2). Giant papillae are seen as the disease progresses due to fibrous tissue proliferation and can reach 7–8 mm in diameter (so-called "cobblestone" papillae). Fibrin may accumulate on the giant papillae and is known as the Maxwell-Lyons sign. VKC patients can also show Dennie Morgan's line. Persistent forms of VKC are associated with subepithelial fibrosis that appears as a white linear scar running parallel to the lid margin (Arlt's line). *Limbal involvement* includes transient confluent gelatinous limbal papillae and clumps of necrotic eosinophils with dead epithelial cells and neutrophils on the limbus or conjunctiva seen as yellow-white points (Horner's points and Trantas dots) and conjunctival hyperemia with edema (Figs. 4.3 and 4.4) (Kumar 2009). Trantas dots tend to appear when VKC is active, and disappear when symptoms decrease (Friedlaender 2011), while the cobblestones persist even during quiescent phases of the disease. Corneal involvement is associated with more severe disease. Corneal epithelial punctate keratitis (called keratitis epithelialis vernalis of El Tobgy) may evolve to macroerosion, ulcers and plaques, which are all expressions of epithelial toxicity caused by factors released from activated eosinophils (Leonardi et al. 2008). The classic corneal change seen more commonly in patients with superior tarsal involvement, is the development of a noninfectious shield ulcer appearing as an irregular oval corneal plaque with elevated hypertrophic epithelial cells with fibrin and

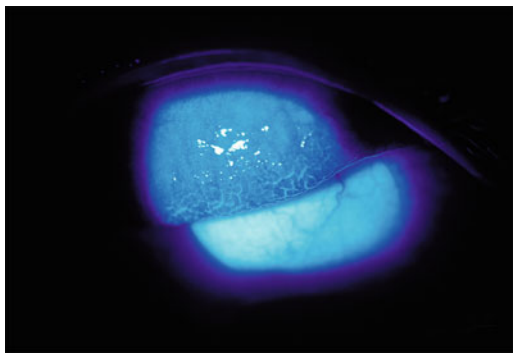

Fig. 4.2 Papillae in upper tarsal conjunctiva in vernal keratoconjunctivitis

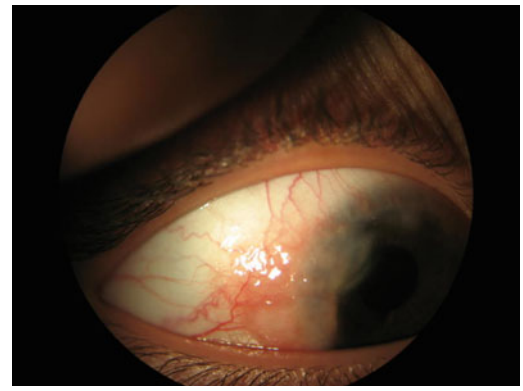

Fig. 4.3 Limbal involvement in vernal keratoconjunctivitis: limbal gelatinous hyperplasia with Horner–Trantas dots

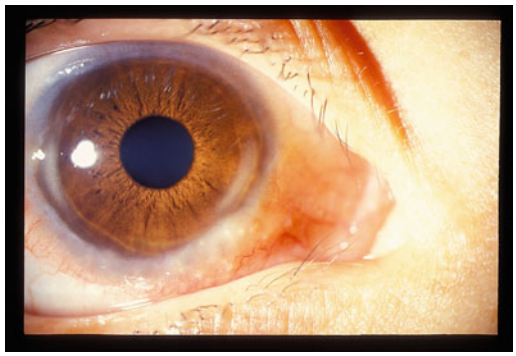

Fig. 4.4 Limbal involvement with limbal hyperplasia, pannus and pseudogerontoxon in vernal keratoconjunctivitis

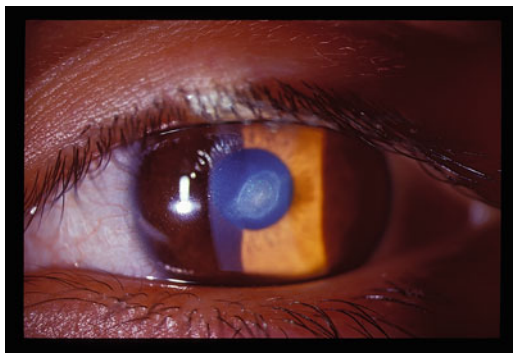

Fig. 4.5 Shield ulcer in vernal keratoconjunctivitis

mucin that stains with fluorescein and contains eosinophils and epithelial cells (Fig. 4.5) (Udell et al. 1981; Abelson and Granet 2006). Superficial corneal neovascularization and sometimes filamentary keratitis may also occur (Zicari et al. 2013).

Although VKC is a bilateral disease, it may affect one eye more than the other.

Ocular complications of VKC include steroid-induced cataract, glaucoma and dry eye, corneal scarring, irregular astigmatism, microbial keratitis, limbal tissue hyperplasia, and keratoconus (Tabbara 1999; Sridhar et al. 2003). Amblyopia seen among VKC may be caused by corneal opacity, irregular astigmatism, and keratoconus (Kumar 2009). A common corneal degenerative change is pseudogerontoxon, in which there is increased lipid deposition in the peripheral portion of the cornea resembling corneal arcus senilis (Fig. 4.4).

No precise diagnostic criteria have been established for this disease. Diagnosis is based on typical and characteristic clinical signs and symptoms; thus many mild or atypical cases may escape diagnosis. The diagnosis is based on the classical symptoms of allergic conjunctivitis (itching, tearing and hyperemia), and on specific ocular signs such as proliferative lesions in the conjunctiva including giant cobblestone papillae on the upper palpebral conjunctiva, limbal proliferation with limbal gelatinous hyperplasia and Horner–Trantas dots (Fig. 4.3) and the corneal findings described above. Even though atopy is common among VKC patients, only 50% of patients with VKC has positive Skin Prick Test and/or elevated allergen-specific antibodies (Pucci et al. 2003; Bonini 2004). Increased total IgE antibodies in serum and lacrimal fluid eosinophils in the conjunctival smear are common findings.

Pathogenesis

Ocular symptoms result from a nonspecific hyperreactivity induced by nonspecific stimuli, such as wind, dust, and sunlight, which is not related to allergen levels in the environment (La Rosa et al. 2013). Immunological data has proved that the pathogenesis of VKC is a type 1 and a type 4 hypersensitivity reaction. Recently, many authors have suggested the existence of a cooperation between the allergic (Th2 mediated) and the inflammatory (Th1 mediated) responses (Leonardi et al. 2006; Zicari et al. 2013). The immunopathogenesis of VKC is multifactorial involving a Th2 mediated mechanism with an overexpression of Th2-derived cytokines, growth factors, mast cells, eosinophils, neutrophils, lymphocytes, and corneal fibroblasts that perpetuate the ocular allergic inflammation (Leonardi et al. 1999; Trocme and Sra 2002; Kumagai et al. 2006). In VKC, antigen presenting cells, such as Langerhan's cells, are associated with co-stimulatory molecules (CD86) that provide an important mechanism for Th2 cell activation (by

interacting with CD28) and further cytokine release (Abu-El-Asrar et al. 2001a).

In the type 1 hypersensitivity reaction, ligands expressed in conjunctival B cells such as CD23, CD21, and CD40 are crucial for the interactions in the production of IgE (Abu-El-Asrar et al. 2001b). The tears of VKC patients contain high levels of IgE, histamine and mast cell mediators, including major basic protein (MBP), eosinophil cationic protein (ECP), Charcot–Leyden crystals, basophils, IgE- and IgG-specific for aeroallergens (e.g., ragweed pollen) and eosinophils (Ballow and Mendelson 1980; Irani et al. 1990; Bielory 2000).

Chemokines such as IL-4 and IL-13 are involved in the formation of giant papillae by inducing the production of extracellular matrix and the proliferation of conjunctival fibroblasts (Leonardi et al. 2007). IL-8 in the extracellular space of the conjunctival epithelium plays an important role in the recruitment of neutrophils and eosinophils and in the pathogenesis of corneal damage in severe allergic diseases (Miyoshi et al. 2001). Degranulated eosinophils and their toxic enzymes such as ECP and MBP have been found in the tears and conjunctiva as well as in the periphery of corneal ulcers, suggesting their etiopathogenic role in many of the problems associated with VKC (Bielory 2000).

The increased conjunctival infiltration with eosinophils, basophils, mast cells, plasma cells, lymphocytes, macrophages, and fibroblasts, when compared to seasonal and perennial allergic conjunctivitis, may contribute to the serious complications seen in VKC (Trocme and Sra 2002). Granules with cytotoxic mediators are secreted by eosinophils releasing major basic protein, eosinophil cationic protein, eosinophil peroxidase, and gelatinase B which damage corneal epithelium and affect wound healing (Trocmé et al. 1993, 1997; Abu-El-Asrar et al. 2001c). Enzymatic degradation of histamine has been shown to be significantly lower in patients with VKC compared with normal patients in both tears and plasma, suggesting that this dysfunction may be a primary factor in the pathophysiology of VKC (Abelson et al. 1995).

Treatment of Allergic Eye Diseases

Treatment of pediatric ocular allergy should be managed by the ophthalmologist in conjunction with the allergist and in a multifactorial approach. Table 4.1 shows a summary of a suggested treatment approach. Avoidance of offending allergens as much as possible in conjunction to allergy medications is the mainstay therapy. For severe cases, topical corticosteroids and immunotherapy may be necessary. It is important to optimize the treatment of children suffering from allergic disease to improve their quality of life and avoid secondary complications.

Primary Interventions

Primary interventions, such as environmental modification and minimizing or avoiding the offending allergens as much as possible, are an important first step for all types of allergic conjunctivitis. For the more common allergens, simple measures including installing high-efficiency air filters and air conditioning, meticulous removal of dust such as vacuum cleaners with special filters, removal of drapes and carpets, protective goggles, sealing bedding, washing linens in hot

Table 4.1 Summary of suggested treatment approach

Mild seasonal allergies
1. Avoidance of allergens and rubbing
2. Preservative-free artificial tears
3. Multimodal allergy medications over the counter, used as needed
Vernal keratoconjunctivitis (*VKC*) *or atopic keratoconjunctivitis* (*AKC*)
1. As above plus
2. Multimodal allergy medications used continuously
3. Cyclosporine 0.05% up to 4 times daily
4. Topical steroids for acute flares
5. Consider immunomodulatory shots
6. Control of dermatitis (AKC)
7. Control of systemic allergy (AKC and VKC)

water, avoidance of pets or keeping pets out of the sleeping areas and washing the child's hair in the evening prior to sleeping, can keep the allergen away from the eyes and the upper respiratory system. Some of these recommendations, especially involving beloved pets, can be difficult to implement. Cold compresses may aid in symptom relief, especially ocular pruritus. Eye lubricants, ideally preservative-free artificial tears, provide a barrier function and help to improve the first-line defense at the level of the conjunctival mucosa, helping to wash out or dilute allergens and inflammatory mediators of the ocular surface. Ointments are commonly used at night and provide moisture to the ocular surface while the child sleeps. Although frequently unsuccessful, discouraging of rubbing the itchy eyes is important.

Secondary Interventions

Topical pharmacological interventions may be required when non-pharmacological strategies do not provide adequate symptom relief. Milder cases can be treated with short-term topical ophthalmic therapy for temporary symptom relief such as decongestants, antihistamine with/without decongestants combination, mast cell stabilizers, a multiple action anti-allergic agent and anti-inflammatory agents.

Topical decongestants have shown to be effective, administered up to four times daily. These medications act as vasoconstrictors, effectively reducing ocular erythema, but have no effect on the allergic inflammatory response. Adverse effects include burning and stinging on instillation, mydriasis and rebound hyperemia with chronic use, and tachyphylaxis (Abelson et al. 1990). Their primary contraindication is in patients with narrow angle glaucoma. Phenylephrine and tetrahydrozoline are sympathomimetic agents that decrease congestion and edema through α-receptor stimulation.

Antihistamines competitively and reversibly block histamine receptors. Topical treatments are preferred over systemic for ocular allergies because of their greater efficacy in relieving itching and redness. However, systemic control of allergy is an important part of the management of ocular allergy. These medications may need to be given up to 4 times per day, and may be irritating to the eye with prolonged use (La Rosa et al. 2013). Combined use of an antihistamine and a vasoconstricting agent is more effective than use of either agent alone. Moderate to severe cases may require longer usage of the above agents and the addition of an oral antihistamine. The combination of H1 receptor blockers with oral antihistamines provides a greater relief than oral antihistamines alone. Newer second-generation oral antihistamines (i.e., terfinadine or loratadine) may be preferred over first-generation antihistamines because they have reduced side effects such as somnolence; however they can induce ocular drying, and worsening allergic symptoms (La Rosa et al. 2013). In addition, ocular challenge testing has shown that use of systemic antihistamines can also result in a several-fold increase in allergen tolerance in both children and adults (Abelson and Granet 2006).

Mast cell stabilizers inhibit the degranulation of mast cells and thus suppress release of inflammatory mediators (e.g., histamine, leukotriene, thromboxane A2). These agents inhibit the early phase reaction of type I allergy and conjunctival local infiltration of inflammatory cells, both of which result in a reduction of the late phase reaction. Mast cell stabilizers do not relieve existing symptoms but they can be used on a prophylactic basis to decrease/prevent degranulation of mast cells, preventing release of histamine and other chemotactic factors. They require a loading period during which they must be applied before the antigen exposure. The exact mechanism of action is not known, but these agents may stabilize cell membranes through increased calcium influx or a reduction in membrane fluidity. Lodoxamine 0.1% has been used continuously for up to 3 months in children aged 2 years and older and pemirolast potassium 0.1% has been used to treat children 2 years and older without serious adverse effects (Abelson and Granet 2006).

Multimodal anti-allergic agents are the drugs of choice for providing immediate symptomatic relief. These multiple action drugs include

olopatadine, ketotifen, azelastine, epinastine, and bepotastine, amongst others. They have multiple pharmacological effects such as histamine receptor antagonist action (H1, H2), stabilization of mast cell degranulation, and suppression of activation and infiltration of eosinophils, generation of leukotrienes and cytokine release. Olopatadine 0.1% is both a mast cell stabilizer and antihistamine with high affinity and selectivity for H1 receptors. In both adults and children as young as 4 years old, it has been shown to be superior to numerous anti-allergic agents (Abelson and Granet 2006). It is one of few agents approved by the US Food and Drug Administration (FDA) for treatment of all signs and symptoms of allergic conjunctivitis. Ketotifen 0.025%, a noncompetitive H1 antagonist and mast cell stabilizer, has proved safe and effective in the treatment of allergic conjunctivitis in children, although several studies have shown to cause mild stinging and shorter long-term duration of action than olopatadine (Abelson and Granet 2006). Azelastine 0.05%, a second-generation H1 receptor antagonist that inhibits histamine release from mast cells, downregulates ICAM-1 expression and prevents activation of inflammatory cells, has been shown to be safe in children aged 2 and older with allergic conjunctivitis (Abelson and Granet 2006).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally ineffective in chronic allergic conjunctivitis. Their therapeutic use is related to their ability to block prostaglandin biosynthesis by inhibiting the activity of cyclooxygenase. They can be used as additive drugs in order to reduce hyperemia and pruritus related to prostaglandin D2 and E2, but they do not inhibit histamine (Saari 2010). An adjuvant course of aspirin, can be an effective strategy in treating severe cases of VKC (Abelson and Granet 2006).

Tertiary Interventions

If the previously mentioned approaches are not effective, immunomodulatory medications should be introduced.

Corticosteroids are one of the most potent agents used in the more severe variants of ocular allergy. Corticosteroids possess immunosuppressive and anti-proliferative properties, but their potential ocular adverse effects, such as delayed wound healing, secondary infection, elevated intraocular pressure, and cataracts must be taken into account. Newer topical steroids may have fewer side effects. Topical steroids are used for short courses in patients with inadequate response to secondary interventions and often tapered over several weeks after the acute flare while cell mast stabilizers are continued. Some children with severe disease may need longer courses of topical steroids. Corticosteroids require a loading period typically of 2 weeks before the maximum treatment effect is seen.

"*Steroid-sparing therapy*" calcineurin inhibitors such as cyclosporine or tacrolimus may be used as chronic therapy to reduce dependence on topical steroids.

Cyclosporine, a fungal antimetabolite used as immunomodulator, inhibits various inflammatory mediators and the development of mast cell-mediated allergic conjunctivitis. The use of topical cyclosporine 1% has shown to be effective to control symptoms and local inflammation in severe forms of VKC in childhood when applied at the beginning of the disease and for a long-time period (Tesse et al. 2010). Because cyclosporin A is lipophilic, it must be dissolved in an alcohol–oil base, which may cause ocular irritation (i.e., burning, tearing, erythema, and itching).

Tacrolimus is a macrolide antibiotic that has potent immunomodulatory properties. Tacrolimus acts primarily on T lymphocytes by inhibiting the production of lymphokines, particularly IL-2, as well as IL-3, IL-5, TNF-α, and IFN-γ. Tacrolimus blocks degranulation of mast cells as well as activation of their cytokines. This drug is highly efficient to prevent post-transplant rejection in patients resistant to steroids and cyclosporine. In this regard, tacrolimus is between 10 and 100 times more powerful than the latter (Hooks 1994). It has been effective in the treatment of a variety of other ocular immune-mediated diseases such as corneal graft

rejection, keratitis, scleritis, ocular pemphigoid, and uveitis (Bielory 2000). Regarding the current limited data from literature, ocular application of tacrolimus 0.1%, 0.03% and 0.02% seems effective in treating patients with allergic keratoconjunctivitis; however, ocular irritation may limit its use. Because of the risk of development of herpes keratitis, adequate follow-up is advised (Sánchez Ferreiro and Muñoz Bellido 2013; Westland et al. 2013). At present, tacrolimus cream is available in two approved concentrations (0.1 and 0.3%) by the FDA for skin use in the treatment of atopic dermatitis, but topical ophthalmic drops must be compounded.

Immunotherapy, whether via the subcutaneous route or the intranasal or sublingual route, should be considered in the treatment of persistent severe cases refractory to conventional treatment. Allergen-specific immunotherapy is an effective treatment for patients with allergic rhinoconjunctivitis who have specific IgE antibodies to allergens inducing clinical tolerance to the specific antigen. However, the immune responses to allergen administration are not predictive of the effectiveness of the therapy and the therapy itself can produce systemic reactions depending on the type of allergen administered (La Rosa et al. 2013). The sublingual (oral) immunotherapy is gaining momentum among allergists and it has been shown to control ocular signs and symptoms although less well than nasal symptoms, thus it requires further evaluation for the ocular allergy relief (La Rosa et al. 2011).

Systemic immune suppression is indicated for severe cases of ocular allergy unresponsive to topical treatment where progressive cicatrization is vision-threatening; this therapy should be managed in conjunction with a pediatric rheumatologist.

In the future, newer, more selective drugs like anti-chemokine receptor antibodies, leukotriene receptor antagonists, liposomal delivery systems, anti-IgE therapy and plasmid DNA immunization may become available for treatment of ocular allergy (Abelson and Granet 2006).

Conclusion

Ocular allergy has a wide spectrum of presentation. SAC and PAC, characterized by a type 1 hypersensitivity reaction, are the least severe and easier to manage. VKC and AKC are more serious allergic disorders, characterized by type 1 and 4 hypersensitivity reactions with massive involvement of T cells, macrophages, and eosinophils which may cause severe complications. It is an important ocular disease due to potential sight threatening complications. Thus, it is critical to manage these patients in a multifactorial fashion in conjunction with the pediatrician, allergist, and ophthalmologist. The main objective is to be able to get these children through the disease successfully preventing the complications and possible iatrogenia.

Compliance with Ethical Requirements Kathryn Colby and Andrea Cruzat declare that they have no conflict of interest. No human studies or animal studies were carried out by the authors for this article.

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Corneal Diseases in Children: Ocular Surface Diseases

5

Danielle Trief and Kathryn Colby

Tear Film Dysfunction

A healthy tear film provides a smooth and uniform refractive surface for the eyes, lubricates the ocular surface, allows comfortable movement of the lids over the eyes, provides trophic support to the cells of the ocular surface, and defends against microbial infection. The tear film is a trilaminar structure, composed of mucin, aqueous, and lipid. The mucin layer is most proximal to the corneal surface and is secreted by goblet cells. It allows for the even distribution of tears. The aqueous comprises the central layer and is secreted by the lacrimal glands. The lipid layer is the most superficial, and is secreted by the meibomian glands. The lipid layer retards evaporation, preventing early breakup of the tear film. Dysfunction in any of these three layers can result in instability of the tear film. Blinking redistributes the tear film every five to six seconds in adults, although blink rates tend to be less in children and in infants (Jones and Nischal 2013).

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In addition to mucin, aqueous, and lipid, the tear film contains epidermal and tissue growth factors that are important for corneal healing (Nava et al. 1997). There are also cytokines, vitamins, and nutrients that support epithelial cell homeostasis and immunity. Tear film dysfunction can result in corneal and conjunctival scarring and infection.

The term "dry eye" encompasses a heterogeneous group of diseases characterized by increased osmolality of the tear film and inflammation of the ocular surface with accompanying symptoms of discomfort (Bron et al. 2014). It can be broadly divided into decreased aqueous tear production due to lacrimal disease or dysfunction, or increased tear evaporation, primarily secondary to meibomian gland disease. In clinical practice, many patients have concomitant lacrimal gland and meibomian gland disease.

Compared to adults, children are less likely to have dry eye, and also tend to complain less about tear dysfunction. In one study, children with the same objective ocular disease scores as adults, reported milder symptoms (Han et al. 2013). Screening tools like the ocular surface index may be difficult for children to understand and contain inapplicable criteria like "difficulty driving." Some authors have modified these surveys to make them applicable to children (Han et al. 2013). Practitioners should look for signs of tear film dysfunction like frequent blinking, eye rubbing, or conjunctival injection, as there may be disease in the absent of complaints.

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Tear Film Evaluation

There are several tools available to screen for tear film abnormalities and ocular surface disease in the pediatric population. Noninvasive tear film break up time measures the time it takes between blinks for the cornea tear film to become disrupted. The pre-corneal tear film is observed. It is initially uniform and regular, reflecting a uniform image to the observer. With time, the tear film begins to break and reflects a distorted image. In adults, this occurs at a mean of 11.2–16.7 s (Nichols et al. 2002). There is greater tear film stability in children, with mean tear break up times of 21.76 s (Jones and Nischal 2013). Patients with dry eye often have tear break up times of less than 10 s.

The degree of fluorescein staining can also be easily measured in children and can be graded on a 0–3 scale: (Han et al. 2013)

0 represents no staining,
1 mild staining limited to less than 1/3 of the cornea,
2 moderate staining of less than ½ of the cornea,
3 severe staining of greater than ½ of the cornea.

The presence of any corneal fluorescein staining in children is abnormal and should alert the clinician to an underlying pathological process.

In cooperative older children, a Schirmer's test can be used to assess aqueous function. Most children will wet greater than 15 mm of paper in five minutes. Wetting less than 5 mm is abnormal (Alves et al. 2008). Tear osmolarity can also be tested and it may be elevated in aqueous deficiency, excessive evaporation or in combination disease. Of course, a thorough examination of eye lid position, with lids open and closed, meibomian gland and lid margin status, and general health of the ocular surface is necessary in any work up. Areas of scarring and dysfunction should be documented carefully.

Adjuvant tools can be used in specific cases. If there is concern for neurotrophic disease, a Cochet-Bonnet esthesiometer (Luneau Ophthalmologie) or non-contact gas esthesiometer can be used to measure corneal sensation. The Cochet-Bonnet esthesiometer uses nylon monofilaments that have a diameter of 0.027 mm and range from 0 to 6 cm in length, to apply different degrees of pressure to the cornea and quantify the degree of corneal sensation. Impression cytology can be used to provide histological, immunohistological or molecular analysis of the ocular surface. A cellulose acetate filter is applied to the ocular surface to remove the superficial layers of the ocular surface epithelium. Impression cytology is helpful in looking for limbal stem cell deficiency and conjunctivalization of the ocular surface (Singh et al. 2005).

Aqueous Deficiency

The aqueous component of the tear film is produced by the lacrimal gland and the accessory lacrimal glands of Krause and Wolfring, which are located in the superior fornix. Congenital alacrima is quite rare and is characterized by aplasia or hypoplasia of the lacrimal gland (Talsania et al. 2015). It may be independent or associated with aplasia of the lacrimal and salivary glands (ALSG syndrome). The latter is the result of mutations of the fibroblast growth factor 10 gene, which is necessary for the development of both lacrimal and salivary glands in mice (Higashino et al. 1987). Patients with congenital alacrima should be worked up for Allgrove syndrome (Triple A syndrome), which is the triad of alacrima, achalasia, and ACTH-resistant adrenal deficiency (Moore et al. 1991). This rare autosomal recessive disease is most common in French Canadian/Native American pedigree. Patients may present with life-threatening hypoglycemic seizures secondary to glucocorticoid deficiency. The disease has been mapped to chromosome 12q13, the ALADIN gene, which is expressed in both neuroendocrine and cerebral structures, and is involved in the normal development of the peripheral and central nervous system (Tullio-Pelet et al. 2000). In the absence of a functioning lacrimal system, these patients require lifelong tear supplementation.

Ectodermal dysplasia comprises a heterogeneous group of diseases where the primary defects are in the development of embryonic ectoderm derived tissues including the teeth, hair, nails and sweat glands (Alves et al. 2008). Patients may also have hypoplastic lacrimal glands, diminished tear production and a resulting cicatricial conjunctivitis. Other ocular findings include reduction of eyebrows and lashes, lid keratinization, recurrent epithelial defects, and trichiasis. The overall prevalence of ectodermal dysplasia is 100 per million people, but there are over 150 different types of the disease. Kaercher et al. found that 94.4% of patients with ectodermal dysplasia suffered from dry eye (Kaercher 2004). Over 90% had reduction in eyebrows and eyelashes, and 90% had changes in meibomian glands. Patient complained of burning, foreign body sensation and photophobia. On exam, 20% of patients had corneal pannus, but this tended to occur later in life (second–third decade). The keratopathy was thought to be secondary to tear film dysfunction.

Cystic fibrosis affects all secretary epithelium, including the lacrimal gland. Children with cystic fibrosis have decreased Schirmer scores, fluorescein tear break up time, and low tear film instability (Mrugacz et al. 2008). Impression cytology reveals increased inflammatory signs in the conjunctiva, including presence of neutrophils and goblet cell loss (Alves et al. 2008). Cystic fibrosis is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regular (CFTR), whose product functions to regulate the chloride channel in epithelial membranes. Patients have recurrent respiratory infections, early pancreatic insufficiency, and raised sweat chloride (O'Sullivan and Freedman 2009).

Sjögren's syndrome is an autoimmune disease characterized by inflammation of the lacrimal and salivary glands, leading to reduced secretion of the aqueous component in both tears and saliva. It is quite uncommon in children compared to adults. In one large study, only 5.5% of patients with Sjögren's syndrome were younger than 16 years old (Ostuni et al. 1996). Furthermore, the presentation in children is often different than adults (Lieberman 2013). Children are more likely to present with recurrent episodes of parotid swelling (parotiditis) (Cimaz et al. 2003). In adults, classification depends on at least two of the three criteria: (1) positive serum markers (Anti-Sjögren's-Syndrome-related Antigen A (anti-SSA), Anti-Sjögren's-Syndrome-related Antigen B (anti-SSB), or rheumatoid factor (RF) with antinuclear antibody (ANA) titer of at least 1:320) (2) labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis (3) keratoconjunctivitis sicca with ocular staining score of at least 3 (Shiboski et al. 2012). There are no defined criteria for the diagnosis of Sjögren's in children. ANA titers as well as foci of lymphocytic sialadenitis are thought to be different in children compared to adults, leading to diagnostic difficulties. However, in a review of published case series of pediatric Sjögren's, Cimaz et al. found that the majority of patients had positive antibodies, low Schirmer scores, and abnormal salivary biopsy results. As is the case in the adults, the disease was much more common in females than males (7:1). The majority of children were treated initially with oral corticosteroids, but some ultimately needed systemic immunomodulators including hydroxychloroquine, cyclosporine, and cyclophosphamide (Cimaz et al. 2003).

Juvenile rheumatoid arthritis (JRA) is another autoimmune condition that can affect basal tear secretion and tear film stability. JRA is defined as an objective synovitis lasting 6 weeks to 3 months before the age of 16 (Ravelli and Martini 2007). Children may have polyarthritis (five or more joints involved) or oligoarthritis (four joints or fewer involved). JRA can be associated with systemic disease including fever, rash, and lymphadenopathy. One study found that children with JRA are more likely to complain of dry eye symptoms than controls (12.5% vs 1.5%) and clinical dry eye signs were detected in 10.9% of patients with JRA compared to none in controls (Akinci et al. 2007). The prevalence of dry eye was not affected by a history of uveitis.

The lacrimal gland can also be damaged from exposure to radiation, leading to aqueous insufficiency. High dose radiation to the orbit, for

example, can result in irreversible damage to the lacrimal gland system. In a series of patients with nasopharyngeal carcinoma, radiation of 45–60 Gray unit (Gy) lead to severe keratopathy (Kwok et al. 1998). The radiation can also directly damage corneal stem cells, leading to corneal vascularization and thinning. To a lesser extent, UV radiation can also damage the cornea. Wavelengths between 200 and 300 nm in the UV spectrum are strongly absorbed by the corneal epithelium cells. With moderate exposure to UV light, there can be full thickness epithelial changes. There are inherent antioxidant defense mechanisms in the cornea that play an important role in healing following UV exposure, including the glucose-6-phosphate dehydrogenase (G6PDH) pathway (Lattimore 1989). However, UV keratitis can result after activities with high UV exposure like skiing (snow blindness), welding (welder's keratitis), and exposure to tanning lamps. The acute effects of UVR are generally delayed for 8–12 h after exposure (Yam and Kwok 2014).

Evaporative Tear Film Dysfunction

The major cause of increased tear evaporation is lipid deficiency. The meibomian glands secret lipids and lipoproteins that stabilize the tear film and reduce evaporation from the surface. Meibomian gland dysfunction affects 10% of the adult population, but it can also be seen quite commonly in children (Mavrakanas et al. 2010). In a large corneal practice, blepharoconjunctivitis with concurrent meibomian gland disease was the most common reason for a pediatric referral (Hammersmith et al. 2005).

Pediatric blepharoconjunctivitis is also sometimes called pediatric rosacea, non-tuberculosis or staphylococcal phlyctenular disease, or childhood acne rosacea. Patients uniformly have meibomitis and often complain of redness, tearing, and foreign body sensation. Exam demonstrates meibomian gland pouting, capping hypertrophy, telangiectasia, phlyctenules, recurrent chalazion, conjunctival hyperemia, and corneal scarring (Hammersmith 2015). Eyelid cultures may grow staph aureus in the majority of patients, and marginal infiltrates can be seen where the lid crosses the limbus (2, 4, 8 and 10 o'clock). Facial signs include erythema, telangiectasia, flushing, papules and pustules on the cheek, chin, and forehead. The disease is bilateral in the majority of cases, but can be asymmetric. If there is significant scarring present, children are at risk for developing amblyopia.

The onset of disease is usually 4–5 years old, and is more common in females than males (Hammersmith et al. 2005). It is more common and can be more severe in Asian and Middle Eastern children. In one large study in Singapore, almost 10% of children required surgical intervention (Teo et al. 2012).

Patients have been found to have higher matrix metallopeptidase-9 activity, correlated with delayed tear clearance and increased tear concentration of pro-inflammatory cytokines. While systemic tetracyclines (doxycycline) are helpful in treating rosacea in adults as they inhibit matrix metalloproteinase activity, tetracyclines should be avoided in children younger than 9-years old as it impedes tooth and bone development. Oral macrolides have been used as an effective alternative in children. Topical fluoroquinolones and steroids can also be used in short-term treatment. Topical steroids must be used cautiously in children because of the risk for cataracts and glaucoma (Hammersmith 2015).

In children and adolescents, contact lens use can also be associated with evaporative tear dysfunction. Evaporation of the tear film over a contact lens is higher than without a contact, and is independent of the lens water content or material. This results in an unstable tear film and increased tear osmolarity (Nichols et al. 2002). In a study of 3443 high school students in Japan, contact lens use was associated with significantly higher prevalence of severe dry eye symptoms in both boys and girls (Uchino et al. 2008).

Multifactorial Tear Film Dysfunction

A number of immune mediated, traumatic, and nutritional conditions can lead to tear film

deficiency by combined aqueous, lipid, and mucin deficiency. These diseases are marked by chronic inflammation, which can lead to conjunctival scarring, loss of limbal stem cells, and subsequent corneal compromise.

Graft versus host disease (GVHD) is an immunologically mediated reaction of donor cells to host tissue. It occurs in the setting of allogeneic blood and bone marrow transplants, where the donor cells (graft) mount an immune response against the recipient (host patient). The immunologic attack typically involves the skin, gastrointestinal system, liver, and eyes (Ferrara et al. 2009). The prevalence varies depending on the degree of mismatch between HLA proteins and ranges from 35 to 45% of recipients of full matched sibling donor grafts, to 60–80% of people receiving one antigen HLA mismatched unrelated donor grafts. It can be divided into acute and chronic stages, depending on whether symptoms occurred before or after the first 100 days of engraftment respectively.

Approximately 50% of children with bone marrow transplant (BMT) complain of dry eye, and 25.7% are found to have ocular manifestations of GVHD (Leite et al. 2006; Lin and Cavanagh 2015). In addition to goblet cells, the conjunctival epithelium contains Langerhans cells and lymphocytes, which play an important role in ocular defense. Following BMT, children have significant up regulation of HLA-DR expression, conjunctival inflammation and subsequent conjunctival metaplasia (Kurpinska et al. 2013). The donor's immunocompetent T cells not only damage the conjunctival goblet cells, but also mount an immunologic attack on the lacrimal glands, producing both aqueous and mucous deficiency. Common findings in ocular GVHD include dry eye, filamentary keratitis, blepharitis, cataract, and ocular hypertension (Lin and Cavanagh 2015; Ng et al. 1999).

Treatment of ocular surface disease from GVHD often involves topical anti-inflammatory drops in addition to lubricating drops. Lin and colleagues found that 90% of their patients with GVHD required one or more therapies in addition to artificial tears (Lin and Cavanagh 2015). Topical anti-inflammatory drops included cyclosporine, loteprednol, and prednisolone acetate. Some patients also required serum tears and custom scleral contact lenses (Soni and Jeng 2015; Gungor et al. 2008). The combination of topical anti-inflammatory drops and serum tears stabilized symptoms in 80% of patients.

Stevens–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are immune-mediated diseases characterized by damage to the skin and mucous membranes triggered by exposure to a medication or infectious agent. SJS involves less than 10% of the total body surface area (TBSA), whereas TEN involves more than 30% (Quirke et al. 2015). In adults, the rate of SJS/TEN is 2–7 per million and carries a mortality rate between 5 and 30%. The incidence is higher in children, up to 35.5 cases per million per year (Ma et al. 2015). The mortality rate is lower in the pediatric population, but younger patients tend to have more severe ocular involvement than older patients (Quirke et al. 2015; Sotozono et al. 2015). The most common causative agents are antibiotics, anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDs).

Patients may experience a prodromal fever, sore throat and fatigue, followed by progressive sloughing of the skin and mucous membranes. There is typically an acute phase lasting 2–4 weeks, followed by a chronic phase. Acutely, patients experience a membranous conjunctivitis, corneal epithelial abnormalities, symblepharon, and pannus. These findings are the result of a severe cytokine storm at the disease onset (Araki et al. 2009). Chronically, there can be eyelid scarring producing entropion, ectropion, and severe damage to meibomian glands. Conjunctival scarring can lead to a loss of goblet cells and damage to the accessory glands of Krause and Wolfring and lacrimal ducts. All three components of the tear film can thus be affected, resulting in severe dry eye and conjunctival keratinization. The acute and chronic inflammation seen in SJS can also lead to corneal limbal stem cell deficiency.

Acute treatment of SJS/TEN is aimed at maintaining a healthy ocular surface and reducing inflammation. Patients are often admitted to a

burn unit and receive multidisciplinary care including fluid resuscitation, nutritional support, and wound care. The causative agent should be immediately discontinued. The ocular surface should be treated with frequent lubrication, topical antibiotics, and topical steroids. Studies have found that topical steroids at disease onset can reduce the degree of ocular sequelae (Yagi et al. 2011).

Amniotic membrane transplantation in the acute phase of SJS may also prevent scarring (Ciralsky et al. 2013; Gregory 2011). Amniotic membrane is rich in growth factors and protease inhibitors, and has been found to have potent anti-inflammatory effects. Furthermore, by covering the bulbar and palpebral conjunctiva, amniotic membrane can minimize friction between the lids and the globe and prevent scarring.

Chronically, efforts should be made to minimize cicatricization, including managing the dry ocular surface with lubrication, punctual occlusion, and repairing eyelid abnormalities. Artificial tear formulations (drops, gels, ointments) are often not enough, and patients require autologous serum tears or short courses of anti-inflammatory agents. Specialized scleral contact lenses like the fluid filled prosthetic replacement of the ocular surface ecosystem (PROSE) lens can bath the entire corneal surface in a pool of oxygenated artificial tears. PROSE treatment has been found to offer sustained improvement in visual acuity and visual function in patients with SJS (Papakostas et al. 2015). The PROSE lens can be custom fit for pediatric patients (Gungor et al. 2008). Patients with limbal stem cell deficiency may benefit from a limbal stem cell transplant. However, SJS is a bilateral disease, and autologous as opposed to allogeneic limbal tissue may be required, necessitating systemic immunosuppression (Ciralsky et al. 2013).

If there is significant corneal scarring, patients may need a keratoplasty for visual improvement. Traditional penetrating keratoplasty (PK) has a poor prognosis in SJS-TEN patients because of prolonged inflammation leading to persistent epithelial defects, corneal melting and graft failure (Tugal-Tutkun et al. 1995). Alternatively, the Boston Keratoprosthesis (KPro) can be used (Sayegh et al. 2008). It exists as a collar button design consisting of polymethyl methacrylate optic that clamps within a donor ring of corneal tissue, and is then sutured in place like a traditional graft (Fig. 5.1). This "artificial cornea" can provide optical clarity through the optic, even in the setting of severe scarring. However, the prolonged inflammation associated with SJS-TEN, can lead to melt of the tissue around the KPro and aqueous leakage. These patients must be followed diligently.

SJS-TEN is a chronic inflammatory disease that can lead to severe ocular surface scarring, and can be very difficult to treat (Fig. 5.2). In a retrospective review of 41 patients under 18 years old with SJS, 100% experienced long-term complications of their disease and 30% required follow up procedures (Quirke et al. 2015).

Chemical trauma to the ocular surface is another potential cicatrizing condition. Chemical injuries represent 11.5–22.1% of all ocular traumas, and two-thirds of the injuries occur in young male patients. Chemical injuries can be either alkali or acidic in nature. Alkali agents are lipophilic and therefore penetrate tissues more

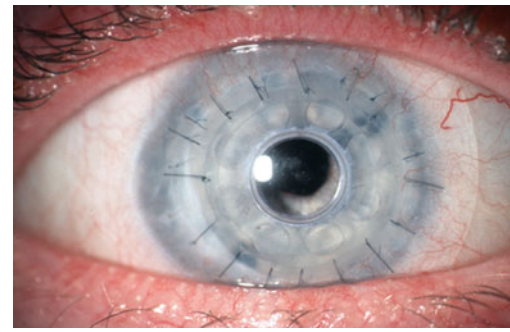

Fig. 5.1 Boston type I keratoprosthesis (KPro) in a teenager with a history of Stevens–Johnson syndrome. The device previously consisted of three components: a front plate with an optical stem, a back plate, and a titanium locking ring. The most recent model consists of two components: a front plate and a back plate, which snap together without the locking ring. The front and back plates come together with donor corneal tissue sandwiched in between. The KPro is covered by a bandage contact lens

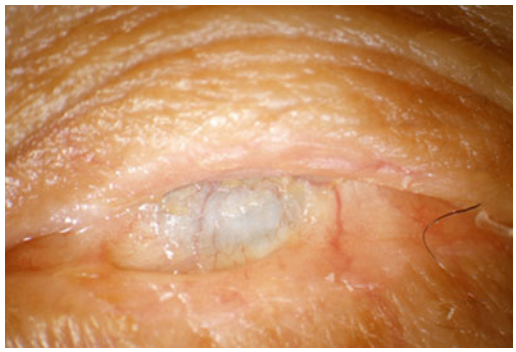

Fig. 5.2 Severe keratinization of both the conjunctiva and cornea, symblepharon and ocular surface scarring in a patient with a history of Stevens–Johnson syndrome

rapidly than acids. They saponify the fatty acids of cell membranes, penetrate the corneal stroma, and destroy proteoglycan ground substance and collagen bundles. These damaged tissues secrete proteolytic enzymes, which can lead to further damage. By contrast, acids tend to penetrate less as they cause denaturing and precipitation of proteins. These coagulated proteins act as a barrier to prevent further penetration (Fish and Davidson 2010). The extent of ocular injury depends on the strength and concentration of the chemical agent, the volume of solution, and the duration of exposure.

The chemicals can damage conjunctival goblet cells and produce limbal ischemia. Destruction of the delicate limbal stem cells can result in permanent corneal opacification. In addition to corneal scarring, patients with severe chemical injury can develop glaucoma, cataract, and lid malposition. Two major classification schemes for corneal burns are the Roper-Hall and the Dua classification (Roper-Hall 1965; Dua et al. 2001). Both are used to predict the outcome of corneal burns. The Roper-Hall classification is based on the degree of corneal involvement and limbal ischemia. The Dua classification is based on an estimate of limbal and conjunctival involvement.

Initial treatment of ocular chemical injury should be directed toward removing all trapped debris and irrigating the eye to return it to a neutral pH. Patients with mild to moderate injury have a good visual prognosis and can often be treated with medical therapy alone. Initial topical medical therapy includes antibiotics, steroids, lubricating eye drops, and a long acting cycloplegic for pain. Steroid drops should be tapered after about a week because the balance of collagen synthesis versus collagen breakdown may tip unfavorably toward collagen breakdown (Donshik et al. 1978). In patients over the age of 9, oral tetracyclines can be employed to reduce the effects of matrix metalloproteinases that can degrade type I collagen. Some authors also advocate for oral or topical vitamin C, which may promote collagen synthesis and reduce corneal ulceration (Pfister et al. 1991).

Amniotic membrane transplantation has also been used in chemical injury for its anti-inflammatory properties (Lo et al. 2013). In one randomized control trial, patients with moderate burns were found to have significantly better final visual acuity with AMT compared to medical therapy alone (Tandon et al. 2011). Similar to SJS-TEN, severe chemical injury can result in a chronic low grade inflammation and keratinization of the ocular surface. Necrotic epithelium should be debrided. If there is significant limbal stem cell loss, limbal stem cell transplant can be attempted (Morgan and Murray 1996). Penetrating keratoplasty or a KPro can be used for corneal scarring, but most authors recommend delaying corneal surgery to minimize inflammation and the incidence of postoperative complications (Kramer 1983). In the pediatric population, consideration must also be made to the risk of amblyopia from corneal opacity, and children may therefore require earlier intervention.

The prognosis of chemical injury is quite variable. Compared to adults, ocular chemical injuries in pediatric patients pose a greater challenge because early diagnosis and intervention may be more difficult. In a retrospective study of 134 pediatric patients in India with ocular burns, the median visual acuity at final follow up was 3/60. Over half of the injuries occurred in patients of preschool age (0–5 years old), and patients required an average of 2.3 surgeries (Vajpayee et al. 2014).

Nutritional deficiencies can also lead to tear film instability and severe ocular surface disease.

Until the late twentieth century, vitamin A deficiency was the leading cause of childhood blindness in developing countries (Humphrey et al. 1992). A series of studies in the 1980s revealed that not only is vitamin A critical for retinal function and ocular surface integrity, but lack of vitamin A can lead to significant morbidity and mortality (Sommer et al. 1983). In India, for example, mortality among preschool-age children was lowered by 54% upon distribution of small, weekly doses of vitamin A (Rahmathullah et al. 1990). Vitamin A distribution programs are now credited with saving the sight and lives of nearly half a million children every year (Sommer 2014). However, vitamin A deficiency still remains a problem in some developing countries. Vitamin A deficiency can also be seen in developed countries in the setting of anorexia/bulimia, vegetarian or vegan diet, cystic fibrosis, short bowel syndrome, liver disease, or other malabsorption syndromes (Braunstein et al. 2010).

Vitamin A is a fat soluble vitamin that is critical in the homeostasis of the visual pigment of photoreceptors. Deficiency can thus lead to nyctalopia (night blindness). Deficiency can also cause a keratinizing metaplasia of the mucosal surfaces throughout the body, including the lungs and intestine. The conjunctival epithelium can change from a normal columnar to a stratified squamous type. There is subsequent loss of goblet cells and conjunctival "xerosis" or dryness. On exam, patients may show the pathognomonic Bitot spots, which are tangles of keratin admixed with saprophytic bacteria on the conjunctiva. Vitamin A deficiency has also been shown to reduce aqueous tear production (Sommer and Emran 1982). In more advanced disease, the cornea can become keratinized and ulcerate, producing permanent vision loss.

Once vitamin A deficiency is recognized, patients should have prompt treatment given the high rates of morbidity and mortality. In children over 12 months of age and all women of childbearing age, vitamin A supplementation can be given orally as 110 mg of retinal palmitate or 66 mg retinal acetate for two days in a row and then again two weeks later to boost liver reserves. Children 6–12 months should be given 1/2 the dose, and children less than 6 months should be given one quarter of the dose (Krachmer et al. 2011). In the absence of significant scarring, vitamin A supplementation can lead to swift healing and good visual recovery.

Pediatric allergic eye disease is quite common and can be associated with ocular surface disease. Patients have chronic inflammation of the conjunctiva and cornea, which can lead to a loss of goblet cells, limbal stem cell deficiency, and corneal scarring (Vichyanond et al. 2014). Schirmer values are significantly lower in patients with childhood onset atopic keratoconjunctivitis compared to adult onset atopic keratoconjunctivitis and controls (Onguchi et al. 2006). Similarly, children with vernal keratoconjunctivitis have been found to have reduced tear break up time and ocular surface remodeling from persistent inflammation (Vichyanond et al. 2014; Villani et al. 2015). For a review of pediatric allergic eye disease, please see Chap. 4.

Neurotrophic Keratitis

The cornea is the most densely innervated tissue in our body. This innervation is necessary to regulate corneal epithelial integrity, proliferation, and wound healing. In humans, the first branch (ophthalmic branch) of the trigeminal nerve provides innervation to the cornea, and damage to the trigeminal nerve leads to decrease or absent corneal sensation and the development of neurotrophic keratitis. The reduction in corneal sensitivity ultimately leads to corneal epithelial changes, corneal ulceration, stromal scarring, and neovascularization (Ramaesh et al. 2007). The ophthalmic branch of the trigeminal nerve has two reflex arcs: a motor arc that regulates eye movement (blinking) and an autonomic arc that regulates the secretion of goblet cells, lacrimal and meibomian glands (Mantelli et al. 2015). Taken together, these two arcs maintain the stability of the pre-ocular tear film. While many of the changes seen in the neurotrophic cornea are a result of epithelial breakdown, there is increasing evidence that alteration of corneal sensitivity

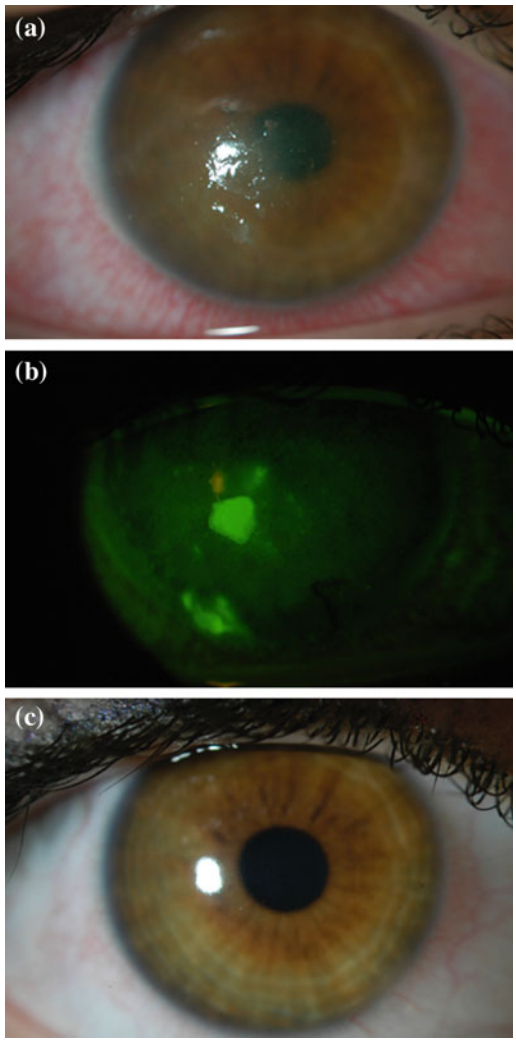

Fig. 5.3 16-year-old patient with a neurotrophic cornea in the setting of a meningioma affecting her trigeminal nucleus (**a**). Note the heaped and irregular epithelium (**b**). The epithelium improved dramatically following regular PROSE use (**c**)

may also affect all corneal structures, including corneal endothelial morphology (Lambiase et al. 2013).

The trigeminal nerve also supplies trophic factors to the cornea, playing a key role in maintaining anatomic integrity and function of the ocular surface. It influences the release of cytokines, neuropeptides, and neuromediators. Impairment of the nerve causes metabolic epithelial disturbances and persistent epithelial defects (Fig. 5.3) (Bonini et al. 2003). Management of neurotrophic keratitis should be based on clinical severity and aimed at promoting corneal wound healing and halting progression of the disease, which if unchecked can lead to corneal melting and perforation (Sacchetti and Lambiase 2014).

When neurotrophic disease is suspected, corneal sensitivity should be measured before the application of fluorescein. It can be measured by testing sensitivity with the tip of a cotton swab, or it can be quantified with esthesiometers like the Cochet-Bonnet esthesiometer (Luneau Ophthalmologie). Practitioners should also look for the presence of other cranial nerve involvement. If there is concomitant dysfunction of the third, fourth, or sixth cranial nerve, cavernous sinus pathology should be considered (Newman 2007). Concomitant dysfunction of the seventh or eighth cranial nerve can be seen with acoustic neuromas or in the setting of surgical damage. The iris should be carefully inspected, as sector iris atrophy can be seen with herpetic disease. The tear film can be analyzed by Schirmer testing, tear break up time, and tear osmolarity. Confocal imaging can be used to evaluate corneal nerve pathology.

Neurotrophic corneal disease can result from damage to the trigeminal nucleus, root, ganglion, or any segment of the ophthalmic branch of the cranial nerve. Infectious disease, most notably the herpetic diseases: herpes simplex virus (HSV) and varicella zoster virus (VZV) can also lead to neurotrophic keratopathy. Other etiologies include congenital neurotrophic cornea, iatrogenic injury (surgery damaging the trigeminal nerve, refractive surgery leading to reduced sensation), topical medications (beta blockers, NSAIDs, trifluridine), and chemical injuries. In adults, long standing diabetes and advanced age are associated with reduced corneal sensation, but this is less of a problem in the pediatric population. Neurotrophic keratitis is thought to affect 5/10,000 individuals (Sacchetti and Lambiase 2014).

Ocular infections from HSV are quite common in the pediatric population and are often initially misdiagnosed. HSV can present as either a blepharoconjunctivitis or a keratitis, and the latter is associated with reduced corneal

sensation in 64% of children. Recurrence of HSV keratitis is more common in children than adults, seen in upwards of 50% of children, necessitating long-term antiviral prophylaxis (Liu et al. 2012). By contrast, herpes zoster ophthalmicus (HZO) from VZV is quite rare in children, but is more commonly associated with neurotrophic corneal disease in adults (Ghaznawi et al. 2011).

Congenital corneal anesthesia is a rare condition that usually presents bilaterally, before the age of three, with associated painless corneal opacities and sterile ulceration (Ramaesh et al. 2007). Rosenberg divided congenital corneal anesthesia in three distinct groups: group 1 is an isolated trigeminal anesthesia due to primary hypoplasia of the hindbrain, group 2 is associated with mesenchymal anomalies, and includes Mobius syndrome and Riley–Day syndrome/Familial Dysautonomia, and group 3 is associated with focal brainstem signs without evidence of mesenchymal dysplasia. The etiology is thought to be due to prenatal injury (Rosenberg 1984).

Familial Dysautonomia (FD, also known as Riley–Day syndrome) is an autosomal recessive disease characterized by extensive central and peripheral autonomic disturbances as well as small fiber sensory dysfunction. Patients have decreased pain perception along the trigeminal nerve, diminished corneal reflexes, and decreased taste perception. Consistent with neurotrophic disease, patients have insensitivity to corneal trauma, decreased blinking, and alacrima (Alves et al. 2008). Autonomic dysfunction includes postural hypotension and oropharyngeal incoordination. There is progressive neuronal degeneration throughout life, and patients have a shortened lifespan, frequently dying from infection (Shohat and Weisz Hubshman 1993). The genetic defect has been mapped to the DYS gene on chromosome 9q31-33. It is principally seen in patients of Ashkenazi Jewish descent, where the carrier frequency is 1 in 32. The overall presence of FD is 1 in 1,000,000 (Blumenfeld et al. 1993).

Mobius syndrome is a rare developmental anomaly of the hindbrain that leads to a non-progressive congenital paralysis of the facial and abducens nerve. In a minority of cases, the trigeminal nerve can also be involved. Corneal damage from neurotrophic keratopathy can be compounded with exposure keratopathy from seventh nerve paralysis (MacKinnon et al. 2014).

The trigeminal nerve can be damaged in the setting of surgical procedures for tumors and maxillary fractures, and ablative procedures in trigeminal neuralgia. Lambiase et al. conducted a retrospective review of patients aged 1–19 who experienced unilateral neurotrophic keratitis after neurosurgery (Lambiase et al. 2013). Indications for neurosurgery included acoustic neuroma, meningioma and chondroma. All patients showed superficial punctate keratitis and dry eye as evidenced by tear film function tests. On in vivo confocal imaging, patients had reduced epithelial and endothelial keratocyte densities.

Early treatment for neurotrophic keratitis is aimed at maintaining a healthy ocular surface through the use of artificial tears, N-acetylcysteine, and systemic tetracycline if the child is old enough. For persistent epithelial defects, a bandage contact lens can be used short term or specialized scleral lenses like the PROSE lens can be used long term (Fig. 5.3c). For moderate-to-severe disease, amniotic membranes, tarsorrhaphies, or conjunctival flaps can be used. In the pediatric population, amblyopia must always be considered with these occlusive therapies. Newer treatments like nerve growth factor hold some promise to accelerate epithelial healing (Lambiase et al. 2013; Bonini et al. 2000).

Exposure Keratitis and Eyelid Disorders

The eyelids provide a moveable mucosal lining that can cover the entire ocular surface, preventing dehydration and trauma to the underlying globe. Eyelid movement is critical to tear film dynamics (pumping and distribution). A complete blink also leads to meibomian gland secretion of lipid, which decreases tear film evaporation. Poor eyelid functioning can result in exposure keratopathy, tear film abnormalities, and ocular surface scarring.

During sleep, the lipid layer of the tear film coupled with good eyelid closure prevents the evaporation of tears, maintaining moisture of the cornea. The Bell's phenomenon, where there is upward rotation of the eyeball during eyelid closure, further protects the cornea. Lagophthalmos is the inability of the eyelids to fully close, and results in increased tear evaporation, corneal drying, and ocular surface breakdown. In early exposure keratopathy, there are superficial punctate micro epithelial erosions in the inferior one-third of the cornea (in the area of exposure). These can eventually coalesce to marco epithelial defects and ulceration (Pereira and Gloria 2010).

Lagophthalmos can be seen following surgical repair for congenital ptosis. Children with congenital ptosis often have poor levator function and undergo a frontalis suspension procedure, where the frontalis muscle is linked to the tarsus of the upper lid. Children have varying degrees of lagophthalmos following this procedure (Kim et al. 2012). An intact Bell's phenomenon has been found to be protective, leading to less tear film and ocular surface instability. In fact, some authors have recommended that children with poor Bell's phenomenon undergo less surgical correction for congenital ptosis than patients with an intact Bell's phenomenon (Yoon et al. 2008).

Lagophthalmos can also be seen in facial nerve palsies. In a review of children with Mobius syndrome, for example, lagophthalmos was present in 83% of cases (Carta et al. 2011). It can also be associated with Grave's disease. Children comprise only 5.8% of patients with Grave's disease and tend to have less severe ophthalmic pathology then adults (Durairaj et al. 2006). Lagophthalmos was seen in 37.1% of pediatric patients with Grave's disease. In the setting of Grave's disease, exposure keratopathy can also result from eyelid retraction and exophthalmos, which were seen in 82.9 and 74.3% respectively in pediatric patients.

During sleep, there is a tonic muscular activity in the orbicularis oculi muscle with concomitant inhibition of tonus of levator palpebral superioris. This delicate coordination between muscles can be compromised in the intensive care unit (ICU) setting as a result of metabolic derangements, mechanical ventilation, and decreased level of consciousness. Sedatives in the ICU setting inhibit active contraction of the orbicularis oculi muscle, resulting in lagophthalmos. Exposure keratopathy can be seen in 3.6–60% of ICU patients (Grixti et al. 2012). Sedated patients are unable to protect their eyes, blink, or complain about ophthalmic symptoms. Moreover, the medical staff is often concerned about restoring hemodynamic stability, and ophthalmic disease may go unnoticed. Critically ill patients are at risk of developing microbial keratitis secondary to exposure, immune suppression, and positive pressure ventilation. In a study of pediatric ICU patients, the ocular infection rate was 7% (Milliken et al. 1988). ICU practitioners should pay particular attention to exposure keratopathy and treat with lubrication and temporary eyelid closure (taping, polyethylene films, tarsorrhaphy) when necessary.

Eyelid malpositioning can also lead to increased exposure and lagophthalmos. Ectropion, or a turning out of the lids away from the globe, can be seen congenitally, following trauma or infection, or in the setting of scarring from oculocutaneous conditions like ichthyosis or xerodermal pigmentosa.

Ichthyosis is a general term used to describe a diverse group of skin disorders, characterized by excessively dry skin and accumulation of scale. Ichthyosis vulgaris is the most common, affecting 1 in 250–300 people. Lamellar ichthyosis and congenital ichthyosiform erythroderma are much rarer variants, but cicatricial ectropion is commonly seen and may require surgical correction. Lamellar ichthyosis is present at birth. The entire skin surface is encased in a colloidan like membrane, which sloughs over the first few weeks of life (Oestreicher and Nelson 1990). Infants subsequently have large plate-like scales and scarring across their entire skin surface. Children with keratitis ichthyosis deafness (KID) syndrome have thickened keratinized lids as well as corneal stromal vascularization and deafness. The corneal disease is secondary to a generalized ectodermal disturbance and limbal stem cell deficiency (Messmer et al. 2005). It is caused by mutations in the GJB2 gene, coding

for connexin 26, a component in gap junctions in epithelial cells. Connexin 26 may act as a tumor suppressor, and these patients are at an increased risk of squamous cell cancer (Kone-Paut et al. 1998).

Xeroderma Pigmentosa is a rare autosomal recessive disorder that is the result of an enzymatic defect in the ability to repair DNA damage by shortwave length light (Goyal et al. 1994). Infants can show freckling in the first year of life. The eyelids often atrophy and may have madarosis, ectropion, and malignant degeneration. Patients are at high risk of malignant skin neoplasms. Squamous cell carcinoma of the limbus, for example, can be seen in 20% of patients.

Eyelid anatomy can also be compromised by infectious etiologies. Trachoma is the leading cause of infectious blindness in the world, and has caused corneal scarring and blindness in 4.9 million living people. Another 10 million people are suffering from trachoma and at risk of blindness (Mabey et al. 2003). Its hallmark is a chronic keratoconjunctivitis, caused by the bacteria *Chlamydia trachomatis*. The infection usually takes place early in childhood and it is nearly always bilateral. It begins in the upper tarsal conjunctiva and leads to severe inflammation, which in turn produces tissue destruction and scarring. Follicles appear at the limbus during the acute infection, and when healed produce Herbert's pits, characteristic scars at the limbus. This can be followed by further corneal scarring and vascularization. Recurrent inflammation can also lead to scarring of the palpebral conjunctiva. A characteristic linear scar can be present in the sulcus subtarsalis, called Arlt's line. Entropion, or turning in of the lid against the globe, and trichiasis can produce further ocular surface damage.

Trachoma is primarily a disease of overcrowding and poor hygiene. Risk factors for children to develop trachoma include poor facial cleanliness, living more than two hours away from a water source, and familial cattle ownership (Hsieh et al. 2000). Trachoma can be treated with topical tetracycline for a minimum of 6 weeks. A single dose of oral azithromycin 1 g also shows great promise, and has been used to eradicate trachoma in several countries (Sommer et al. 2014).

Limbal Stem Cell Deficiency (LCSD)

In the healthy eye, there is a subpopulation of stem cells that reside at the corneoscleral limbus that serve to repopulate the corneal epithelium. These limbal stem cells are found in the basal layer of the limbal epithelium, arranged in the palisades of Vogt configuration. The corneal epithelium undergoes a constant process of cell renewal and regeneration. Damage to the limbal stem cells can result in epithelial breakdown with chronic inflammation. Ultimately, there may be ingrowth of conjunctiva, vascularization and corneal scarring (Hatch and Dana 2009). LCSD can be seen in a number of congenital conditions including aniridia and ectodermal dysplasia. As discussed above, it can also be seen following trauma (chemical burns) and Stevens–Johnson syndrome. Severe contact lens over wear, multiple ocular surgeries (especially with the use of mitomycin c), and medication toxicity can also lead to LCSD.

Congenital aniridia is characterized by hypoplasia of the iris. It occurs at a frequency of 1/64,000–1/96,000 births and is autosomal dominantly inherited in two-thirds of patients, and sporadic in the remaining one-third (Lee and Colby 2013). Patients with sporadic inheritance have an increased risk of developing Wilms' tumor and require genetic testing or frequent screening (Gronskov et al. 2001). Aniridia is associated with other ophthalmic pathology including foveal and optic nerve hypoplasia, glaucoma, and cataracts. We have learned, through impression cytology, that there is a reduction of limbal stem cells in aniridia. Over time, this leads to aniridic keratopathy (Fig. 5.4). Characteristically, patients develop an irregular and thickened epithelium during childhood, which progresses to superficial and then deep neovascularization. Confocal microscopy has shown disruption of the Vogt palisades at the limbus and, in severe cases, conjunctivalization

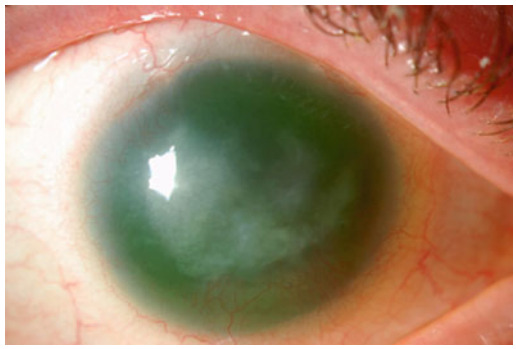

Fig. 5.4 Aniridic-associated keratopathy from a 20-year-old patient. Note the pannus, irregular epithelium and stromal scarring

of the ocular surface (Le et al. 2013). Patients with aniridia are also more likely to have abnormal tear film stability and meibomian gland dysfunction (Jastaneiah and Al-Rajhi 2005).

If there is partial LCSD, the dystrophic epithelium can be debrided (superficial keratectomy). Amniotic membrane can be placed after debridement (Kheirkhah et al. 2008). This procedure, however, does not repair the limbal stem cells and the abnormal epithelium can regrow. Penetrating keratoplasty has been attempted for scarring associated with aniridic keratopathy, but has limited success. In a review of 22 eyes that underwent penetrating keratoplasty without ocular surface surgery, all 22 failed (Mayer et al. 2003). By contrast, allogenic keratolimbal transplants have been successful in aniridia. In a retrospective review of 31 eyes of 23 patients with aniridic keratopathy, 23 eyes (70%) had stable ocular surfaces after keratolimbal allografts (Holland et al. 2003). Visual acuity also improved in these eyes and patients who underwent subsequent penetrating keratoplasty had lower rates of failure. Given that aniridia is a bilateral disease, the stem cell grafts need to come from cadaveric donor tissue, and patients need to be systemically immunosuppressed. The Boston KPro has also been used in patients with aniridia and does not require systemic immunosuppression. In a review of seven patients who underwent KPro surgery for aniridia, six had improvement in visual acuity (Rixen et al. 2013). Due to the high risk of glaucoma in aniridia, concomitant glaucoma surgery is indicated in patients undergoing KPro surgery.

Contact lens over wear can be seen in older children and teenagers with regular contact lens use. Wearing contact lenses for long periods of time can lead to hypoxic insult, mechanical trauma, and ocular inflammation, which in turn can lead to LCSD. While LCSD may be reversible in some patients, others develop irreversible scarring and require a limbal stem cell transplant (Kim et al. 2014; Shen et al. 2015). Severe LCSD related to contact lens wear is associated with duration of wear, female sex, and soft contact lens usage (Shen et al. 2015). Exam findings include a whorl-like epitheliopathy, opaque epithelium arising from the limbus, late fluorescein staining of the involved epithelium, and a superficial neovascularization or conjunctivalization.

LCSD can also be seen as a result of iatrogenic damage either from medication toxicity or surgery. In adults, long-term use of glaucoma drops can lead to LCSD, but this is quite rare in children. The use of mitomycin C during surgery has been linked to LCSD (Schwartz and Holland 1998). Mitomycin C is a chemotherapeutic agent that can be used topically to prevent scarring, haze, or recurrence of lesions in glaucoma and corneal procedures. However, the antimetabolite activity of mitomycin C also targets the actively replicated limbal stem cells, and can produce permanent damage and cell loss (Lam et al. 2015). Limbal-based surgeries in children, for example, the excision of corneal limbal dermoids, can lead to limbal stem cell loss and formation of pseudo pterygium (Lang et al. 2014).

Conclusions

Ocular surface diseases in children are chronic, often site threatening conditions that necessitate diligent follow up and care. Children may be less apt to complain about surface discomfort than adults, and practitioners should maintain a high index of suspicion for surface disease when the appropriate signs are present. While lubricating

eye drops may be a good initial step, children with tear film dysfunction may require short courses of topical anti-inflammatory agents and antibiotics. In children with blepharoconjunctivitis, oral macrolides are a good alternative to doxycycline, which is contraindicated in the pediatric population. Autologous serum drops and specialized contact lenses like the PROSE lens can be used in recalcitrant cases. Autoimmune, toxic, and nutritional cicatrizing conditions like Stevens–Johnson Syndrome, chemical burns, and vitamin A deficiency, necessitate early recognition and intervention for optimal outcomes. The ocular surface is also dependent on the proper functioning and anatomy of the surrounding lids, and lid malposition/scarring should be corrected to limit exposure keratopathy and mechanical damage. If there is significant corneal scarring in the setting of ocular surface disease, a traditional penetrating keratoplasty may not survive due to underlying inflammation and limbal stem cell deficiency. In advanced cases, patients may benefit from limbal stem cell transplantation, conjunctival flap, or keratoprosthesis surgery.

Compliance with Ethical Requirements Danielle Trief and Kathryn Colby declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

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Corneal Diseases in Children: Congenital Anomalies

6

Marie-Claude Robert and Kathryn Colby

Congenital Corneal Anomalies: Anterior Segment Dysgenesis and Anomalies of Size and Shape

As a highly specialized, transparent, and avascular structure, the cornea may be subject to several types of congenital malformations. This chapter will cover the normal development of the anterior segment and discuss important genetic contributions to pathologic embryogenesis. The differential diagnosis of neonatal corneal opacity will be approached using both traditional and novel classification systems. As such, the different forms of anterior segment dysgenesis (ASD) as well as congenital anomalies of corneal size and shape will be reviewed. Each of these entities will be approached in the context of their ocular and systemic clinical manifestations, management, and visual prognosis.

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Embryogenesis

The embryogenesis of the anterior segment begins with the induction of the lens plate by the underlying optic vesicle on the 27th day of gestation (Ozanics and Jakobiec 1982). This region of elongated, columnar surface ectodermal cells invaginates on the 29th day to form the lens pit and, in the fifth week, separates from the surface ectoderm to form the lens vesicle (Duke-Elder and Cook 1963). The surface ectoderm then differentiates into primitive corneal epithelium (Wulle and Richter 1978).

The development of the anterior segment is the landmark of the seventh week. Neural crest cells, which had previously migrated around the optic vesicle, continue their migration in three waves (Fig. 6.1) (Bahn et al. 1984). The sclera is also derived from neural crest cells, with the exception of a portion of the temporal sclera, which is derived from mesoderm. Neural crest cells arise from the neuroectoderm found at the crest of the neural fold in the third gestational week. These cells migrate to distant sites throughout the body and are responsible for the development of several other important ocular and non-ocular structures (Table 6.1).

The anterior chamber first appears as a potential space between the corneal endothelium and the iris stroma in the eighth week and grows to a slit-like space by the end of the third month of gestation (Barishak 2001). A marked increase in the curvature of the cornea also occurs in the third month, leading to the

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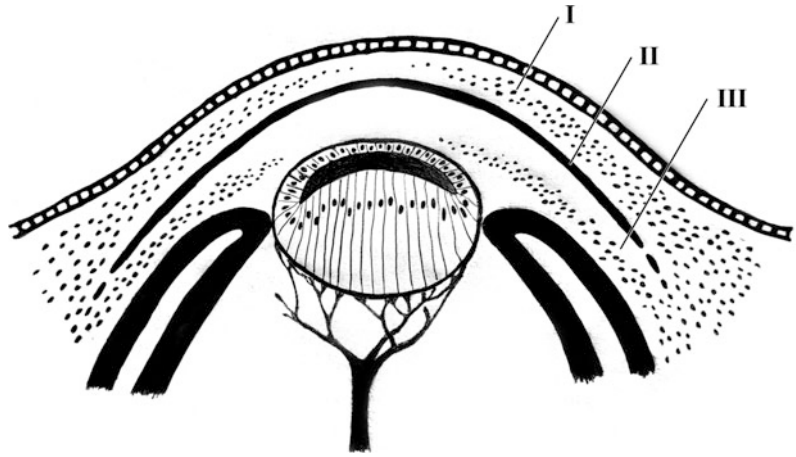

Fig. 6.1 The development of the anterior segment is characterized by the migration of three successive waves of neural crest cells. *I* The first wave of neural crest cells migrates between the surface ectoderm and the lens. These cells will differentiate into the corneal endothelium as well as the endothelial cells of the trabecular meshwork. The corneal endothelium will start to lay down Descemet membrane in the eighth week. *II* The second wave of cells migrates between the primitive corneal epithelium and endothelium, giving rise to keratocytes and the corneal stroma. *III* The third wave of neural crest cell migration occurs between the primitive corneal endothelium and the lens to form the iris stroma

Table 6.1 Ocular and systemic neural crest derivatives

Ocular and orbital structures	Systemic structures
Corneal stroma	Teeth (odontoblasts and dental papillae)
Sclera	Dermis, smooth muscle, and adipose tissue of skin of head and neck
Corneal endothelium	Melanocytes
Trabecular meshwork	Cranial nerves III, V, VII, VIII, IX and X
Iris and choroidal stroma	Sensory neurons and dorsal root ganglia
Ciliary muscle	Sympathetic and parasympathetic ganglia
Melanocytes	Schwann cells of peripheral nerves
Sheaths and tendons of extraocular muscles	Pituitary gland
Meningeal sheaths of the optic nerve	Adrenal medulla
Schwann cells of ciliary nerves	Parafollicular cells of thyroid
Ciliary ganglion	Thymus
Orbital bones, cartilage and connective tissues	Salivary and lacrimal glands
Muscular layer and connective tissue sheaths of all ocular and orbital vessels	Craniofacial cartilage and bone
	Bones of middle ear
	Tracheal and laryngeal cartilage
	Semilunar heart valves
	Cardiac septum
	Muscular layer and connective tissue sheaths of the large arteries

Anomalies in neural crest cell-derived systemic structures should be sought in the clinical evaluation of children with anterior segment dysgenesis

demarcation of the corneoscleral limbus (Duke-Elder and Cook 1963; Hogan et al. 1971). The diameter of the cornea increases from 4.2 mm in the 16th week of gestation to 9.6 mm at term (Barishak 2001).

Genetics

The development of the anterior segment has several genetic influences. Transcription factors, such as homeobox genes, are particularly

important in this process as they act as "master control" genes in embryological development by activating or suppressing the expression of subordinate genes. Defects in homeobox genes have been found in several conditions with either congenital corneal opacity or ASD (Table 6.2).

Table 6.2 Genetics of anterior segment dysgenesis, congenital/neonatal corneal opacity, and anomalies of corneal size and shape

Disease	Gene	Locus
CHED[a]	SLC4A11	20p13
CHSD	DCN	12q22
PPCD PPCD1[a] PPCD2 PPCD3	– COL8A2 ZEB1[b]	20p11.2-q11.2 1p34.3-p32.3 10p11.2
XECD	–	Xq25
CYP1B1 cytopathy	CYP1B1	2p22.2
Iridocorneal adhesions	PITX2[b], FOXC1, CYP1B1, PAX6[b]	–
Primary aphakia and lens fails to separate from cornea	FOXE3	1p33
Peters anomaly	CYP1B1 PAX6[b] PITX2[b]	2p22.2 11p13 4q25
Peters-plus syndrome	B3GALTL	13q12.3
Aniridia	PAX6[b]	11p13
Primary congenital glaucoma GLC3A GLC3D	CYP1B1 LTBP2	2p22.2 14q24.3
Intracorneal cyst	Digenic FOXC1 and PITX2[b]	6p25.3/4q25
Axenfeld-Rieger syndrome	FOXC1 PITX2[b]	6p25.3 4q25
Megalocornea	CHRDL1	Xq23
Cornea plana		
CNA1 and CNA2	KERA	12q21.33

[a]The autosomal-dominant form of CHED (CHED1) has been reclassified as PPCD1 by the International Committee for Classification of Corneal Dystrophies. Under the most recent classification, only the autosomal-recessive form (CHED2) should be identified as CHED

[b]Identifies homeobox genes

Anterior Segment Dysgenesis

ASD is a general term that encompasses several congenital entities including Peters anomaly, sclerocornea, aniridia, and Axenfeld-Rieger syndrome. No genotype–phenotype relationship is implied by this term.

The differential diagnosis of congenital and neonatal corneal opacities has been traditionally taught using the STUMPED (*S*clerocornea, *T*ears in Descemet membrane, *U*lcers, *M*etabolic diseases, *P*eters anomaly, *E*ndothelial dystrophies, *D*ermoids) acronym. Recently, a different classification system has been suggested to improve the consistency of the terminology used in the literature, facilitate the establishment of phenotype–genotype correlations, and optimize the management of patients with neonatal corneal opacity (Nischal 2007, 2012). Both classification systems are compared in Table 6.3.

The traditional classification is wrought with confusing inaccuracies. For example, the term sclerocornea is often used to designate total opacification of the cornea. However, this term should be reserved for cases of scleralization of the peripheral cornea. Conversely, the term Peters anomaly is used as a waste basket for different forms of central corneal opacification (Mataftsi et al. 2011). A more specific classification scheme is necessary to improve our understanding and management of these conditions.

Congenital and neonatal corneal opacification can result from either primary or secondary corneal disease. Primary causes include developmental anomalies that are present at birth in which the primary defect localizes to the cornea. Secondary causes of corneal opacification include the more complex kerato-irido-lenticular and irido-trabecular dysgeneses, as well as anomalies acquired from readily identifiable insults such as infection or trauma.

Primary Corneal Opacification

Causes of primary corneal opacification include the corneal dystrophies, dermoids, peripheral (isolated) sclerocornea, and CYP1B1 cytopathy.

Table 6.3 Traditional and novel classification of congenital and neonatal corneal opacities

Traditional (STUMPED)	Novel classification
*S*clerocornea	***Primary corneal disease***
*T*ears in Descemet membrane Congenital (infantile) glaucoma Forceps injury and other trauma	Corneal dystrophies Congenital hereditary endothelial Dystrophy Posterior polymorphous corneal Dystrophy Congenital hereditary stromal Dystrophy X-linked endothelial corneal Dystrophy Corneal dermoid Peripheral sclerocornea CYP1B1 cytopathy
*U*lcers Viral Bacterial Fungal Neurotrophic	
*M*etabolic diseases Mucopolysaccharidoses Mucolipidoses	
*P*eters anomaly	***Secondary corneal disease***
*E*ndothelial dystrophies Congenital hereditary endothelial Dystrophy Posterior polymorphous dystrophy	***Congenital*** Kerato-irido-lenticular dysgenesis Iridocorneal adhesions Lens fails to separate from cornea Lens separates but fails to form Thereafter Lens separates and forms, but there is Late corneal apposition Lens fails to form Irido-trabecular dysgenesis Primary congenital glaucoma. Intracorneal cyst Axenfeld-Rieger syndrome Congenital aniridia ***Acquired*** Infection Viral Bacterial Trauma Forceps injury Amniocentesis injury Metabolic Mucolipidosis IV
*D*ermoids	

Corneal Dystrophies

Congenital hereditary endothelial dystrophy (CHED), congenital hereditary stromal dystrophy (CHSD), posterior polymorphous corneal dystrophy (PPCD), and X-linked endothelial corneal dystrophy (XECD) are the four corneal dystrophies present in infancy.

CHED

CHED is characterized by bilateral, symmetric, and diffuse corneal edema due to a primary dysfunction of the corneal endothelium. Histopathological examination of excised corneal buttons shows an abnormal, degenerated corneal endothelium, thickening of the posterior non-banded layer of Descemet membrane as well as stromal and epithelial edema (Kirkness et al. 1987; Ehlers et al. 1998). CHED was previously thought to occur with both autosomal-dominant (CHED1) and autosomal-recessive (CHED2) patterns of inheritance. However, a review of CHED1 pedigrees led to the reclassification of this disease within the PPCD spectrum, leaving only the autosomal-recessive form of CHED (Aldave et al. 2013a, b; Weiss et al. 2015). Thus, CHED is characterized by dense but non-progressive corneal edema present at birth. Photophobia and epiphora are absent. These patients develop

nystagmus due to early opacification of the visual axis (Judisch and Maumenee 1978). Mutations in the SLC4A11 gene, which codes for a sodium-borate cotransporter, have been identified in several lineages with CHED (Vithana et al. 2006; Jiao and Sultana 2007). The incidence of CHED appears to be higher in families of Middle Eastern descent (Al-Rajhi and Wagoner 1997).

As an isolated disease of the corneal endothelium, CHED is believed to have a relatively good prognosis following corneal transplantation. However, when using the new classification and isolating congenital cases of CHED, the prognosis appears more guarded, with a graft survival rate of 56% (Al-Rajhi and Wagoner 1997).

Descemet stripping-automated endothelial keratoplasty (DSAEK) shows promise in the surgical management of CHED. Stripping of the endothelium and Descemet membrane appears to be optional as it does not offer a significant advantage in graft adherence or postoperative visual acuity when compared to non-stripping procedures (Ashar et al. 2013a). Endothelial keratoplasty allows for earlier visual rehabilitation when compared to full-thickness transplantation, but challenges such as poor visualization due to dense opacity, management of the phakic lens, and postoperative positioning need to be considered on an individual basis (Ashar et al. 2013b).

CHSD

CHSD is an extremely rare dystrophy characterized by limbus-to-limbus corneal clouding. Ill-defined, flake-like opacities are found throughout the corneal stroma, but appear to be most dense anteriorly. The opacities are present at, or shortly, after birth, and accumulate over years. Corneal thickness may be normal or increased (Bedrup et al. 2005; Pouliquen et al. 1979). Most patients require corneal transplantation by early adulthood. Excellent visual outcomes are achievable following penetrating keratoplasty, but opacities may recur in the graft (Bedrup et al. 2005). CHSD has been linked to mutations in the decorin (DCN) gene which leads to truncated decorin protein aggregation and accumulation between collagen lamellae (Bedrup et al. 2010).

PPCD

Bilateral polymorphous changes of the posterior cornea are the distinctive finding in PPCD. Slit lamp examination reveals grouped vesicles, geographic lesions, and broad bands with scalloped edges. Such alterations can be visualized with specular and confocal microscopy (Cibis et al. 1977). Stromal edema, corectopia, and iridocorneal adhesion may also be observed. Glaucoma, which can present with either an open- or a closed-angle pathophysiology, is common.

The corneal endothelium in PPCD shows epithelial characteristics on histopathologic exam. The endothelium is multilayered; and microvilli, cytokeratin, and intercellular desmosomes are present. Descemet membrane is diffusely thickened and multilaminated (Moroi et al. 2003; Krachmer 1985). Because of their ability to proliferate, the abnormal endothelial cells can migrate to cover the trabecular meshwork, leading to impaired aqueous humor outflow.

PPCD is an autosomal-dominant corneal dystrophy. Mutations at three loci have been identified (Table 6.2) (Gwilliam et al. 2005; Biswas et al. 2001; Krafchak et al. 2005). While the locus for PPCD1 is known, the causative gene remains to be identified. The gene for PPCD2 codes for the alpha 2 chain of collagen type VIII (COL8A2). PPCD3 is caused by mutations in the zinc-finger E-box binding homeobox 1 gene (ZEB1), which is also known as transcription factor 8 (TCF8). Irregular astigmatism and excessive corneal steepening have been associated with PPCD3 (Aldave et al. 2013a, b).

Corneal transplantation is required in only a minority of patients and typically not until adulthood. Both penetrating keratoplasty and DSAEK have been reported to give good outcomes (Sella et al. 2013). However, the disease may recur in the graft with migration of host endothelium onto the donor (Sekundo et al. 1994). Graft survival may also be limited by the presence of glaucoma, especially when iridocorneal adhesions are present (Krachmer 1985).

XECD

XECD is a recently reported corneal dystrophy (Schmid et al. 2006). In the most severe cases,

patients present at birth with significant bilateral corneal clouding with a ground glass or milky appearance. Milder cases are found to have endothelial lesions resembling moon craters and subepithelial band keratopathy. Asymptomatic carriers of the disease trait also demonstrate these moon crater-like lesions of the posterior cornea. Histopathologic examination reveals irregular thickening and small excavations in Descemet membrane. The endothelial cells have an atypical distribution with multilayering in some areas, while other areas are left bare. The corneal epithelium and Bowman layer appear thinned and the anterior corneal stroma shows disorganization of collagen lamellae. The prognosis following penetrating keratoplasty is good, with no disease recurrence reported to date (Schmid et al. 2006).

Epibulbar Choristomas (Dermoids)

Epibulbar choristomas, congenital tumors consisting of normal tissue in an ectopic location, have an incidence of approximately 1 in 10,000. Dermoids are choristomas consisting of skin and dermal appendages only while complex choristomas contain additional tissue types such as cartilage, bone, and lacrimal gland.

Most cases of epibulbar choristomas occur as an isolated ocular finding. However, in one-third of cases, they occur as part of several syndromes such as Goldenhar syndrome and epidermal nevus syndrome (Mansour et al. 1989). Epibulbar choristomas are most often found at the inferotemporal limbus. However, they can also involve the central cornea. These lesions tend to be oval or round and yellowish white. A lipid arcus may be seen in the adjacent cornea and fine hairs may grow at the surface of the lesion. Elevated choristomas can cause corneal dellen formation and ocular irritation. By causing flattening of the adjacent cornea and astigmatism, limbal lesions may lead to anisometropic amblyopia. Choristomas are generally stationary, although some enlargement may be seen at the time of puberty (Trubnik et al. 2011).

The indications for surgical intervention include significant astigmatism, amblyopia, corneal irritation, and poor cosmesis. While surgical removal of the lesion may not lead to significant change in corneal astigmatism, the resulting normalized ocular surface contour allows for fitting with a rigid contact lens (Scott and Tan 2001). The elevated portion of the lesion may be removed by simple excision, shave dissection, or superficial keratectomy. These procedures leave a scar in the underlying cornea and, in some cases, an unsightly pseudopterygium may occur postoperatively. Lamellar keratoplasty using a fresh or gamma-irradiated corneoscleral donor graft often leads to better cosmetic results (Panda et al. 2002). Alternatively, multilayered amniotic membrane and fibrin tissue glue can be used to fill the resulting defect (Pirouzian et al. 2011). However, excision procedures carry a risk of corneal perforation as some choristomas may extend deeply into the stroma (Watts et al. 2002). To mitigate this risk, ultrasound biomicroscopy (UBM) can be performed to assess lesion depth preoperatively. Corneal tissue should also be available during surgery. Gamma-irradiated corneal tissue is particularly well suited for this purpose because of its long shelf life at room temperature. Penetrating keratoplasty is indicated when the dermoid involves the visual axis.

Peripheral Sclerocornea

Sclerocornea refers to peripheral whitening of the cornea that may extend toward the visual axis. As mentioned previously, the term sclerocornea should never be applied to total corneal opacification. Sclerocornea is congenital and non-progressive. It occurs bilaterally in 90% of cases. With loss of a clearly demarcated limbus, normal vessels from the sclera, episclera, and conjunctiva cross onto the area of scleralization. As the normal sclera has a flatter curvature than the cornea, 80% of eyes with sclerocornea will also have cornea plana. Dysgenesis of the anterior chamber angle with consequent glaucoma is common. Less commonly associated ocular malformations include microphthalmos, iridocorneal adhesions, persistent pupillary membranes, coloboma, iris dysgenesis, posterior embryotoxon, cataract, nystagmus, and esotropia (Kenyon 1975; Elliott et al. 1985; Harissi-Dagher and Colby 2008).

The histopathology of sclerocornea reveals features typical of scleral tissue. Contrary to the uniform, parallel, and organized lamellar structure of corneal collagen, scleral collagen shows fibers of variable diameter, which are arranged in an irregular, non-lamellar fashion. The underlying Descemet membrane and endothelium may be attenuated or absent (Kanai et al. 1971).

Half of the cases of sclerocornea are sporadic. For others, both autosomal-recessive and autosomal-dominant patterns of inheritance have been reported. The autosomal-recessive form is classically described as being more severe. However, many of the previously reported severe autosomal-recessive cases manifested total corneal opacification and should not have been designated as sclerocornea. Similarly, many systemic findings and syndromes have been associated with 'sclerocornea', but rather referred to total corneal opacification (Elliott et al. 1985). MIDAS syndrome (*mi*crophthalmia, *d*ermal *a*plasia and *s*clerocornea), which is also known as MLS syndrome (*m*icrophthalmia with *l*inear *s*kin defects), or the Xp22.3 microdeletion syndrome, is one important example of a syndrome presenting with peripheral sclerocornea (Cape et al. 2004). These patients require a systemic work-up searching for concomitant congenital heart defects, hypospadias, and neurodevelopmental anomalies.

Most cases of sclerocornea will only require careful refraction and amblyopia management. Corneal transplantation is considered for opacities impeding on the visual axis. Unfortunately, penetrating keratoplasty has a poor surgical outcome in sclerocornea when compared to other causes of congenital corneal opacification. Graft failure occurs in 75% of cases and the average time to failure is 36 months (Kim et al. 2013). These poor outcomes are explained by the presence of peripheral vascularization as well as the small corneal diameter seen in sclerocornea.

CYP1B1 Cytopathy

Mutations in the CYP1B1 gene are known to cause primary congenital glaucoma (GLC3A). CYP1B1 mutations have also been reported in rare cases of congenital corneal opacification with iridocorneal and/or keratolenticular adhesion as well as posterior embryotoxon and iris hypoplasia (Vincent et al. 2001; Edward et al. 2004; Chavarria-Soley et al. 2006; Kelberman et al. 2011). The corneal phenotype of CYP1B1 cytopathy resembles the original description of the von Hippel internal ulcer. Clinical exam shows diffuse, limbus-to-limbus corneal opacity and absent iridocorneal and kerato-irido-lenticular adhesions. On histopathology, loss of central Bowman layer, Descemet membrane, and endothelium as well as infiltration by stromal cells is seen. Corneal transplantation has a good survival rate in these cases, but the visual prognosis is guarded due to progressive glaucoma (Kelberman et al. 2011).

Secondary Corneal Opacification

Secondary corneal opacification may be congenital or develop later in the neonatal period.

Congenital

The congenital causes of secondary corneal opacification include kerato-irido-lenticular and irido-trabecular dysgenesis. UBM evaluation is helpful to delineate the extent of iridocorneal adhesions and the degree of differentiation of the crystalline lens. For familiarity, the traditional Peters anomaly is discussed along the different forms of kerato-irido-lenticular dysgenesis (KILD).

Kerato-Irido-Lenticular Dysgenesis (KILD) Versus Peters Anomaly

In the traditional nomenclature, Peters anomaly is defined by the presence of a central leukoma with a defect in the underlying posterior cornea plus iridocorneal adhesions. The peripheral cornea is typically clear. On histology, the central posterior corneal stroma, descemet membrane, and endothelium are absent in the area of opacification. Iris strands extend from the iris collarette onto the cornea, more or less delineating the area of opacity. The phenotype is subclassified into two types. Peters anomaly type 1 occurs in cases with a central leukoma and

iridocorneal adhesions but a normal lens. Peters anomaly type 2 is characterized by keratolenticular adhesions. The lens is almost invariably cataractous. Peters anomaly is bilateral in 80% of cases but may be asymmetric (Waring et al. 1975; Kenyon 1975; Reese and Ellsworth 1966).

Glaucoma occurs in 50–70% of patients with Peters anomaly due to dysgenesis of the trabecular meshwork and Schlemm canal (Yang et al. 2004). Cataract or keratolenticular adhesions are additional risk factors for the development of glaucoma. The glaucoma associated with Peters anomaly is often severe and difficult to control despite aggressive medical and surgical intervention (Yang et al. 2004).

Other ocular findings that may accompany Peters anomaly include microphthalmos, microcornea, cornea plana, sclerocornea, uveal coloboma, ptosis, as well as optic nerve and foveal hypoplasia.

Peters anomaly is typically an isolated ocular defect. Systemic findings are seen in the Peters-plus syndrome, a separate autosomal-recessive disease also known as the Krause–Kivlin syndrome (van Schooneveld et al. 1984; Kivlin et al. 1986). These include short stature, short limbs, abnormal ears, thin upper lip, cleft lip, and palate and mental retardation. Other reported systemic associations include congenital central nervous system, hearing, cardiac, genitourinary, and spinal defects (Traboulsi and Maumenee 1992).

The management of Peters anomaly should involve a careful medical work-up with attention to the organ systems listed above, amblyopia management, as well as control of IOP. Surgical intervention to clear the visual axis should be guided by the overall potential for functional vision. Some milder cases of corneal opacification may spontaneously regress over time. In the presence of a small corneal leukoma and no cataract, an optical iridectomy has satisfactory outcomes while being the least invasive approach (Zaidman et al. 1998). Corneal transplantation may be considered in selected cases, but graft survival rates depend highly on the underlying phenotype (Yang et al. 2009). Implantation of a Boston keratoprosthesis can be considered as an alternative, as it quickly establishes a clear visual axis and facilitates the refractive component of amblyopia management (Aquavella et al. 2007). However, long-term outcomes of keratoprosthesis surgery in children have not been published to date and the potential for blinding complications should not be underestimated.

A more accurate assessment of the surgical risk–benefit ratio for secondary corneal opacification may be achieved using the classification proposed by Nischal (2012). This new terminology sub-classifies KILD into five entities.

1. **Iridocorneal adhesions** describe what was traditionally referred to as Peters anomaly type 1. This malformation causes an avascular leukoma that may involve the center, periphery, or entire area of the cornea. Because the lesion is avascular, these eyes tend to do well following keratoplasty. In one series, 54% of children in this category achieved a visual acuity of 20/100 or better after keratoplasty (Zaidman et al. 2007). Mutations in PITX2, FOXC1, CYP1B1, and PAX6 have been associated with iridocorneal adhesions (Nischal 2012).
2. If the **lens fails to separate from cornea**, a vascularized corneal opacity occupies either the central or the entire cornea (Peters anomaly type II using the traditional nomenclature). The lens remains adherent to the cornea following failure of the lens vesicle to separate from the surface ectoderm. The anterior lens capsule appears to be absent in the area of adhesion and the lens itself is often cataractous. The prognosis for corneal transplantation is limited by the necessary concomitant removal of the lens, leaving the patient aphakic and at high risk of anterior vitreous prolapse. Penetrating keratoplasty has a much more guarded prognosis with a success rate of only 14% (Bhandari et al. 2011). Heterozygous mutations in FOXE3 have been reported to cause this entity (Iseri et al. 2009; Semina et al. 2001).
3. When the **lens separates but fails to form thereafter**, the cornea is completely opaque and vascularized. Only a small lens remnant

is visible on UBM. The prognosis for corneal transplantation is poor.

4. If the **lens separates and forms, but there is late corneal apposition**, corneal opacification is generally central and avascular. As evidence of prior lens separation from the cornea, the anterior lens capsule is intact and can be seen on UBM. The pathophysiology may involve hypoxia, retrolental membranes that contract and push the lens anteriorly as seen in persistent fetal vasculature or vitreoretinal dysplasias or lens–cornea touch from a very shallow anterior chamber as is seen in aniridia (Nischal 2012). Lens extraction alone may allow the cornea to clear, rendering corneal transplantation unnecessary. To avoid further damage to the endothelium, the anterior lens capsule should not be peeled from the posterior cornea.
5. The **lens fails to form** in primary aphakia. This rare entity is accompanied by secondary opacification of the cornea. The corneal stroma appears silver or gray and, because it is thin, transilluminates easily. Ocular associations include microphthalmia, iris dysplasia, retinal dysplasia, and glaucoma. Corneal transplantation has extremely poor prognosis and is associated with a rapid progression to phthisis. Mutations in both copies of the FOXE3 gene are responsible for primary aphakia (Valleix et al. 2006; Ali et al. 2010).

Irido-Trabecular Dysgenesis

Primary congenital glaucoma is responsible for approximately half the cases of neonatal corneal opacity (Bermejo and Martinez-Frias 1998). Corneal opacity develops secondary to corneal edema following IOP-dependent damage to Descemet membrane and the corneal endothelium. Clinical examination reveals the classic triad of buphthalmos, epiphora, and photophotobia. More specific findings include an increased corneal diameter, corneal edema with horizontal or concentric breaks in Descemet membrane (Haab striae), increased IOP, axial myopia, as well as characteristic angle and optic nerve changes. The corneal opacification typically resolves with IOP control, unless chronic edema has led to permanent stromal scarring. Penetrating or endothelial keratoplasty can be considered to improve vision. However, graft failure is common and seen in 30–50% of cases, mostly due to inadequately controlled IOP (Toker et al. 2003; Ariyasu et al. 1994).

Axenfeld-Rieger syndrome (ARS) is a disease spectrum encompassing several anterior segment malformations (Alward 2000).

Axenfeld anomaly is defined as the combination of posterior embryotoxon and iris strands bridging the iridocorneal angle. Posterior embryotoxon, denoting a thickened and anteriorly displaced Schwalbe line, is an isolated finding in 15% of the normal population. Fifty percent of patients with Axenfeld anomaly develop glaucoma; this combination was previously termed Axenfeld syndrome.

Rieger anomaly is characterized by iris hypoplasia, corectopia, pseudopolycoria, and ectropion of the iris pigment epithelium. The congenital and stationary nature of these clinical findings distinguish Rieger anomaly from the irido-corneo-endothelial (ICE) syndrome.

Rieger syndrome combines features of Rieger anomaly with systemic findings including pituitary, craniofacial, cardiac, skeletal, dental, and umbilical anomalies. Telecanthus, hypertelorism, a broad and flat nasal bridge, maxillary hypoplasia, and small or absent teeth make up the typical facies of Rieger syndrome.

The unification of ARS into a single entity was made possible through advances in molecular genetics and the recognition of genotype–phenotype overlap among these above-stated entities. Mutations in PITX2 and FOXC1 are known to lead to the spectrum of ARS phenotypes.

Glaucoma occurs in 50% of ARS (Alward 2000). It usually presents early, from infancy to young adulthood. Glaucoma is the main target of ophthalmic follow-up in these patients.

Congenital aniridia is defined by the classic clinical triad of iris and foveal hypoplasia and nystagmus. Although the disease manifests

throughout the eye, aniridia is often classified among the anterior segment dysgeneses. Despite the name "aniridia", the iris changes seen in this disease are actually quite variable forms of iris hypoplasia. They range from the near complete lack of iris, with the development of only a short iris stump, to mild iris transillumination defects or pupillary anomalies. Additional features include cataract (seen in 50–85% of cases), glaucoma (30–50% of cases), optic nerve hypoplasia (10% of cases), and keratopathy (20% of cases) (Hingorani et al. 2012; Lee et al. 2008). Aniridic keratopathy is caused by progressive limbal stem cell deficiency, usually starting in the first decade of life. The prevalence of aniridia is approximately 1:47,000–1:72,000 (Edén et al. 2008a, b).

Congenital aniridia is caused by loss of function of one copy of the PAX6 gene. Two-thirds of cases of aniridia are familial and transmitted in an autosomal-dominant fashion. The remaining one-third of aniridia cases occurs sporadically. Up to one-third of sporadic aniridia may be associated with the WAGR syndrome (any combination of *W*ilms (nephroblastoma) tumor, *a*niridia, *g*enitourinary abnormalities, and mental *r*etardation) (Ivanov et al. 1995; Edén et al. 2008b). WAGR syndrome is caused by gene deletion of PAX6 and the nearby WT1 gene. Gillespie syndrome is a rare autosomal-recessive disease combining aniridia with cerebellar ataxia and developmental delay that is caused by heterozygous mutation in PAX6 (Graziano et al. 2007).

Genetic testing should be performed on all newly diagnosed cases of aniridia to identify if a PAX6/WT1 deletion is present. Identification of a WT1 deletion confers a 50% risk of developing a Wilms tumor, even in patients with familial aniridia (Robinson et al. 2008; Fantes et al. 1992). Therefore, these patients need lifelong, regular clinical evaluation by an oncologist.

The initial management of aniridia involves regular eye examinations, correction of refractive error, and amblyopia therapy. Tinted glasses are used to reduce photophobia. Referral to a low-vision specialist may optimize the child's development. Aniridic keratopathy is initially managed with conservative measures to protect the ocular surface. Lubrication is important as these patients have a higher prevalence of dry eye. Serum tears and amniotic membrane transplantation have been suggested to support existing limbal stem cells (López-García et al. 2006). Surgical management of corneal opacification due to aniridic keratopathy is usually not necessary before the patient reaches adulthood. Surgical intervention should address the underlying limbal stem cell deficiency as penetrating keratoplasty alone is ineffective and ill-advised. Rather, limbal stem cell transplantation with or without subsequent penetrating keratoplasty or implantation of a permanent keratoprosthesis should be considered (Holland et al. 2003; Lee and Colby 2013; Lee et al. 2008).

Acquired

The acquired causes of corneal opacification include infectious, traumatic, and metabolic causes. Infectious keratitis is discussed in Chap. 3.

Trauma

Intrauterine, peripartum, or postnatal trauma may result in corneal opacification. The proper diagnosis is contingent on clinical suspicion and taking a relevant medical history. Non-accidental trauma should always be considered in atypical cases.

Intrauterine corneal perforation may rarely occur during diagnostic amniocentesis performed in the second trimester. Typically, other signs of periocular trauma are evident such as eyelid coloboma, iris abnormalities, cataract, or retinal detachment (Merin and Beyth 1980; Gobert et al. 1995). Forceps injury is a well-recognized cause of peripartum corneal damage. Compression of the globe by the forceps blade leads to breaks in Descemet membrane and corneal edema. Due to the orientation of the forceps, these breaks tend to be vertical or oblique and parallel to one another. Vacuum extraction may also lead to a similar type of corneal injury (Honig et al. 1995). Myopic astigmatism in the axis of the Descemet

break is often encountered. Proper refraction to prevent anisometropic amblyopia is an integral part of the disease management. While some corneas clear with expectant management, penetrating or endothelial keratoplasty should be considered in cases with persistent edema to prevent progression to stromal scarring and vascularization (Hayashi et al. 2013).

Metabolic

Metabolic disorders, with the exception of mucolipidosis IV, rarely lead to corneal clouding in infancy. For example, patients with mucopolysaccharidoses (MPS) present at several months to several years of age, depending on the disease type. All forms of MPS may eventually develop corneal clouding due to the stromal accumulation of glycosaminoglycans (Ashworth et al. 2006).

Mucolipidosis IV typically presents with severe congenital corneal clouding and psychomotor retardation. In contrast to MPS, there are no skeletal or facial anomalies. Most of the corneal opacity results from the intracellular accumulation of mucopolysaccharides and complex lipids in the corneal epithelium (Kenyon et al. 1979). The stroma itself remains quite clear and thus, penetrating keratoplasty is not indicated. There has been some success treating the corneal opacification with conjunctival transplantation (Dangel et al. 1985).

Anomalies of Size and Shape

The normal human cornea undergoes significant change in size and shape in the first few months of life. The newborn cornea has a horizontal diameter of 9.5 mm to 10.5 mm. By 2 years of age, the cornea will have grown to its adult size of 12 mm (Duke-Elder and Cook 1963). Moreover, the cornea of the newborn is steep with a mean keratometry of 48 D (Snir et al. 2004). This curvature will progressively decrease over the next 4.5 years, where it stabilizes at 42.7 D (Asbell et al. 1990). This section will discuss anomalies of corneal size, microcornea and megalocornea, and shape, cornea plana and keratoglobus.

Microcornea

Microcornea is defined as a horizontal corneal diameter of 9 mm or less in the neonate or 10 mm or less after 2 years of age. Most cases of microcornea have an autosomal-dominant pattern of inheritance. Microcornea is often seen in the setting of other ocular abnormalities including cataracts, uveal colobomas, optic nerve hypoplasia, and persistent fetal vasculature. The cornea is clear but usually quite flat. However, the overall refractive error can change "be myopic to hyperopic" to "range from myopia to hyperopia". Glaucoma is a common association and may be due to dysgenesis of the aqueous humor outflow tracts or to a posterior pushing mechanism from a disproportionally large lens (Waring and Rodrigues 1982). Microcornea is a risk factor for the development of aphakic glaucoma following pediatric cataract surgery (Wallace and Plager 1996). Microcornea may also be seen in the context of a small and malformed globe (microphthalmos) or of a small but normal globe (nanophthalmos). The distinction is achieved through careful ultrasound evaluation. If the anterior chamber is shallow, but the axial length is normal, the term anterior microphthalmos applies.

Several syndromes may present with microcornea. For example, oculodentodigital dysplasia is an autosomal-dominant syndrome combining microcornea, microphthalmos, a typical facial appearance (thin nose with hypoplastic and anterverted nostrils), syndactyly and hypoplasia of the teeth and enamel (Sugar et al. 1966). Other syndromes associated with nanophthalmos and microcornea include myotonic dystrophy, achondroplasia, and the fetal alcohol syndrome (Weiss et al. 1989).

The management of microcornea involves the detection and treatment of the associated glaucoma and refractive error. Bullous keratopathy, which may develop after glaucoma surgery, is amenable to DSAEK using a modified technique (Yokogawa et al. 2013).

Megalocornea

Megalocornea is a stationary, bilateral, and symmetric corneal enlargement, defined by horizontal corneal diameters of greater than 12 mm in newborns or 13 mm in adults. It is an X-linked recessive disease caused by mutations in the CHRDL1 gene. As such, males are affected more frequently than females. The cornea usually remains clear although an association with arcus juvenilis and mosaic corneal dystrophy (posterior crocodile shagreen) has also been described. The central topography is within normal limits, distinguishing megalocornea from ectatic disorders. The anterior chamber tends to be deep and so the condition can alternatively be named anterior megalophthalmos. Megalocornea is differentiated from buphthalmos by a normal IOP, axial length, and optic nerve head. However, glaucoma may develop later in life. Other ocular associations include pigment dispersion, prominent iris processes, iris stromal hypoplasia, miosis, iridodonesis, phacodonesis, and posterior subcapsular cataract. While megalocornea is usually an isolated ocular condition, several systemic associations have been reported. These include mental retardation, Down syndrome, ichthyosis, dwarfism, Marfan syndrome, osteogenesis imperfecta, craniosynostosis, Alport syndrome, and tuberous sclerosis (Mackey et al. 1991).

Cornea Plana

Cornea plana refers to a congenitally flat cornea, which may be transmitted in an autosomal-dominant (CNA1) or autosomal-recessive (CNA2) pattern. Both forms are caused by mutations in the KERA gene which produces altered keratocan, a corneal proteoglycan (Pellegata et al. 2000). While rare, cornea plana has a higher prevalence among Finnish and Saudi populations (Eriksson et al. 1973; Khan et al. 2006).

By definition, the corneal curvature is less than 43D. However, most cases are much flatter and average 38 D in autosomal-dominant and 30 D in autosomal-recessive lineages (Tahvanainen et al. 1996). Indeed, autosomal-recessive cornea plana tends to be more severe for both the level of corneal flattening and the presence of ocular comorbidities (Eriksson et al. 1973). These include high hyperopia (+10 D), peripheral sclerocornea, arcus lipoides, microcornea, stromal opacities, iridocorneal adhesions, and glaucoma. Angle-closure glaucoma may develop due to the low corneal vault and consequently shallow anterior chamber, while open-angle glaucoma develops secondary to goniodysgenesis. Refractive accommodative esotropia and amblyopia may result from uncorrected high hyperopia (Al Hazimi and Khan 2013). Therefore, the management of cornea plana focuses on the detection and treatment of glaucoma and refractive error. Corneal transplantation, which may be warranted in cases with significant central opacification, holds a higher risk of rejection and postsurgical glaucoma.

Keratoglobus

Keratoglobus is a congenital ectatic corneal disorder characterized by bilateral and symmetric thinning and anterior bulging of the cornea. The cornea is approximately one-third of the normal thickness, with maximal thinning occurring in the corneal mid-periphery. Keratometry values measure well into the 50 to 60 diopter range. Iron lines, Vogt striae, and apical scarring are typically absent. However, spontaneous breaks in Descemet membrane and acute corneal hydrops occur in approximately 10% of eyes, a rate four time greater than seen in keratoconus (Basu et al. 2011).

Keratoglobus can occur as part of the autosomal-recessive brittle cornea syndrome. This disease was formerly referred to as Ehlers–Danlos syndrome type VIB. Blue sclera, corneal rupture after minimal trauma, hyperelastic skin, and hypermobile joins are associated features.

Patients with keratoglobus should wear protective eyewear to minimize the risk of even minor ocular trauma. Eye rubbing should be discouraged. Refractive error needs to be

carefully monitored and corrected to avoid amblyopia. Acute hydrops with Descemet tear is usually treated with expectant management. Corneal transplantation may be indicated as an optical and tectonic procedure. Penetrating keratoplasty is complicated by the thickness mismatch between host and donor corneas when using a regular sized button (Cameron 1993). Corneal wound repair can also be problematic due to the thin corneal tissue. As such, several technique variations using large-diameter grafts, corneoscleral ring grafts, inlay lamellar keratoplasty, and epikeratoplasty have been described (Javadi et al. 2007; Vajpayee et al. 2002; Jones and Kirkness 2001; Karimian et al. 2014; Kanellopoulos and Pe 2005).

General Approach to the Child with Congenital Corneal Anomalies

A comprehensive medical and ocular history should be performed in all children presenting with congenital corneal anomalies. Details of the gestation and birth should be obtained to rule out teratogenic exposure or iatrogenic trauma. A thorough family history of eye disease is essential and office examination of the parents and other family members may be revelatory. A disease pedigree should be created if familial eye disease is elicited. In addition, parents should be specifically questioned about consanguineous relations within the family tree.

There is no need for routine genetic testing at this time. However, consultation with a geneticist may be useful or necessary in selected cases such as to rule out a WT1 mutation in patients with congenital aniridia. With advances in our understanding of genotype–phenotype correlations, genetic evaluation may become important for the management of disease in the near future. As several entities are associated with significant systemic comorbidities, evaluation by a skilled pediatrician is recommended.

An examination under anesthesia is useful to fully characterize the extent of ocular involvement. When the slit lamp view is suboptimal, UBM can be useful to properly classify disease and ultimately, provide the family with an accurate prognosis. Of note, eyes with abnormal crystalline lens anatomy have the worse outcomes following penetrating keratoplasty. The risks of surgical intervention in such cases need to be carefully weighed. Glaucoma remains an important issue in children with congenital corneal disease and should not be neglected. Further, children with a normal contralateral eye benefit from protective eyewear, follow-up, and minimal surgical intervention. Surgery is usually reserved for children with bilateral disease.

In conclusion, the embryogenesis of anterior segment requires important contributions from neural crest cells and surface ectoderm and proper orchestration by several transcription factors. The sequence of anterior segment development forms the basis of the newer classification of congenital and neonatal corneal opacities. The descriptive terminology used in this classification relies on excellent slit lamp evaluation as well as additional imaging using UBM. The more widespread use of this scheme in the literature and in clinical practice is likely to improve the management of patients with ASD. As always, a collaborative approach between ophthalmologists, low-vision specialists, geneticists, and pediatricians is required to optimize whole-patient outcomes over the long term.

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Corneal Diseases in Children: Keratoconus

7

Elena Albé

Keratoconus is the most common ectatic disorder of the cornea and is a cause of significant visual loss in children. The disease is bilateral, but frequently asymmetric. Keratoconus has historically been thought to be noninflammatory in etiology, although its exact mechanism is unproven at present. Keratoconus is characterized by changes in corneal collagen structure and organization that cause biomechanical instability with subsequent development of irregular astigmatism, progressive myopia, corneal thinning, and central corneal scarring, all of which result in mild to marked impairment in visual acuity (Tuori et al. 1997; Cheng et al. 2001; Radner et al. 1998; Rabinowitz 1998). The prevalence of keratoconus is approximately 50–230/100,000 in the general population (Rabinowitz 1998). The disease affects both males and females. Onset of keratoconus is most common during adolescence and puberty (Rabinowitz 1998), although it can occasionally be present in children as young as four years, especially in the setting of chronic eye rubbing. Keratoconus is typically progressive until the third or fourth decade of life, when it usually arrests, although progression may persist longer than this. Corneal hydrops, acute corneal edema due to a break in Descemet's membrane, which causes profound vision reduction, photophobia and tearing, has been described in atopic children as young as 6 years (Rahman and Anwar 2006; Panahi-Bazaz et al. 2014; Ioannidis et al. 2005; Downie 2014).

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Development of the Cornea and Refractive Error

It is generally accepted that the most pronounced growth of the cornea stops by age 6, although the exact timing of corneal growth is still debated (von Reuss 1881; Greeff 1892; Grod 1910; Asbell et al. 1990; Oyster 1999; Ehlers et al. 1968; Ko et al. 2001; Hymes 1929; Duke-Elder 1963; Ronneburger et al. 2006). During the prenatal period, the diameter of the cornea has been demonstrated to increase in a linear fashion from an average of 2.7 mm at 12 weeks to 9.7 mm at 40 weeks (Ehlers et al. 1968; Ko et al. 2001). Hymes found that the rapid phase of corneal growth after birth ended between 9 months and 1.5 years (Hymes 1929), a conclusion that was largely accepted by Duke-Elder who noted, however, that some growth might be evident up to the end of the second year (Duke-Elder 1963). Ronneburger et al. concluded that the fastest growth of the cornea after birth occurs in the early months of life and represents a rapid deceleration of the fetal growth of the cornea (Ronneburger et al. 2006).

A number of other changes take place in the eye during postnatal development, including an increase in the axial length of the eyeball and the size of the lens (Oyster 1999; Larsen 1971). Changes in curvature and thickness of the cornea

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also occur with age (Kotulak and Brungardt 1980; De Silva et al. 2011; Uva et al. 2011; Ehlers et al. 1976; Inagaki 1986). Studies of premature infants have demonstrated that corneal curvature and central corneal thickness change dramatically after birth, with the corneal curvature changing from 65 diopters at 28 weeks to 49 diopters at 42 weeks of post-conceptional age. The flattening of the cornea continues after birth, with average keratometry readings of 45 diopters by eight weeks of age. Change in corneal curvature slows at this point. Central corneal thickness decreases from 794 to 559 μm during the prenatal and neonatal period, with stabilization by 3 years of age (De Silva et al. 2011; Uva et al. 2011; Ehlers et al. 1976).

Müller and Doughty have included in their study of corneal growth an extensive review of the literature of corneal diameter measurements. It increases at the rate of 1.1 mm per month over the fetal period with growth in corneal diameter of 0.14 mm per month over the first year of life; after 1 year of life the growth rate abruptly slows to a mean of just 0.01 mm per month. They also have failed to detect growth of the cornea above six years of age (Müller and Doughty 2002).

The adult structure of the cornea is reached at 6 months of age. A decrease in corneal power with a corneal flattening counteracts the effects of axial elongation, crystalline lens flattening and thinning, and the decrease in lens power that are the hallmarks of normal eye growth in emmetropes from ages 6 and 15 years (Lesueur et al. 1994; Zadnik et al. 2004). In normal eyes no changes in lens thickness, corneal curvature radius, and corneal astigmatism have been detected between age 10–18 (Fledelius 1982).

Astigmatism is common in early infancy, but decreases in prevalence from 3 to 9 months subsequently remaining stable between 9 and 36 months. The reduction in astigmatism in infants appears to be caused by decreases in the with-the-rule toricity of the cornea and the against-the-rule lenticular toricity (produced by the toricity of the posterior lens surface). The cornea and anterior lens surface became more spherical with age, contributing to the shift away from with-the-rule refractive astigmatism (Mutti et al. 2004; Howland and Sayles 1985). Between 9 and 21 months of age, there is a rapid emmetropization in normal children (Ehrlich et al. 1997).

Etiology of Keratoconus

The etiology of keratoconus is not well understood. Genetic, biochemical, and physical factors have been hypothesized to play a role. A reduced number of collagen crosslinks and a higher susceptibility to pepsin digestion have been suggested as possible explanations for the overall structural weakness of the corneal in keratoconus, which results in corneal stiffness that is only 60% of the normal cornea (Rabinowitz 1998). The mechanisms that underlie this observation remain poorly understood. Defective formation of extracellular constituents of corneal tissue, fewer collagen lamellae, fewer collagen fibrils per lamella, and closer packing of collagen fibrils have all been suggested as possible factors in the decreased mechanical stability of the cornea that plays an important role in the progressive ectasia that characterizes keratoconus (Andreassen et al. 1980).

Although typically keratoconus is an isolated condition, there have been associations with multiple other eye and systemic conditions including retinitis pigmentosa, blue sclera, magnesium deficiency, Down syndrome, Turner syndrome, Marfan syndrome, Ehlers–Danlos syndrome, mental retardation, Leber congenital amaurosis, osteogenesis imperfect, and pseudoxanthoma elasticum (Rabinowitz 1998; Cullen and Butler 1963).

Keratoconus has a hereditary component, as there is a greater incidence of keratoconus in relatives of patients with the disorder, as compared to the general population (Carmi et al. 2006). Approximately 6–24% of cases reported in literature demonstrate clinically recognized familial aggregation (Rabinowitz 2003; Edwards et al. 2001). Both dominant and recessive models have been observed in individual keratoconus

pedigrees (Wang et al. 2000; Falls and Allen 1969). In addition, segregation analyses (Wang et al. 2000), twin studies (Zadnik et al. 1984), and gene mapping studies (Tyynismaa et al. 2002; Brancati et al. 2004; Hutchings et al. 2005; Tang et al. 2005; Li et al. 2006) have also indicated the important role of genetic factors (Li et al. 2007).

In the vast majority of cases (in excess of 90%), keratoconus is bilateral; however, the severity of the disease may be asymmetric. In many cases the disorder may start in one eye, but over time the other eye becomes involved (Holland et al. 1997). Although keratoconus is most frequently diagnosed after adolescence, the corneal ectasia likely starts at a much younger age (Rabinowitz 1998).

Epigenetic and environmental factors certainly play a role in expression and progression of keratoconus. Many pediatric keratoconus patients have comorbidities including atopic dermatitis (Cullen and Butler 1963), and ocular allergic tendencies that vary in severity from mild seasonal allergic conjunctivitis to more severe diseases such as vernal keratoconjunctivitis (VKC) (Arora et al. 2012). VKC compounds the problems with keratoconus as continued surface inflammation and the tendency towards eye rubbing accelerate keratoconus progression, often leading to advanced disease at a young age (Rahman and Anwar 2006; Panahi-Bazaz et al. 2014; Ioannidis et al. 2005; Cullen and Butler 1963). Therefore, children with atopy should be referred for a comprehensive ophthalmic examination, even in the apparent absence of visual symptoms, to ensure the timely diagnosis and management of any atopy-associated ocular disease, including keratoconus. Prompt referral is particularly essential for young atopic children, since keratoconus in this setting can quickly advance to the stage beyond which corneal crosslinking can be performed safely, thus worsening the prognosis for maintenance of stable vision (Downie 2014). Patients and parents should be counseled about the importance of avoiding eye rubbing. Management of systemic allergic disease is essential to minimize ocular complications. The management of allergic eye disease in children is discussed in Chap. 4 (Cruzat and Colby).

Recent studies suggest that thyroid gland dysfunction due to inflammatory or immunological causes can be associated with keratoconus. Patients with hypothyroidism should have corneal topography to assess for early stage keratoconus. In addition, patients with keratoconus should be evaluated for thyroid dysfunction (Gatzioufas et al. 2014). Other reports suggest that hormonal changes occurring during pregnancy, including a modified function of the thyroid gland (Gatzioufas and Thanos 2008), may adversely affect corneal biomechanics and may have a severe impact on the progression of keratoconus (Soeters et al. 2012; Hoogewoud et al. 2013; Bilgihan et al. 2011).

Pathology

Keratoconus caused pathologic changes in multiple layers of the cornea (Sherwin and Brookes 2004). The epithelium shows central thinning, with irregular or thickened basement membrane and defects in the Bowman layer. Stromal scarring and evidence of apoptosis have been identified in proximity to breaks in the Bowman layer (Kaldawy et al. 2002; Sykakis et al. 2012). In vivo confocal microscopy has demonstrated decreased sub-basal nerve density correlating with decreased corneal sensation, as well as reduced basal epithelial density (Patel et al. 2008). There is a loss of stromal collagen lamellae and altered collagen fibril orientation. Decreased keratocyte density, particularly in the central anterior stroma, has also been reported (Mathew et al. 2011). Descemet membrane and endothelium are generally unaffected, except in cases with corneal hydrops, although elongation of endothelial cells with pleomorphism has been reported in a small percentage of cases (Rabinowitz 1998). Changes from corneal hydrops, demonstrated on histopathology and more recently with anterior segment optical coherence

tomography, include epithelial and stromal edema, intrastromal fluid clefts, and detachment of the Descemet membrane (Basu et al. 2012a, b).

Signs and Symptoms of Keratoconus

The disease course of keratoconus differs from patient to patient and from eye to eye. Early in the disease there may be no symptoms, and the only sign may be an inability to refract the patient to a clear 20/20 or a refraction showing a mild astigmatism, usually at 70° in the right eye and 110° in the left eye. The problem becomes evident to the patient when the cornea begins to thin and gradually curves outwards, deforming into a cone shape. The irregular shape changes the refractive power of the cornea, producing image distortion and blurring of vision. The patient initially complains of worsening in visual quality, image distortion, and progressive blurring of vision.

In the early stages of the disease, the visual symptoms can usually be corrected with glasses. One sign of disease progression is the need for frequent changes in glass prescription to compensate for the rapid change in corneal shape. Eventually spectacles will no longer be able to correct for the corneal ectasia and hard contact lenses are needed. However, in the later stages of the disease even contact lenses are poorly tolerated because the cornea becomes more irregular in shape, thus compromising contact lens fit and comfort.

In moderate to advanced cases, conical protrusion of the cornea with stromal thinning, an iron line partially or completely surrounding the cone (Fleischer ring) and fine vertical lines in the posterior stroma (Vogt striae) can be detected during slit lamp examination. Anterior stromal scars may be seen at the apex of the cone in contact lens wearers with severe stage keratoconus, the result of chronic bearing of the contact lens on the protruding cornea. Other clinical signs include Munson's sign, a V-shaped conformation of the lower lid produced by the ectatic cornea in downgaze, and Rizzuti's sign, a sharply focused beam of light near the nasal limbus, produced by lateral illumination of the cornea in patients with advanced keratoconus. These diagnostic clinical signs have been largely supplanted by corneal topography, which can diagnose even early ectasia.

Tools to Aid in Diagnosis of Keratoconus and Disease Progression

Several devices can help the clinicians in the early detection of the disease before signs are visible on exam. Computer-assisted videophotokeratoscopy (VK) is a sensitive means for detecting subtle changes in the topography of the corneal surface and allows for a detailed qualitative and quantitative analysis of corneal shape (Klyce 1984; Rabinowitz and Rasheed 1999). Placido disk-based computer videokeratoscopes have the combined features of both a keratometer and photokeratoscope, and can record curvature changes in both the central and paracentral cornea, and are thus well suited for detecting subtle topographic changes present in 'early' keratoconus and for documenting serial changes in corneal curvature over time (Wilson and Klyce 1991; Maguire and Bourne 1989; Maguire and Lowry 1991). In recent years, several quantitative indices that assign numeric values to certain topographic patterns have been developed to reduce interpretation of complicated videokeratographs into more manageable, easily interpretable quantitative indices (Rabinowitz and Rasheed 1999; Wilson and Klyce 1991; Maguire and Lowry 1991). Certain VK indices (Central K, I-S and KISA) are significantly increased in keratoconus patients and unaffected relatives of keratoconus patients as compared with normal controls (Wang et al. 2000). Thus, the progression of these indices may be an early sign of the development of keratoconus.

The advent of refractive surgery in the 1990s and the coincident risk of iatrogenic ectasia or unmasking of keratoconus spurred the

development of newer diagnostic devices aimed at early detection of subclinical keratoconus. The Orbscan (Bausch and Lomb, Rochester, NY, USA) utilized slit scanning technology to provide wide-field pachymetry, anterior and posterior elevation, and keratometry maps. A later iteration, the Orbscan II, combined slit scanning with Placido-based topography analysis, and was shown to be more sensitive for detection of early keratoconus. Maximum posterior elevation compared with the best fit sphere (BFS), irregularity in the central 3 mm and 5 mm zones, as well as pachymetry have been found to be useful in discriminating keratoconus suspects from normal subjects (Lim et al. 2007). Increase in apex elevation, displacement of the corneal apex, decrease in thinnest-point pachymetry, and an increase in the mean simulated keratometry minimum value have been documented on serial analysis of progressive keratoconus (Sahin et al. 2008).

The Scheimpflug principle has been exploited in corneal tomographers such as the Pentacam (Oculus, Wetzlar, Germany) to provide three-dimensional mapping of the cornea, including direct measurement of anterior and posterior corneal surfaces, pachymetry, as well as anterior chamber angle characterization. A much touted feature of the Pentacam is the Belin/Ambrosio-enhanced ectasia display, which excludes a 4 mm zone centered on the thinnest portion of the cornea from the reference shape calculation. The resulting "enhanced BFS" is supposed to approximate a normal cornea closely, making subtle elevations more pronounced and possibly aiding in detection of early or subclinical keratoconus. Various indices in normal eyes, keratoconus suspects, as well as established keratoconus patients have been measured, although definite superiority over earlier devices is yet to be proven (Quisling et al. 2006; Ambrósio et al. 2006; Piñero et al. 2010; Uçakhan et al. 2011; Piñero et al. 2012; Muftuoglu et al. 2013). Recent interest has focused on characterization of aberrometry profiles as well as understanding of corneal biomechanics in keratoconus using instruments such as the Ocular Response Analyzer (Reichert Inc, Depew, NY, USA). Compared with controls, keratoconic eyes have been found to have excessive higher order aberrations and lower values of corneal hysteresis and corneal resistance factor (Maeda et al. 2002; Schweitzer et al. 2010; Johnson et al. 2011; Fontes et al. 2011; Alio et al. 2011).

Pentacam Scheimpflug tomography can detect most subclinical keratoconus cases with unremarkable topography, but performance is not as good as reported and varies considerably for each index. The overall deviation, average and maximum pachymetric progression, and maximum relational thickness indices offer the highest sensitivity, which can be improved by using optimized cutoff values. Specificity constitutes an issue for some indices and up to 10% of subclinical keratoconus cases may go undetected by this technology.

Numerous clinical studies have been carried out to recognize and measure the progressive mechanical strength reduction of the keratoconic cornea over time (Maumenee 1974; Jafri et al. 2004; Gasset et al. 1978). Measurement of corneal biomechanical behavior after crosslinking (Wittig-Silva et al. 2008; Raiskup-Wolf et al. 2008) has demonstrated that this procedure increases corneal biomechanical rigidity by approximately 300% (Wollensak et al. 2003b), increases the collagen fiber diameter by 12.2% (Wollensak et al. 2004), and promotes formation of high molecular weight collagen polymers, with a remarkable chemical stability (Wollensak and Iomdina 2009).

The Reichert Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, New York) and the Corvis (Oculus, Inc), the first simple devices able to provide an in vivo dynamic measurement of corneal viscoelastic behavior (Luce 2005; Shah et al. 2007; Ortiz et al. 2007), show a significant reduction in two parameters called corneal hysteresis (CH) and corneal resistance factor (CRF), in keratoconic eyes compared with normal eyes and can be used with topography and tomography for the early detection of the disease.

Corneal Cross Linking

Corneal collagen crosslinking (CXL), was introduced by Wollensak et al. as a treatment to stabilize progressive keratoconus, preserve existing levels of vision and reduce the need for corneal transplantation (Wollensak et al. 2003a, b; Kohlhaas et al. 2006; Spoerl et al. 1998; Spoerl and Seiler 1999; Spoerl et al. 2004; Schilde et al. 2008). Corneal crosslinking occurs with age via intrinsic enzymatic pathways utilizing transglutaminase and lysyl oxidase (Wollensak et al. 2003a). The procedure itself, which uses ultraviolet A (UVA) light and riboflavin (photosensitizer, vitamin B2), is believed to induce physical crosslinking of collagen fibrils. Topically applied riboflavin absorbs UVA and acts as a photosensitizer to produce free radicals (oxygen singlets) that subsequently activate the native lysyl oxidase pathway (Wollensak et al. 2003a). By absorbing UVA, the riboflavin also prevents damage to deeper ocular structures, including the endothelium, lens, and retina (Wollensak et al. 2003a; Romano et al. 2012). Although there is no definite evidence that CXL produces corneal collagen and proteoglycan crosslinks, since these molecular bonds cannot be seen microscopically, ex vivo laboratory studies have demonstrated an increase in collagen fiber diameter, in stress–strain measurements of stromal tissue, and in resistance to enzymatic digestion and matrix metalloproteinase cleavage, and are believed to play a role in stabilizing the keratoconic cornea and preventing disease progression (Wollensak et al. 2003b).

Since the first report of human studies of CXL by Wollensak et al. in 2003, there have numerous publications in the peer-reviewed literature with a variety of methodologies (retrospective, prospective uncontrolled and randomized controlled trials), addressing the safety and efficacy of CXL in treating adult eyes with keratoconus as well as other corneal ectatic conditions (Wittig-Silva et al. 2008; Raiskup-Wolf et al. 2008; Wollensak et al. 2003a). These studies have provided sufficient evidence that CXL is successful in slowing or halting keratoconus progression and may even demonstrate visual, topographic and aberrometric improvement by induced corneal flattening and reduction in irregular astigmatism. Importantly, medium and long-term studies have validated an excellent safety profile for standard CXL (epithelium-off Dresden protocol), with respect to the health of corneal endothelium, lens and retina despite the potential cytotoxic effect of the UVA light. Since no permanent side effects and an acceptable complication rate were observed in adults with keratoconus (Spoerl et al. 2007; Vinciguerra et al. 2009a, b; Vinciguerra et al. 2010) when strict inclusion criteria were followed, the introduction of corneal collagen crosslinking in routine clinical practice has changed the management of keratoconus in the both the adult and the pediatric population outside the US. General practice requires documented evidence of keratoconus progression before performing CXL, although some experts argue that this is not necessary. To reduce risk of endothelial damage, a minimum corneal thickness of greater than 400 microns is recommended, although strategies such as hypotonic riboflavin may allow safe treatment of thinner corneas.

Corneal Cross Linking in Children

Pediatric keratoconus, occurring in patients under the age of 18, exhibits several unique characteristics. Studies have shown that pediatric keratoconus is often more advanced at diagnosis than in keratoconus in adults, with 27.8% of children beings stage 4 at diagnosis versus 7.8% of adults being stage at diagnosis (Léoni-Mesplié et al. 2012). In addition, keratoconus in children demonstrates a higher rate and rapidity of progression as compared to adult keratoconus (Li et al. 2007; Chatzis and Hafezi 2012; Al Suhaibani et al. 2007; Ertan and Muftuoglu 2008). The biomechanical rigidity of the cornea is inversely related to age (Kamiya et al. 2009) and children

with keratoconus are frequent eye rubbers, especially children with coexisting VKC or other allergic eye diseases.

The impact of keratoconus in children is great. Reduced vision negatively affects the quality of life and social and educational development in children. Use of rigid contact lenses, the mainstay of vision correction in keratoconus, is more challenging in children. Corneal transplantation, the only option for visual restoration in advanced keratoconus, has a much worse prognosis in children (Lowe et al. 2011; Vanathi et al. 2009). Thus, a treatment that can prevent progression of keratoconus and reduce the need for corneal transplantation has obvious advantages in the pediatric population.

Practical Aspects of Cross Linking in Children

Personal experience teaches that according to the mental state and co-operation of an individual child, either general or topical anesthesia can be used for CXL. Some patients as young as 7 years can tolerate CXL under local anesthesia, especially with the support of a parent in the operating room. Other patients, even teenagers, may require general anesthesia. The duration of the procedure at present is a challenge for treatment of pediatric patients. Rapid riboflavin delivery by iontophoresis and accelerated UVA exposure (ACC CXL) may be utilized in pediatric keratoconus in the future to reduce treatment time for CXL, if these advances are validated in the adult population.

Thirty minutes before the procedure, systemic pain medication is administered and pilocarpine 2% drops are instilled in the eye to be treated. CXL is typically performed under sterile conditions in the surgical suite; some surgeons perform CXL in a laser suite or minor operating room. After topical anesthesia is applied, the patient is draped, the ocular surface is rinsed with balanced salt solution, and a lid speculum is applied. The central 9 mm of the corneal epithelium is removed with the aid of a mechanized (Amoils) brush. Before beginning UVA irradiation a photosensitizing riboflavin 0.1% solution (10 mg riboflavin-5-phosphate in 20% dextran-T-500) is applied onto the cornea every minute for 30 min to achieve adequate penetration of the solution. Using a slit lamp with the blue filter, the surgeon confirms the presence of riboflavin in the anterior chamber before ultraviolet irradiation is started. The cornea then is exposed to an ultraviolet source emanating from a solid-state device emitting light at a wavelength of 370 nm and an irradiance of 3 mW/cm^2 or 5.4 J/cm^2. Exposure lasts for 30 min, during which time the riboflavin solution is re-applied every 5 min. The cropped light beam has a 7.5-mm diameter. A calibrated ultraviolet A meter is used before treatment to check the irradiance at a 1.0-cm distance. Intraoperative pachymetry is usually performed throughout the procedure to assure that the corneal thickness remains at least 400 microns. The patient should be coached to maintain fixation on the target during irradiation; the surgeon monitors the centering of treatment. Topical anesthetics are re-applied as needed during irradiation. After surgery is complete, the patient receives cyclopentolate and levofloxacin drops. A soft bandage contact lens is applied and remains until the corneal epithelium regrows (typically 3–4 days). Topical antibiotic is given until re-epithelialization has occurred. Topical steroids are given (our regimen calls for 0.15% dexamethasone drops 3 times daily for 20 days). We also prescribe sodium hyaluronate 0.15% drops 6 times daily for 45 days to lubricate the ocular surface. In addition, patients receive oral amino acid supplements for 7 days. Patients are followed daily until re-epithelialization is complete. Proper hygiene and compliance with the medication regimen is essential to minimize the risk of any corneal infection. The use of amino acid supplements and antioxidants in the immediate preoperative and postoperative period is

recommended to promote corneal re-epithelialization. For the first month after treatment the patient should avoid saunas, swimming pools and baths and direct sunlight exposure. Sunglasses are encouraged to reduce additional UV exposure.

Trans-epithelial Crosslinking

Studies have shown that the corneal epithelium is a significant barrier for penetration of both UVA light and riboflavin, which is a hydrophilic molecule that cannot easily pass through the tight junctions of the intact epithelial barrier. Trans-epithelial CXL remains attractive in theory, however, especially in the pediatric keratoconic population since postoperative pain and risk of corneal infections are reduced and visual recovery is quicker when the epithelium remains intact.

A variety of approaches have been used to enhance the efficacy of trans-epithelial CXL, including use of 20% alcohol solutions or tetracaine 1% to loosen epithelial tight junctions, partial epithelial removal or femtosecond-created intrastromal pockets. Novel formulations of riboflavin (trometamol and sodium ethylene-diaminetetraacetic acid or sodium or benzalkonium chloride added to riboflavin) have been developed to facilitate trans-epithelial absorption; however, to date, none has been close to reaching the efficacy of the epithelium-off technique. Spoerl reported no changes in the biomechanical properties of corneal tissue where the CXL was performed with the intact epithelium (Raiskup-Wolf et al. 2008) confirming the need for epithelial removal to allow sufficient stromal uptake of riboflavin.

A promising technique is enhanced trans-epithelial riboflavin absorption using iontophoretic delivery. Riboflavin is a small negatively charged molecule at physiological pH and is easily soluble in water, therefore iontophoretic transfer is potentially possible. Ultrasound, nano-emulsion systems and other epithelial permeation enhancers such as vitamin E-TPGS are currently under preclinical investigation to enhance trans-epithelial riboflavin stromal absorption.

Accelerated Crosslinking

Following the Bunsen-Roscoe law of reciprocity, the same UVA dosage can be administered by increasing the UVA fluence while simultaneously reducing the exposure time, maintaining efficacy and safety of the technique with a substantial reduction in the treatment time. Preclinical in vivo studies have been encouraging (Beshtawi et al. 2013), however, a sudden decrease of efficacy has been observed with very high intensity UV light greater than 45 mW/cm^2, probably due to a reduced availability of oxygen, which has been shown to limit the photochemical crosslinking process (McCall et al. 2010). So far few studies with a limited followup of 6 month have been demonstrating the same efficacy of accelerated crosslinking to standard 3 mW/cm^2 UVA energy at 30 min of exposure.

Cross Linking Results in Pediatric Patients

There have been several published studies presenting outcomes of CXL treatments (standard epithelium-off and trans-epithelial) in pediatric and adolescent keratoconic patients under the age of 19 years (Arora et al. 2012; Chatzis and Hafezi 2012; Soeters et al. 2014; Vinciguerra et al. 2012; Caporossi et al. 2013; Magli et al. 2013; Buzzonetti and Petrocelli 2012; Zotta et al. 2012; Kankariya et al. 2013; Sloot et al. 2013). The peer-reviewed studies have followed a variety of methodologies (case series, retrospective noncomparative, retrospective comparative and prospective studies) and demonstrated outcomes of CXL in terms of efficacy and safety over a followup ranging from one year to four years after CXL.

Standard epithelium-off crosslinking induces improvement of both uncorrected (UCVA) and best corrected (BSCVA) vision during the first year after CXL, which remains stable for up to

3 years after the procedure. The visual acuity improvement results from progressive topographic flattening of the cornea over time with a reduction of simulated keratometry, minimum keratometry, mean average corneal power, and asymmetry indices. Soeters et al. observed that before CXL, cones of pediatric keratoconic corneas were located more centrally than in the older age group (Soeters et al. 2014).

Significant reductions in mean spherical equivalent were observed especially the first year after CXL with a reduction in corneal aberrations, including coma. Minimum corneal thickness was reduced in the first 6 months after CXL, but recovered to the preoperative values within one year after the procedure. No endothelial loss was observed within the first 4 years after the procedure. Abrasion-related discomfort was reported by most patients in the immediate postoperative period. No ocular or systemic adverse events were noted, apart from a low incidence of blepharitis and photophobia up to 4 months after the procedure. No significant intraocular pressure change was seen. In most of the eyes, CXL-specific golden striae (Suri et al. 2012) developed and some eyes shown moderate haze that disappeared after the use of topical steroids.

Transient haze appearing at 2–6 weeks and clearing at 9–12 months is the result of an increased density of extracellular matrix and arises at a depth of 300–350 microns. It forms the demarcation line which can be seen at slit lamp examination or with OCT. Persistent haze has been observed in eyes with corneal apex power higher than 72D, keratometry higher than 3 mm and central pachymetry thinner than 420 micron. Sterile infiltrates may occur in the early postoperative period and usually resolve with the use of topical steroids.

A prospective study from Caporossi et al. (2013) (Siena CXL Pediatrics trial) noted that there was a better and faster visual recovery in eyes with less than 450 um corneal thickness as compared with thicker cornea group. Vinciguerra et al. published a comparative analysis that included 400 eyes of 301 patients divided into four age groups. The outcomes stratified by age indicated the efficacy of corneal CXL in stabilizing the progression of the disease in all age groups with better functional and morphologic results in the population between 18 and 39 years of age (Vinciguerra et al. 2013). Magli et al. and Salman et al. demonstrated stability of keratoconus in pediatric patients treated with trans-epithelial CXL. The procedure was showed to be less painful and provided similar effectiveness and fewer complications than epithelium-off CXL at 1 year followup (Magli et al. 2013; Salman 2013).

In contrast to these studies, Buzzonetti and Petrocelli (2012) despite concluding that trans-epithelial CXL appears to be a safe treatment in children, demonstrated that K readings and HOA aberrations significantly worsened during followup. Confocal microscopy demonstrated demarcation line at a depth of only 105 μm in contrast to the demarcation line typically seen at 300 μm in standard CXL treatment. They therefore concluded that trans-epithelial CXL does not effectively halt keratoconus progression as compared with standard CXL. The same conclusion was reported by Caporossi et al. showing instability of functional results in pediatric patients who underwent trans-epithelial CXL. 50% of these patients were retreated after 12 months of followup (Caporossi et al. 2013). These publications have demonstrated that visual, refractive and topographic stabilization and improvements after pediatric CXL are similar to that reported for adult treatment, with stability or improvement maintained for up to four years followup when treated with the standard (epithelium-off) protocol. The efficacy of trans-epithelial CXL in children remains unproven.

We therefore recommend using the standard CXL procedure (epithelium-off Dresden protocol) in pediatric keratoconus, which has been shown to be successful in stabilization in most studies. Nevertheless, Chatzis and Hafezi (2012) have reported stabilization for 2 years and late regression of the ‘standard CXL’ effect at 3 years followup, suggesting that pediatric CXL may not provide long-term stability comparable to adult treatment and may require retreatment especially in the subset of patients who continue with eye rubbing.

Since keratoconus can be rapidly progressive in young patients, it is generally recommended to follow pediatric keratoconus patients very closely (every 1–3 months rather than 6–12 months as is done in adults) to identify the earliest signs of progression and offer them CXL. If longer-term followup demonstrates continued efficacy and, more importantly, continued safety of CXL in the pediatric population, performing CXL without waiting for definite progression might become the standard of care. Some authors currently advocate performing CXL as soon as diagnosis of pediatric keratoconus is made due to the safety of the procedure and to the very high rate of keratoconus progression in children (as high as 88% in some studies), without waiting for documentation of progression (Chatzis and Hafezi 2012; Soeters et al. 2014; Ahn et al. 2013). This remains an area for further study.

Management of Visual Impairment

Management of visual impairment in pediatric patients follows the same stepwise pattern used for adults. Early disease, where the astigmatism is only minimally irregular, is managed with spectacles or monofocal or toric soft contact lenses. Rigid gas permeable contact lenses are the mainstay of vision correction for patients with moderate or severe keratoconus. Hybrid lenses, scleral lenses and individually designed lenses, including the Boston scleral lens (PROSE device), are used for if standard rigid lenses are not tolerated. Contact lens use in children is covered in detail in Chap. 9 (Jacobs).

Approximately 20% of keratoconus patients demonstrate contact lens intolerance, and depending on the corneal thickness and the presence of corneal scarring, one may consider intracorneal ring segment (ICRS) implantation (requiring 400 u thickness at corneal mid-periphery with clear central cornea) or corneal transplant (very thin cornea and/or presence of stromal scar) (Zare et al. 2007; Bahar et al. 2008; Bromley and Randleman 2010). ICRS are not preferred in the pediatric age group for variety of reasons, including the aggressive nature of keratoconus, tendency for eye rubbing and concerns regrading compliance. Although the option of ICRS (less invasive) is not commonly utilized in pediatric eyes, in adolescent patients with end stage keratcoconus and imminent keratoplaty (more invasive), this option may be worth considering. ICRS are crescent-shaped polymethyl methacrylate implants that are inserted in intrastromal channels (created either manually or with a femtosecond laser) at 70% depth of the thinnest pachymetry underlying the segments. This results in an arc-shortening effect and redistribution of corneal peripheral lamellae to produce flattening of the central cornea. This reversible procedure regularizes the central cornea and has demonstrated improvement in both corrected and uncorrected vision, as well as improved tolerance of hard contact lenses (Pinero and Alio 2010). The femtosecond laser makes tunnel creation faster, easier and more reproducible than manual dissection (Rabinowitz et al. 2006).

In very advanced disease, corneal transplantation to replace the pathological keratoconic corneal tissue with healthy donor cornea is advocated. Deep anterior lamellar keratoplasty (DALK) selectively replaces pathological corneal stroma in keratoconic eyes, while preserving the patient's own corneal endothelium. DALK offers several advantages over penetrating keratoplasty, including a reduced rate of endothelial cell loss and immunologic rejection, both of which are advantageous in children (Suri et al. 2012; Vinciguerra et al. 2013). Additional benefits include the possibility of early steroid withdrawal (reducing steroid related morbidities such as glaucoma and cataract), early suture removal, better tectonic support and the extra-ocular nature of the procedure (Kankariya et al. 2013). Additional information regarding corneal surgery in children can be found in Chap. 8 (Colby).

Conclusions

Keratoconus is a common cause of vision loss in children. Early diagnosis and treatment with corneal crosslinking when appropriate will reduce the visual burden of this disease. Most children do well with contact lenses, although advanced cases may require surgical management. Associated atopy should be managed and eye rubbing is to be avoided.

Compliance with Ethical Requirements Elena Albe declares that she has no conflict of interest. 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 carried out by the author for this chapter.

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Corneal Diseases in Children: Surgery

8

Christina Rapp Prescott and Kathryn Colby

Introduction

Corneal surgery in children presents a unique set of challenges. Children who undergo corneal surgery, specifically corneal transplantation, face failure rates much higher than their adult counterparts. The surgery itself is more technically challenging; postoperative management requires numerous examinations under anesthesia; and amblyopia may undermine even an anatomically successful graft. For these reasons, pediatric corneal surgery is rarely performed, except in the most highly specialized pediatric corneal practices. This chapter will provide guidelines, based on the existing literature and the authors' experience; however, individual surgical techniques may vary significantly.

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Penetrating Keratoplasty

Indications: Underlying pathology for corneal transplantation in children can be divided into congenital versus acquired. Due to the rarity of pediatric keratoplasty, and variability between published case series, it is difficult to assign specific percentages to indications. Not surprisingly, congenital opacities are the most common indications for transplantation in very young children, and acquired corneal opacities are more common in older children. Specific congenital indications include corneal clouding due to irido-corneal adhesions with or without associated lens involvement (previously known as Peters' Anomaly), congenital hereditary endothelial dystrophy (CHED), congenital glaucoma, sclerocornea, posterior polymorphous corneal dystrophy (PPCD), limbal dermoid, metabolic disorders, intrauterine infections, and birth trauma (Vanathi et al. 2009; Huang et al. 2009; Dana et al. 1995). Acquired corneal opacities are predominantly postinfectious or posttraumatic scars and corneal ectasia. Congenital indications may vary according to region of the world. For example, in the US, CHED is uncommon, while it is a more common reason for keratoplasty in other countries (Al-Ghamdi et al. 2007; Hong et al. 2008).

Parents or other caregivers must be counseled appropriately, and often extensively, prior to any surgical intervention. They must commit to lifelong follow-up, including frequent administration of ocular medications, regular examinations,

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often under anesthesia, and likely multiple surgeries. They must also have realistic expectations for vision; ambulatory vision is reasonable, driving vision is not usually achievable. Finally, the increased risk of graft failure and other complications including glaucoma must be understood and accepted. The importance of postoperative amblyopia management should be stressed. Pediatric keratoplasty is tremendous time commitment for the family and a wise surgeon does a thorough evaluation of the social support network of the family prior to recommending surgery.

Due to the high risk of graft failure, as well as other complications, if both eyes have corneal pathology, it is often prudent to proceed with surgery on one eye initially. The second eye may observed until the first graft fails or until the child is older and the risk of rejection is less. If the pathology is unilateral, and the child has good vision in the other eye, strong consideration should be given to observation only (no surgery), since the improvement in overall visual function is often limited when the fellow eye is normal, even in the setting of a clear graft. If there is some vision in the affected eye, amblyopia therapy, including both refractive correction, usually in the form of a soft contact lens, and occlusion treatment, should be performed.

Once the decision has been made to proceed with penetrating keratoplasty, there are still additional factors to consider. The sooner a clear visual axis is established, the lower the risk of amblyopia, especially if amblyopia therapy is started soon after surgery. However, the earlier surgery is performed, the greater the risks, both for surgery itself (including the necessary general anesthesia) and from subsequent complications, including glaucoma, cataract, retinal detachment, and transplant rejection and infection. Though there is no optimal time to perform surgery, once the decision is made to proceed, most providers recommend performing surgery around the age of 3 months (for congenital corneal pathology).

For many pediatric patients requiring transplantation, pathology is not limited to the cornea. Prior to corneal transplantation, a complete ocular exam, with imaging as indicated, must be performed and a plan formulated for any additional ocular pathology present or anticipated. The most common indication for pediatric penetrating keratoplasty is irido-corneal adhesions (previously called Peters Anomaly), and these patients have varying degrees of associated anterior segment dysgenesis. Depending on lens position and clarity, the decision should be made whether to perform a lensectomy at the time of transplantation (if so, the patient should be left aphakic). Depending on the severity of their condition, patients with congenital glaucoma may undergo glaucoma surgery prior to corneal transplantation. If not, the decision should be made whether to place a tube shunt at the time of keratoplasty. Since the visual potential maybe limited by glaucoma, the families must be counseled appropriately. For congenital corneal pathology, genotyping should be considered (Nischal 2015).

Anesthesia: Though most corneal surgery in adults is performed under monitored anesthesia care, usually with a supplemental subtenons or retrobulbar block, general anesthesia is necessary for pediatric corneal surgery. A supplemental block may still be performed to help reduce postoperative pain as well as possibly reducing the required depth of anesthesia during surgery. A pediatric anesthesiologist is helpful in allowing a safe surgery. Every effort should be made to reduce positive pressure (patient positioning/depth of anesthesia) during surgery.

Surgical Technique

Graft preparation: Graft preparation begins prior to surgery, with communication with the eye bank. Due to the differences in biomechanics between pediatric cornea and adult cornea, it is preferable, though not always possible, to obtain relatively young donor tissue. However, due to reduced tissue rigidity of very young tissue, we generally prefer tissue from donors of at least age 4.

The desired graft size is determined after detailed examination of the child with corneal measurements. Vertical and horizontal diameters of the cornea and corneal thickness should be

measured at the beginning of surgery, so the trephination can be planned accordingly. Due to the lifetime risk of subsequent surgeries, including possible repeat corneal transplantation, we recommend selecting a relatively small size host trephination, usually around 6 mm in diameter in infants and 7 mm in diameter in older children. We typically oversize the donor cornea button by 1 mm, relative to the host trephination, in infants and very young children and by 0.5 mm in older children. Once the desired graft size is determined, the appropriate sized corneal donor trephine is selected. In rare cases, where the donor button needs to be smaller than the available corneal donor trephine, an appropriate sized skin biopsy punch can be used instead.

The donor tissue should be examined under a microscope on a separate sterile field prior to trephining the host cornea. A sterile marking pen can be used to mark the center of the cornea on the epithelial surface. The graft is then centered on the donor punch block, endothelial side up, and the corneal donor trephine (or skin biopsy punch) is centered over the cornea. Using one hand to stabilize the block and the other hand to control the blade, in one smooth motion, the blade is lowered until it contacts the block. Then, prior to removing the blade, a forceps is used to rotate the rim of the donor, to confirm complete trephination. The tissue can now be placed in corneal preservation medium and kept covered in a sterile container until needed.

Surgery: Pediatric patients are more likely to experience positive pressure during surgery, and all efforts should be made to minimize this. Due to the complex hemodynamics of children, mannitol is not routinely given. A Honan balloon should be placed for 5 min on the closed operative eye just prior to surgery; and a Flieringa ring should be sutured (using 6-0 vicryl) 2 mm peripheral to the limbus prior to trephination. Due to reduced scleral rigidity in children, extra care must be taken to ensure that the needle does not penetrate too deeply and perforate the globe when suturing the ring.

The center of the cornea is marked with a sterile marking pen; if an eccentric graft is planned, the center of the planned area of trephination is marked. An 8-ray corneal marker is typically used to mark the cornea, regardless of planned suture technique. Then, partial (50–75%) trephination, using the measured corneal thickness as a guide, is performed with either a vacuum trephine or a manual trephine. A 15° blade is typically used to make a full thickness incision along the trephined area. Once the anterior chamber is entered, a viscoelastic is injected to maintain anterior chamber stability and protect the adjacent ocular structures.

Peripheral iridotomies (PI) are not always performed in adult keratoplasties, but should be performed in all pediatric cases due to the higher risk of angle closure. We typically place the PI superiorly, at either the 11 or 1 o'clock position.

Once the anterior chamber is entered, the host button can be removed using right and left or universal corneal cutting scissors. Typically, the entire button is removed prior to suturing on the donor cornea, as in adults. However, in children, especially infants, we recommend using a modified technique. As each quadrant is cut, we suture the host cornea back in position, using the non-cardinal markings as guides. It is critical to ensure that the cut is clean with no residual tags. This results in a host cornea that has been cut completely, but is held in place by 4 sutures. Once complete dissection is confirmed, a bed of viscoelastic is placed on the surface of the host cornea and the donor tissue is placed on top. The donor endothelium is protected by the viscoelastic. Four 10.0 nylon sutures are placed to secure the donor to the host bed. The "stay" sutures placed in the host are cut and the host tissue is removed from under the donor button. Though this technique may result in an increase in endothelial cell loss, it greatly reduces the risk of surgical complications including iris prolapse, unintended lens removal, vitreous loss or expulsive hemorrhage. This "sandwich" technique can also be used in high-risk adult corneal transplantation.

Once the 4 cardinal sutures are placed, 12 additional 10-0 nylon sutures are placed, as for an adult transplant. Some surgeons prefer to use 24 sutures instead of the standard 16 sutures in children. A running suture is not appropriate

since early suture removal is needed to reduce corneal neovascularization in children. Once all sutures are placed and appropriate tension is confirmed, knots are buried.

If the patient did not receive a retrobulbar or subtenon's block prior to surgery, one can be placed at the conclusion of the case to help with post-operative pain control. Ceftazidime (100 mg in 0.5 ml) and triamcinolone (20 mg in 0.5 ml) is injected subconjunctivally. Antibiotic or antibiotic/steroid ointment is applied and the eye is patched and shielded. General anesthesia is then reversed. Most children tolerate the procedure well, and postoperative pain if present can be treated with acetaminophen.

Postoperative care: Children demonstrate exuberant inflammatory responses and rapid wound healing, necessitating higher doses of steroids in the postoperative period. This can either be accomplished by increasing frequency of steroid application (every hour initially) or using a higher potency steroid (difluprednate vs. prednisolone acetate) or both. On the first postoperative day, we typically begin topical prednisolone acetate 1% every hour, a topical fluoroquinolone administered four times daily, cyclopentolate 1% two times daily, and an antibiotic/steroid ointment at bedtime. When the child is seen on postoperative day one, the importance of frequent drop application must be reinforced.

The taper schedule depends on the age of the child and the indication for surgery, but is typically much slower than for adult patients. After 2 weeks, we usually stop the antibiotic and decrease the steroid to eight times daily. Then we very slowly taper the steroid frequency to once daily over 6 months to a year. After suture removal, we recommend resuming antibiotics for 1 week, and possibly increasing the steroid frequency for a week as well. For patients with ocular surface disease, we continue erythromycin ointment at bedtime long term and add topical cyclosporine two times daily.

These patients require frequent follow-up examinations, at home, in the office, and in the operating room, under anesthesia. Parents or other caregivers must be instructed to monitor the patient daily, using a handheld light, and call immediately if they notice any changes. Sutures loosen quickly and neovascularization can develop rapidly in young children, so early suture removal is essential. In infants, suture removal can start as early as 3 weeks, and all sutures should be removed by 3 months postoperatively. Figure 8.1 shows a child shortly after suture removal.

Once sutures are removed, refraction should be performed and correction given as soon as possible. Many children can tolerate a contact lens, and depending on the difference in refraction between the two eyes, this maybe preferable to glasses. One challenge specific to pediatric patients is the concurrent management of amblyopia. Especially in cases of unilateral pathology, dense amblyopia can develop, leading to poor vision even in the presence of a clear graft.

Prognosis: The prognosis for graft survival as well as graft clarity is significantly worse for pediatric keratoplasty compared to adult keratoplasty. Among children, younger patients have worse outcomes, but it is not clear if this is due to patient age or indication, since younger patients are more likely to have surgery for congenital problems, which are more likely to be associated with other ocular pathology, including congenital glaucoma or anterior segment dysgenesis. In 2009, Yang et al. published a series of 144 surgeries in 72 eyes of children (under age 12 years) with Peters anomaly and only 56% of graft were clear at 6 months (Yang et al. 2009). Comparatively, in 2011 Ganekal published a series of pediatric (5–15 years of age) keratoplasties performed for acquired corneal pathology and 79% of grafts were clear at last follow up (6–18 months) (Ganekal et al. 2011). Other series which include a range of indications for transplantation report graft failure rates from 21 to 65% (Al-Torbak 2004; Lowe et al. 2011; Patel et al. 2005; Low et al. 2014; McClellan et al. 2003; Aasuri et al. 2000).

In 2016 Karadag et al. published a series of 35 children, age 2 months to 12 years, who had

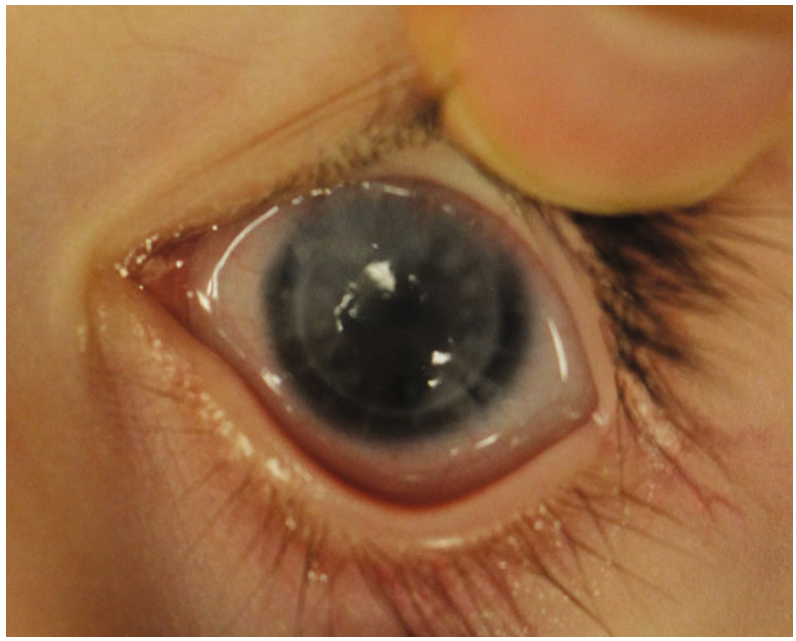

Fig. 8.1 Postoperative photograph of a child following suture removal. Fine neovascularization is visible along the superior suture tracks, showing the importance of early suture removal in children

primary grafts for a variety of indications showed a mean graft survival time of 45.2 ± 5.8 months (Karadag et al. 2016). In their study, the presence of glaucoma was the most significant risk factor for graft failure. Particular attention must be paid to intraocular pressure, especially given the higher requirement for steroids in pediatric keratoplasty. We find the Icare tonometer (Icare USA, Raleigh, North Carolina) is relatively well tolerated by older children and easier to perform than applanation tonometry in transplant patients.

Deep Anterior Lamellar Keratoplasty (DALK)

Indications: For children with corneal pathology that spares the endothelium, DALK is the preferred surgical technique. The benefit of maintaining the host endothelium is even greater in children, due to their increased risk of graft rejection and their high endothelial cell count (Ashar et al. 2013a; Harding et al. 2010). Additionally, the surgery itself is safer, since there is less risk of expulsive hemorrhage (Reinhardt et al. 2011). Unfortunately, congenital corneal pathology rarely spares the endothelium, so this is mostly an option for older children with acquired pathology (secondary to injury or infection) or ectasia.

Surgical Technique

Graft preparation: A potential benefit of DALK is the ability to use one donor tissue for 2 grafts: one DALK and one DMEK. Alternatively, irradiated donor tissue could theoretically be used for DALK, since an intact endothelium is not needed. This would be especially beneficial in areas where there is a corneal tissue shortage. However, since there is a risk of perforation of Descemet's membrane necessitating conversion to a penetrating keratoplasty, we recommend having a full thickness donor graft available when performing DALK.

As for penetrating keratoplasty, the desired graft size should be determined based on corneal measurements and after detailed examination of the child. Since the lifetime risk of graft rejection is significantly less for DALK than for penetrating keratoplasty, we recommend a larger graft size, typically 8 mm in diameter. Unlike in penetrating keratoplasty, the donor cornea button should be no more than 0.5 mm greater than the host trephination.

Donor tissue should be examined under a microscope on a separate sterile field prior to partial trephination of the host cornea. The graft is then cut as for penetrating keratoplasty, placed in corneal preservation medium, and kept covered in a sterile container until needed. After successful lamellar dissection of the host cornea, the endothelium can be removed using either a forceps to peel off the Descemet's membrane or a dry cellulose sponge to rub off Descemet's membrane and the endothelium. Trypan blue dye can be used to stain the membrane prior to removal to improve visualization.

Surgery: Multiple techniques have been described in the literature for DALK, including use of the femtosecond laser. Here we describe our preferred technique, a version of the big bubble technique described by Dr. Anwar. Multiple techniques have been described and controversy exists regarding the need to bare Descemet membrane (dDALK) versus achieving a predescemetic plane (pdDALK) (Sarnicola et al. 2010).

The cornea is marked as for penetrating keratoplasty with a center dot and an 8-ray corneal maker. Partial trephination can be performed with either a manual trephine or a vacuum trephine with a set depth of around 400 μm (or 100 μm less than the thinnest measured preoperative corneal thickness). We then remove the anterior stroma using a crescent blade to improve visualization (though some surgeons prefer to leave the entire stroma intact until after placement of the big bubble).

An angled 15 blade is used to cut a small slit into the posterior stroma, with the blade against the trephine edge. A tunnel is created using a flat spatula and then lengthened using a flat cannula attached to a 3 cc air-filled syringe. Once the tunnel is sufficient in length, the canula tip should be angled slightly down, and air smoothly injected until a big bubble forms. When a white ring reaches the edge of the trephination and the eye feels firm, the bubble is complete. Slowly remove the canula.

The eye is now quite firm, so release some aqueous fluid by making a posterior paracentesis. Inject a small air bubble into the anterior chamber to confirm displacement of the Descemet's membrane. The remaining posterior stroma can now be removed. Using a 15 blade, carefully but quickly nick the posterior stroma to collapse the big bubble. The anterior chamber small bubble will move to the center when the big bubble collapses. Prior to proceeding, viscoelastic should be injected through the nick to push the Descemet's membrane back, and the anterior chamber bubble should return to the periphery.

The remaining posterior stroma is removed in sections. Using blunt Vannas or DALK scissors, make radial cuts to form pie-shaped wedges and remove them. Once all sections are removed, rinse the bed with balanced salt solution to remove all viscoelastic. The graft, as described above, is then sutured to the bed using 16-interupted 10-0 nylon sutures, taking care not to perforate the Descemet's membrane. As for penetrating keratoplasty, suture tension is checked and all knots are buried. Using a portable slit lamp, check for a Descemet's detachment, visible as a double anterior chamber, at the conclusion of the case. If there is an area of detachment, the anterior chamber maybe filled with air and the patient left supine for 10 min or more prior to reversal of anesthesia. Since most children will not be able to follow postoperative positioning instructions, we do not recommend

leaving an air bubble in the anterior chamber at the conclusion of surgery.

As with penetrating keratoplasty, if the patient did not receive a retrobulbar or subtenon's block prior to surgery, one can be placed at the conclusion of the case to help with postoperative pain control. Ceftazidime (100 mg in 0.5 ml) and triamcinolone (20 mg in 0.5 ml) are injected subconjunctivally. Antibiotic or antibiotic/steroid ointment is applied, and the eye is patched and shielded. General anesthesia is then reversed. Most children tolerate the procedure well.

Postoperative care: Initial postoperative care is similar to care after penetrating keratoplasty, but one of the benefits of DALK is that the steroids can be tapered much more quickly. On the first postoperative day, we typically begin topical prednisolone acetate 1% every 2 h (or 8 times daily), a topical fluoroquinolone administered four times daily, and an antibiotic/steroid ointment at bedtime. The steroids should be tapered over 1–3 months, depending on the age of the child, as well as the pathology. Suture removal will also vary with the age of the child, but all sutures are typically removed by 3–4 months, even in older children.

Refractive correction should be given as soon as possible once all sutures are removed. Since DALK is typically perfumed for corneal scarring or ectasia, which are usually unilateral or asymmetric, there is often significant amblyopia present. This should be treated aggressively and as soon as possible to optimize lifelong visual potential.

Endothelial Replacement

Indications: Selective endothelial keratoplasty is the procedure of choice in adults with isolated endothelial dysfunction due to multiple advantages over penetrating keratoplasty including faster visual recovery, smaller incisions with fewer sutures, and preservation of the anterior host cornea. These advantages maybe confer even greater benefits in children. Faster visual recovery, weeks rather than months, is especially beneficial in children, since it decreases the risk of amblyopia. Smaller incisions confer less risk of subsequent postoperative would rupture, which is especially important in active children. Since sutures tend to loosen and vascularize more quickly in children, fewer sutures (and use of dissolvable sutures) lessens suture-related complications and may allow the surgeon to schedule fewer exams under anesthesia in the early postoperative period, since sutures may not need to be removed.

The primary reason that selective endothelial keratoplasty is not more commonly performed in children, despite its significant advantages, is that most pediatric corneal pathology is not limited to the endothelium. The most common indications for endothelial keratoplasty in adults are Fuchs' endothelial dystrophy and pseudophakic bullous keratopathy, neither of which is common in children. Of the most common indications for corneal surgery in children, only CHED and PPCD are localized to the endothelium. The first reported cases of DSAEK in children were published in 2008, and both were performed in aphakic children with endothelial decompensation following complicated ocular surgeries (Jeng et al. 2008; Fernandez et al. 2008). Subsequently, several reports have shown good outcomes of DSAEK in patients with CHED, PPCD, congenital glaucoma, and Peters anomaly, and this is likely to become the standard of care over time as benefits are demonstrated and techniques refined (Ashar et al. 2012; Ashar et al. 2013b; Madi et al. 2012; Hashemi et al. 2012; Kymionis et al. 2012; Ramappa et al. 2012). There is a single case report of DMEK performed in a 12-year-old with Kearns–Sayre syndrome (Gonnermann et al. 2014).

The pros and cons of DMEK versus DSAEK for endothelial keratoplasty are topics of debate in the adult literature; however, in children, DSAEK is the preferred technique for several reasons. DMEK has a higher rate of rebubbling and primary graft failure, even in the most experienced hands (Hamzaoglu et al. 2015). Also, most pediatric indications for endothelial keratoplasty are associated with poor views into

the anterior chamber, making unscrolling and placement of the thinner DMEK graft very difficult. The primary proven benefit of DMEK versus DSAEK is better vision, most notably higher rates of 20/20 and 20/25 Snellen visual acuity. Most children with corneal pathology do not have visual potential in the 20/20 range, so this benefit of DMEK versus DSAEK may not apply. There is some evidence that DMEK may have lower rejection rates than DSAEK. This would be of great benefit to children, so if modifications can be made to decrease the rate of rebubbling and primary graft failure, DMEK maybe worth considering in select children.

Prior to surgery, the decision must be made regarding management of the crystalline lens. Depending on the age of the patient and other ocular pathology, implantation of an intraocular lens may be beneficial to decrease the risk of posterior dislocation of the endothelial graft and allow retention of an air bubble.

Surgical Technique

Graft preparation: Endothelial grafts can be prepared either by the eye bank or by the surgeon. Most surgeons use tissue prepared by the eye bank. The eye bank can mark the graft with a letter, such as "S", to confirm orientation. The size of the graft varies with indication for surgery and surgeon preference, but is typically 6.5–8.5 mm. When using precut tissue, it is critical to ensure that the donor button is attached to the host stroma and aligned properly before placing it on the corneal donor trephine. The graft is then cut as per full thickness keratoplasty. Once the graft is cut to size, a cohesive viscoelastic is placed on the endothelium to protect it prior to placement into an inserter or onto the eye.

Surgery: If the patient is aphakic or phakic, and the lens is not going to be removed during the surgery, topical 2% pilocarpine (3 doses 5 min apart) should be given to constrict the pupil and reduce risk of trauma to the natural lens during surgery.

We first make 3 paracentesis incisions: one superior, one inferior, and one nasal. One of the incisions will be used for the secondary instrument, one will be used to pull the graft through (depending on insertion technique), and one will be for placement of an anterior chamber maintainer. Due to the shallow anterior chamber in most pediatric patients, we routinely use an anterior chamber maintainer. A 2.75 mm main incision is placed temporally, and is widened to 4.5–5 mm just prior to graft insertion. Though some surgeons use a clear corneal incision for DSAEK, we recommend a scleral tunnel incision due to less astigmatism and better wound healing.

Use a sterile marker to mark the center of the cornea and a circular trephine the same size as the donor button to mark the area to be scored. The unhealthy Descemet's membrane/endothelium is stripped off, following the mark, using a reverse Sinskey hook and then an endothelial stripper. Unlike in adult patients, the Descemet's membrane rarely comes off as one smooth membrane, so extra care must be taken to ensure that the stromal bed is bare, especially centrally. The Descemet's membrane, or fragments of Descemet's membrane, is then sent to pathology. The peripheral stromal bed is then scraped to help with adherence.

Peripheral iridotomies are not always performed in adult DSAEK, but should be performed in all pediatric cases due to the higher risk of angle closure. This can be performed through the sideport incision using multiple techniques. One technique is using the port of a vitrector through the adjacent incision.

There are multiple methods of tissue insertion: forceps insertion, suture pull-through, various glides, and inserters. Surgeons should use the technique they are most comfortable with, with modifications as necessary. In children who are phakic, it is critical to avoid contact with the lens, so if a pull through technique is used, nasal and temporal incisions should be shifted 1 mm superiorly.

Once the graft is in place, and correct orientation is confirmed, the primary incision is sutured with three 9-0 vicryl or 8-0 nylon sutures. Since pediatric eyes tend to be softer

than adult eyes, it is best to leave the anterior chamber maintainer in place until the main incision is closed. Once the eye is closed, the anterior chamber maintainer is removed, and a full air bubble is inserted through one of the side incisions.

Since many of these young patients are aphakic, precautions must be taken to ensure that the graft does not dislocate into the posterior segment. One option is to place one or more "safety sutures" into the graft. We typically use two 10-0 nylon sutures, which we pass full thickness through the donor button. It is important to pass the suture from the periphery to the center so as not to dislocate the graft. Sutures are not typically placed in adult DSAEK grafts, since they can lead to wrinkling or the graft, damage to the endothelium along the suture track, and will need to be removed. However, in children who may not be able to position postoperatively, especially in aphakic children, the benefits of suture placement may outweigh the risks.

One reason that endothelial keratoplasty is not as widely performed in children as in adults is that most children are not capable of the postoperative positioning that is usually required. At the conclusion of endothelial keratoplasty, a partial gas bubble (either air or a longer acting gas, such as SF6) is usually left in the anterior chamber. The patient is asked to remain in the supine position for as long as the gas bubble is present to promote graft adherence (24–48 h). In children who are not able to position, the risks of a gas bubble in the anterior chamber postoperatively outweigh the benefits, so the bubble should be removed once the safety sutures are placed if the child will be unable to position. In older children who are able to position, a small air bubble maybe left in place. If an air bubble is going to be left in place, a topical cycloplegic is given at the conclusion of surgery.

Postoperative care: Initial postoperative care is similar to care after penetrating keratoplasty, but one of the benefits of DSAEK is that the steroids can be tapered and sutures removed much more quickly. On the first postoperative day, we typically begin topical prednisolone acetate 1% every 2 h (or 8 times daily), a topical fluoroquinolone administered four times daily, and an antibiotic/steroid ointment at bedtime. If an air bubble was left in place, a topical cycloplegic is used until the air bubble resolves. The steroids should be tapered over 1–3 months, depending on the age of the child, as well as the pathology. Suture removal can be performed at 1–4 weeks, typically during the first postoperative EUA.

Patients need careful monitoring, especially in the immediate postoperative period, to ensure that the graft adheres to the host. Slit lamp exams are necessary to detect interface fluid and determine the need for possible rebubbling or repositioning.

Keratoprosthesis

Indications: Keratoprosthesis offers a number of benefits compared to standard penetrating keratoplasty, including no risk of rejection and rapid visual recovery leading to decreased risk of amblyopia (Aquavella et al. 2007; Traish and Chodosh 2010; Kang et al. 2012). Since the synthetic optic remains clear even if the donor cornea is rejected, rejection is not an issue (although extrusion is and currently limits the longevity of keratoprosthesis in children). Other benefits include absence of astigmatism, due to the synthetic optical center of the keratoprosthesis, which leads to improved vision and easy correction of any residual refractive error with a bandage contact lens, the power of which can be easily determined by retinoscopy. Examinations are easier, since the posterior pole can be visualized through the keratoprosthesis.

However, despite the multiple benefits listed above, keratoprosthesis is a last resort option, especially in children, where the lifetime prognosis is incredibly poor. Though traditional rejection is not an issue, multiple other complications can occur, some of which are specific to the keratoprosthesis (Kang et al. 2012; Sejpal et al. 2011; Sayegh et al. 2008). The most common complication is formation of a retroprosthetic membrane, which can usually be treated with a YAG (neodymium-doped yttrium

aluminium garnet) laser in adults, but which must be surgically removed in children, due to both the density of the membrane and the inability of most children to tolerate a laser procedure without anesthesia. The donor carrier corneal tissue can melt in the setting of a dense retroprosthetic membrane, leading to wound leak or extrusion of the keratoprosthesis. The presence of a synthetic device, coupled with the need for long-term contact lens wear increased the risk of infection, and these infections can be severe, including corneal ulceration and even endophthalmitis. Infection must be distinguished from ocular inflammation, which can develop at any time, though it is most common in the immediate postoperative period. Many of the ocular conditions that are treated with keratoprosthesis are associated with glaucoma, so the risk of glaucoma in the keratoprosthesis patient population is high to start with, but implantation of the device is associated with an increase in glaucoma risk and progression. Due to this risk, patients should be co-managed by a glaucoma specialist and a glaucoma valve should be placed in all children undergoing keratoprosthesis implantation.

Given the multiple risks listed above, the decision to proceed with keratoprosthesis surgery in a child should not be made lightly. The family must understand and accept these risks. They must also be willing and able to cooperate with all necessary postoperative care, regular appointments, examinations under anesthesia, likely additional future surgeries, and home care involving eye drops, specialty contact lenses, and close observation. They should also be shown pictures of the implanted device, so they will be prepared for the appearance of the child's eye. It is critically important that all children with a keratoprosthesis have an experienced keratoprosthesis surgeon readily available to manage the inevitable complications.

Surgical Technique

Graft preparation: The Boston keratoprosthesis is assembled of four parts. The optic is a single piece of polymethyl methacrylate (PMMA) that is constructed to form a front plate and its stem. A corneal allograft (or autograft) sits between the front plate and the back plate. Some surgeons use irradiated corneal tissue for the graft, which has the benefit of a long shelf life and maybe stronger (Akpek et al. 2012). The back plate can be made of PMMA or titanium. Last, a C-shaped titanium-locking ring prevents disassembly. The most recent version of the Boston keratoprosthesis consists of two pieces—the front optical portion and a backplate with the locking ring incorporated. However, this version is only available with an 8.5 mm backplate, which may be too big for most children.

Most pediatric patients will be phakic or aphakic, so the appropriate keratoprosthesis power should be chosen based on the axial length of the eye. In the rare instance that the child is pseudophakic, and the intraocular lens is to remain in place, a pseudophakic keratoprosthesis can be ordered. In addition to the power of the optic, the diameter of the back plate must be selected. There is a smaller keratoprosthesis with a 7.0 mm back plate (instead of the typical 8.5 mm back plate) for use in children. The donor graft diameter should be 0.5 mm greater than the host trephination diameter, and not less than 7 mm.

Prior to proceeding with surgery, the surgeon should examine the keratoprosthesis components (front plate, back plate, locking ring, and locking pin). The donor cornea is trephined twice: the outer trephination is created with a standard corneal donor trephine and the inner opening is made with a 3.0 mm skin biopsy punch (included with the keratoprosthesis).

To assemble the keratoprosthesis, position the optic with the front plate facing down. Then center the donor cornea's inner opening over the stem, endothelial side up. Next, center the back plate over the stem, with the concave side up. Finally, push down the stem onto the donor cornea using the locking pin. When the locking ring is properly positioned, a snap will be heard. Once the keratoprosthesis is assembled, it is inspected under the microscope and then placed in a sterile container in corneal preservation medium until needed.

Surgery: Following construction of the keratoprosthesis, surgery proceeds much like standard penetrating keratoplasty. The patient's cornea is removed using a trephine and corneal scissors, and is sent for pathologic assessment. An iridectomy is performed, typically superiorly. If the patient is phakic, cataract extraction must be also performed. Unlike in adults, placement of an intraocular lens is not recommended.

The assembled keratoprosthesis is brought to the operative field and is secured with 16 interrupted 10-0 nylon sutures. After placement of the first four cardinal sutures position a 2–3 mm corneal shield over the keratoprosthesis optic. At the conclusion of surgery, corneal sutures are buried in the host tissue, the wound checked for leakage, and medications are given peribulbar vancomycin, 25 mg in 0.5 ml, ceftazidime 100 mg in 0.5 ml, and triamcinolone 20 mg in 0.5 ml. A bandage contact lens (included with the keratoprosthesis) is placed followed by a semi-pressure patch and Fox shield.

The decision to perform additional surgeries at the time of keratoprosthesis will depend on the indication for surgery. Surgeries are often performed by a team of surgeons, including a glaucoma specialist to place a glaucoma valve and a retina specialist to perform a pars plana vitrectomy.

Postoperative Care: Topical fluoroquinolone and vancomycin, 14 mg/ml with benzalkonium chloride preservative, are both initially administered four times daily and tapered to once daily. Topical prednisolone acetate 1% is started hourly, but can be tapered more quickly than in penetrating keratoplasty and, unlike in other forms of transplantation, long-term use of topical corticosteroid may not be necessary.

Close, lifelong postoperative care is especially critical, due to the severe complications that can occur even years after surgery. Patients must plan on long-term use of antibiotics and soft contact lenses and monitoring for glaucoma as well as infection. Figure 8.2 shows a child before and after implantation of a type 1 Boston keratoprosthesis.

Ocular Surface Surgery

In addition to the various forms of keratoplasty described above, in rare cases, other types of corneal surgery are performed on children.

Ocular Surface Reconstruction for Limbal Dermoid Cyst

Indications: Though ocular surface tumors are rare in children, benign ocular tumors, most commonly dermoid cysts, can occur. Figure 8.3 shows dermoids of varying size. Depending on the size and location of the tumors, they may need to be removed, either to improve vision or for cosmetic reasons (Pirouzian 2013; Golubovic et al. 1995). When lesions are removed, there are several options for ocular surface reconstruction, depending on the residual defect. Small dermoids may be removed through simple excision, though this may increase the risk of pseudopterygium formation (Lang et al. 2014). For relatively superficial dermoids, amniotic membrane transplantation may help with the healing process. For deeper dermoids, a lamellar patch graft maybe necessary to decrease astigmatism and preserve globe integrity. We will discuss removal of limbal dermoids and reconstruction with amniotic membrane and lamellar keratoplasty (Asoklis et al. 2011).

The choice of reconstructive technique will depend on the depth of the lesion, which may be difficult to determine prior to surgery. The best way to determine the dermoid depth is with a UBM (ultrasound biomicroscopy) during an exam under anesthesia either prior to surgery or at the beginning of surgery. If the dermoid is medium to large and you do not have access to irradiated corneal tissue (VisionGraft, Tissue Banks International, Baltimore, Maryland) it is best to perform the UBM prior to the date of surgery, in case fresh corneal tissue will need to be ordered.

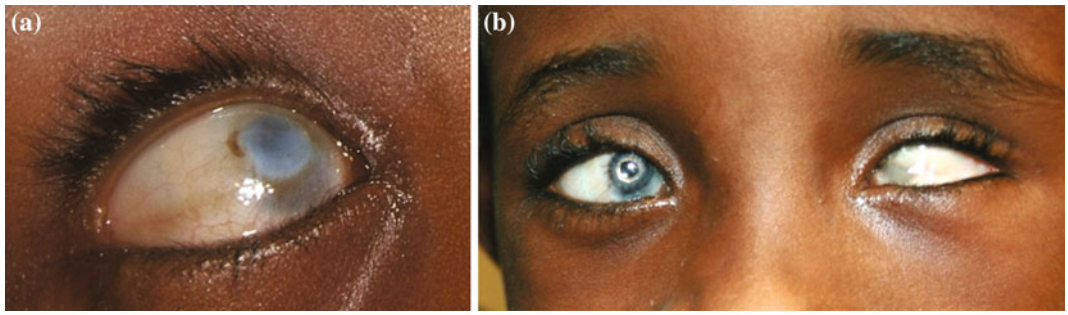

Fig. 8.2 **a** Before and after photographs of a child with bilateral congenital corneal opacification who underwent implantation of a type 1 Boston keratoprosthesis in his right eye. **b** Vision improved initially, but the child eventually developed corneal melting, leading to extrusion of the keratoprosthesis

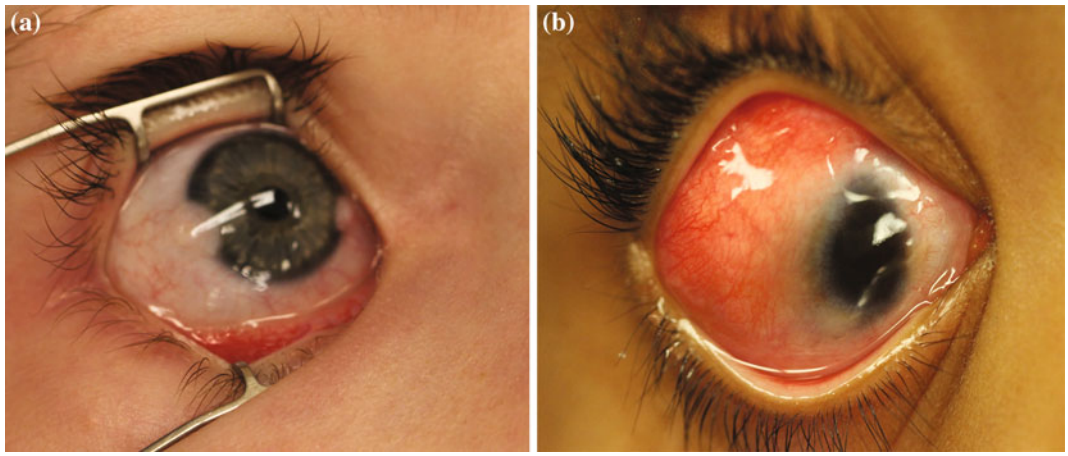

Fig. 8.3 Dermoids can vary greatly in size and appearance, even within one eye. The child in **a** has 2 separate dermoids, a larger one temporally and a smaller one nasally. The child in **b** has a much larger, more diffuse dermoid

Surgical Technique

Tissue options:

Amniotic membrane transplantation: Amnio-Graft (Bio-tissue, Miami, FL) is a cryopreserved amniotic membrane sheet that comes in several sizes (1.5 × 1.0 cm, 2.0 × 1.5 cm, 2.5 × 2.0 cm, and 3.5 × 3.5 cm).

Lamellar keratoplasty: VisionGraft (Tissue Banks International, Baltimore, Maryland) is a gamma-irradiated cornea that remains stable at room temperature for up to 2 years. It is available in full or split thickness. The split thickness graft is available in whole, half, or third cornea sizes.

Surgery: First, mark the borders of the dermoid using a sterile skin marker, then using diamond or crescent blade, find the cleavage plane and starting from the corneal side remove the entire dermoid. For deep dermoids, the risk of globe perforation can outweigh the goal of complete removal. The lesion is sent for pathology with orientation specified. Other tumors, including lacrimal gland choristoma can exist in children (Fig. 8.4).

Once the lesion is removed, the resulting corneal defect is repaired with amniotic membrane application or with a lamellar graft or both.

If the defect is shallow, amniotic membrane can be applied either with fibrin glue or sutures. We prefer glue in children if available, since it is better tolerated. If sutures are to be used, we

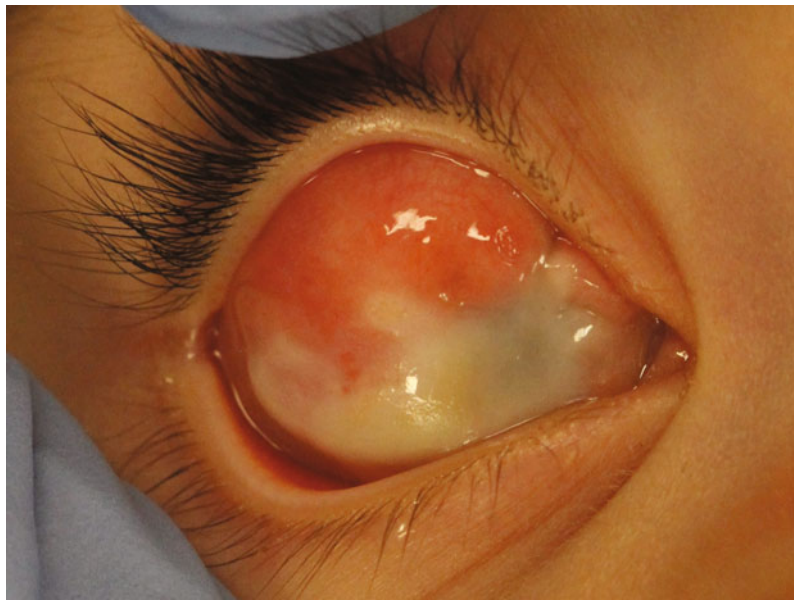

Fig. 8.4 Though rare, children can develop ocular surface tumors other than dermoids. This child presented with a large conjunctival mass that was found to be a lacrimal gland choristoma. These tumors are typically solid, pink, present at birth, and located in the temporal epibulbar area

recommend 10-0 vicryl, so they will not need to be removed.

For deeper lesions, a lamellar patch graft may be necessary. Either fresh or cryopreserved tissue maybe used, and the graft should be cut to match the defect. For large defects, a corneal trephine maybe used and for smaller defects, a skin punch maybe used. Regardless of size of graft, we typically use 8 interrupted 10-0 nylon or vicryl sutures.

Postoperative Care: Postoperative care is focused on reducing inflammation and scarring, as well as preventing infection. A course of topical antibiotics and steroids are given. The antibiotic drops can be discontinued once any epithelial defects are healed. Steroids are typically continued for 4–6 weeks, depending upon clinical course.

Amniotic Membrane Grafting for SJS/TENS

Indications: In the acute phase, the most beneficial surgical intervention is amniotic membrane grafting, which has dramatically improved the lifetime prognosis for patients with SJS/TENS. Darren Gregory has shown that timing of amniotic membrane grafting is critical: the sooner the better, and no longer than 5 days from the initial diagnosis (Gregory 2008; Shay et al. 2009; Fu et al. 2010; Gregory 2011). Any child with a suspected diagnosis of SJS/TENS should be examined urgently by an ophthalmologist, and if there is any ocular involvement, especially corneal epithelial defects, symblepharon, or eyelid margin

excoriation, amniotic membrane grafting should be performed as soon as possible. If the child is not stable for surgery, AmbioDisk (IOP Ophthalmics, Costa Mesa, CA) or ProKera (Bio-tissue, Miami, FL) can be applied at the bedside as a temporary treatment until surgery can be arranged. Since AmbioDisk and ProKera only treat the corneal and limbal surfaces, they are not adequate substitutions for amniotic membrane grafting.

Surgical Technique

Tissue preparation: Commercially available amniotic membrane, the innermost layer of the placenta, composed of a thick basement membrane and an avascular stroma, is available in several versions. The ProKera is a single device that combines amniotic membrane with a stabilization ring, which is placed in the eye much like a large, rigid contact lens. The AmbioDisk is a flat circular piece of amniotic membrane that is placed on the cornea and then either held in place with a soft contact lens or sutured into position (if performed in a surgical setting). As mentioned above, these are useful at the bedside as temporizing measures until the child can be taken to the operating room. AmnioGraft (Bio-tissue, Miami, FL) is a cryopreserved amniotic membrane sheet that comes in several sizes (1.5 × 1.0 cm, 2.0 × 1.5 cm, 2.5 × 2.0 cam, and 3.5 × 3.5 cm). In order to treat the entire ocular surface, including upper and lower eyelids, the largest (3.5 × 3.5, size "C") should be used. Depending on the extent of eyelid involvement, more than one sheet may need to be used.

Surgery: Multiple techniques for amniotic membrane grafting have been described, and techniques can be modified based on the extent of ocular injury. Dr. Darren Gregory has shown that by suturing cryopreserved amniotic membrane to the entire ocular surface, the long-term visual outcomes of patients with SJS/TENS are dramatically improved (Gregory 2008; Shay et al. 2009; Fu et al. 2010; Gregory 2011).

First the lashes are cut, and then amniotic membrane is spread over the tarsal conjunctiva and fornix. The membrane is then reflected to cover the bulbar conjunctiva, using a muscle hook. The membrane must cover all affected surfaces. Once the membrane is properly positioned, it is sutured to the skin using a double-armed 4-0 silk or 6-0 prolene mattress suture. This is performed on each involved eyelid. The graft can be attached to the limbus either using a 10-0 nylon running suture to the episclera or a symblepharon ring.

Postoperative Care: These children must be closely monitored for disease progression, and depending on the severity of the ocular pathology, application of membranes may need to be repeated.

During the acute period the primary goals are to prevent infection and reduce inflammation and scar formation. The use of steroids, both systemic and ocular, is controversial. Even antibiotics can be risky, since the drug that triggered the episode may have been an antibiotic.

Care of these children is especially challenging, since they are often systemically very ill. Many of these patients require extensive care in a specialized burn unit, so it is important for the ophthalmologist to coordinate with the child's other medical providers.

Discussion

Pediatric corneal surgery is extremely challenging, but also incredibly rewarding. Due to the higher risk of surgery in this patient population, surgery should not be performed unless both the surgeon and the family are committed to supporting the child before, during, and after the surgery. The risk of surgery in a child is great, but the potential reward is great as well. Knowing the risks and problems associated with corneal surgery in these special patients should not scare us away from pediatric corneal surgery, but it should motivate us to try to improve it.

Compliance with Ethical Requirements Christina Prescott and Kathryn Colby declare that they have no conflict of interest. No human or animal studies were performed by the authors for this chapter.

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Corneal Diseases in Children: Contact Lenses

9

Deborah S. Jacobs and Aaron Barrett

Introduction

Advances in the field of contact lens have allowed for safe and practical contact lens wear in the pediatric population. Children with large refractive errors, symptomatic anisometropia, irregular astigmatism, or ocular surface disease, particularly during the critical period for amblyopia, stand to benefit the most from contact lens correction. When prescribed in the appropriate setting, contact lenses can be used to treat infants (birth to 2 years of age), young children (2–6 years), children (7–12 years), or teenagers (13–17 years). Although some attention will be paid to cosmetic and activity-related correction of refractive error in children, the main purpose of this chapter is to review the medical uses of contact lenses in children.

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General Principles: Tolerance and Compliance in Children

Any contact lens type and wearing schedule used in adults can be used in children. Although it is common for parents to be concerned about suitability of contact lens wear in children, children and teens fare no worse in compliance than other wearers and they have demonstrated full capability in the handling and care of their lenses (Soni et al. 1995; Walline et al. 2013). As with any contact lens wear, there are risks associated with contact lens wear in the pediatric population. It is estimated that 23% of pediatric emergency department visits for medical device adverse events in the United States are due to ocular complications from contact lens wear (Wang et al. 2010). Adverse events have been associated with long-term soft contact lens use, multipurpose solutions, and extended wear. However, adverse events with soft contact lens wear in children are predominantly mechanical in nature, and significant infiltrative events are few. Risks for adverse events are higher in teenagers, especially in late adolescence, whereas children present with significantly fewer adverse events comparatively (Chalmers et al. 2011; Wagner et al. 2011; Sankaridurg et al. 2013). Relative contraindications to pediatric cosmetic contact lens wear may include significant abnormalities involving the eyelid, tear film, or ocular surface. Also, the risks of complications associated with contact lens wear should be considered against the protective benefit of spectacles, particularly for monocular patients.

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General Principles: Caregiver Issues

There are many factors that determine if contact lens wear is appropriate for an individual child. These include the child's capacity for independent application and removal and lens care, or compliance with caregiver performance of those activities. Other factors that may influence the decision to proceed with contact lens wear include parental and child motivation, maturity of the child, medical risk, cost, and the caregiver's personal experience with contact lens wear. Parents or children may raise the issue of contact lens wear for correction of refractive error for cosmetic reasons or for participation in sports or outdoor activities, seeking general advice from the eye care provider. While 13 years is the mean age that children are fitted with contact lenses, safe and successful lens wear has been demonstrated in children as young as 7 years of age.

General Principles: Contact Lenses for Cosmetic Correction of Refractive Error in Children

There is significant evidence that children are capable of successfully wearing contact lenses, however, only approximately 3% of new contact lens fits in the United States are in children between the ages of 6 and 12 years old (Efron et al. 2011). Children and teenagers have been shown to have similar contact lens-related adverse events, compliance, wearing times, and ocular health (Walline et al. 2013). Contact lenses can improve a child's quality of life, increase self-esteem, and allow for more participation in physical activities than spectacles. Many patients who use contact lenses report greater comfort, better field of vision, and improved quality of vision over spectacles (Walline et al. 2006, 2007, 2009; Rah et al. 2010).

General Principles: Complications of Contact Lens Wear in Children

The most serious risk of contact lens wear in children is the development of microbial keratitis, which can lead to vision loss. Microbial keratitis is a rare complication of contact lens use. The most frequent pathogen is the bacteria *Pseudomonas aeruginosa*, but keratitis can also be caused by unusual organisms such as Acanthamoeba and fungi (Kilvington and Lonnen 2009; Uno et al. 2012). Investigations have demonstrated that overnight wear, regardless of contact lens material, increases the likelihood of microbial keratitis with daily wear of rigid gas permeable lenses associated with the lowest risk. Other modifiable risk factors for developing microbial keratitis include the degree of exposure to infectious organisms, failing to wash hands before lens handling, choice of cleaning, disinfection and storage solutions, adherence to recommended replacement schedule, and practices with regard to use of solutions and storage cases (Stapleton et al. 2008, 2012, 2013). Although there are many lenses are approved by the Food and Drug Administration for extended wear, the risks, benefits of this, and other lens types should be presented to patients and caregiver when contact lenses are being considered.

Review of Contact Lens Types, with Pediatric Considerations

Before fitting a child for contact lenses, an ocular history and comprehensive medical eye examination should be performed with particular attention paid to the patient's ocular surface and function, hygiene, and their ability to adhere to proper lens care. The choice of contact lens for a pediatric patient depends on the indication for fitting, required wearing schedule, and design features necessary to achieve the therapeutic or

refractive goals. Lens material and intended wearing schedule are two variables to be taken into account in contact lens selection for pediatric patients.

Contact Lens Materials

Rigid Gas Permeable Lenses

Advantages of rigid gas permeable (RGP) lenses in children include the ability to correct irregular astigmatism, high oxygen permeability, ease of handling, low cost, and low protein and bacterial adherence. Conversely, pediatric gas permeable wearers experience less comfort, more frequent lens replacement due to loss, and shorter wearing times than those wearing soft contact lenses and are therefore less likely to adapt long term (Shaughnessy et al. 2001; Jones-Jordan et al. 2010). Soft lenses have eclipsed rigid gas permeable lenses for the correction of refractive error in children as well as adults, but gas permeable contact lenses are the lenses of choice in pediatric patients who have corneal surface irregularities or high refractive error, and in some cases of dry eye. Generally, fitting RGP lenses is more skill and time intensive than fitting soft lenses and may require a period of adapation on the part of the patient, all of which are deterrents to clinicians choosing this modality of correction. Rigid gas permeable lenses used in overnight orthokeratology (OOK) which involves overnight wear of a contact lens to reshape the cornea are discussed in Section "Contact Lenses for Myopia Control" below.

Soft Contact Lenses

Soft contact lenses are the primary lens type prescribed for pediatric patients. They are available in wide variety of wearing schedules and materials to suit the needs of the patient. Children have been shown to adapt to and care for soft contact lenses at higher rates that for other lens materials (Walline et al. 2004; Lam et al. 2011).

Hydrogel Lenses

There are a variety of hydrogel materials used in commercially available soft contact lenses. These lenses rely on increased water content to elevate the level of oxygen permeability (Dk) of the contact lens. Higher Dk values increase the amount of oxygen supplied to the cornea decreasing hypoxia-related adverse events. The advantages of hydrogel lenses are comfort, lens stability, and ease of fitting. Disadvantages include the inability to mask corneal irregularity, relatively lower Dk compared to silicone hydrogel lenses, difficulty in handling for children, poor durability, high loss rate, and potential infection if used for extended wear. This material is often used for daily disposable or daily wear lens schedules and is commonly indicated for low and moderate refractive error or any need for tinted or decorative lenses.

Silicone Lenses

The use of silicone lenses is generally confined to the treatment of infantile aphakia after cataract extraction. Silicone lenses (SilSoft, Bausch + Lomb, Bridgewater NJ) are made of 100% silicone polymer. Silicone allows for high oxygen permeability through the thicker lenses required meet the high hyperopic requirement of infantile aphakia. Very high oxygen permeability reduces the tendency for hypoxia under closed lids which is important for infants who do not have day-and-night sleep cycles to allow for "daily wear" as might be possible in older children and adults. Poor wetting is a feature of this material in comparison with hydrogel materials, leading to accumulation of deposits on front and back surfaces, particularly if frequent removal for cleaning is problematic. Silicone lenses can be worn on a daily or extended wear basis with replacement annually or sooner as tendency toward deposits might require. Silicone lenses are thicker and more rigid than soft lenses allowing for easier handling, they tend to adhere to the globe and thus there is higher retention than either soft or rigid gas permeable lenses. They tend to be comfortable with no requirement for adaptation. The advantages of silicone lenses as far as comfort, low loss rate, easy handling, and high Dk for safe continuous wear, especially during hours of sleep, make them the first choice for aphakic infants and toddlers. Disadvantages include high cost, heavy lipid deposits especially

after 3 years of age, inability to mask any but the lowest levels of corneal irregularity, and a limited range of fitting parameters.

Silicone Hydrogel

Silicone hydrogel materials were developed in the last two decades in an effort to increase oxygen permeability to the cornea for the purpose of safer extended wear of contact lenses. It was postulated that increased oxygen transmission would reduce the likelihood of microbial keratitis that is associated with closed lid wear. Improved oxygen delivery to the cornea may also be advantageous in cases of prior hypoxic stress with neovascularization and haze. Silicone hydrogel (SiHy) lenses are more rigid than hydrogel lenses conferring ease of handling and lens stability on the eye, both of which are advantageous in young children, as is their very high Dk which is advantageous for young children who may nap in their lenses. Disadvantages of silicone hydrogels are the inability to mask any but lowest levels of corneal irregularity, higher cost, and tendency to acquire deposits due to the hydrophobic nature of the lens. Although generally more comfortable than RGP or silicone lenses, their rigidity may make them less comfortable than hydrogel lenses. SiHy contact lenses are useful for aphakia, higher refractive errors, and are labeled for therapeutic as well as cosmetic use.

Specialty Lenses

Specialty lenses are lenses of special shape or material(s) that are ordered custom per patient rather than kept in inventory because of the relative paucity of demand. They are fit from trial sets and typically require custom ordering based on specification provided by a clinician with special interest, experience, and training in these lenses. Types of specialty lenses include corneal RGP lenses designed for keratoconus such as the Rose-K (Menicon America, Waltham MA.), SynergEyes hybrid lenses which are comprised of a central RGP optic zone surrounded by a soft hydrogel skirt (SynergEyes, Inc., Carlsbad CA), and large diameter RGP lenses. Large diameter RGP lenses can be categorized as corneo-scleral, mini-scleral, or scleral based on diameter, but challenges with application and removal issues make them infrequent choices in the pediatric age group. Prosthetic replacement of the ocular surface ecosystem (PROSE) uses FDA-approved prosthetic devices for the treatment of distorted corneas and certain ocular surface diseases (Rosenthal and Cotter 2003; Stason et al. 2010). PROSE treatment has been shown to be a successful treatment option for pediatric patients especially after failure of conventional therapy in a broad range of ocular surface and refractive disorders in children (Gungor et al. 2008).

Contact Lens Wearing Schedule

Daily Disposable Lenses

Daily disposable lenses are discarded daily, which eliminates the need for storage and cleaning. Daily disposable lenses are available in both hydrogel and silicone hydrogel materials in an increasing range of spherical and toric powers. Due to simple care regimen, low cost, and high comfort, these lenses are ideal for pediatric patients. Daily disposable lenses are also useful for patients prone to deposits due to allergy or atopy or sensitivities to disinfection, cleaning, and storage solutions. They are also useful for patients who use lenses only sporadically as the risks of storage are eliminated.

Daily Wear Lenses

Daily wear refers to soft contact lenses that are inserted and removed daily. Replacement schedules of daily wear lenses are based on the soft lens material, the patient's ocular surface environment, manufacturer recommendations, and the practitioner's preference. Although several hydrogel and silicone hydrogel lenses are approved for extended wear, daily wear of these material is recommended in general to reduce the likelihood of microbial keratitis, and especially for patients showing signs of hypoxia and those with a history of microbial keratitis. These lenses must be cleaned after nightly removal and then disinfected and stored until next use. Multipurpose solutions have been developed for this

purpose, as have peroxide systems, which are generally associated with the lowest rates of microbial keratitis and hypersensitivity.

Extended Wear Lenses

Extended wear is the continuous use of contact lenses including wear under closed eyelids. The newest lenses approved for extended wear are made of high Dk silicone hydrogel materials that reduce hypoxic stress to the cornea. These lenses can be useful in situations in which napping in lenses is likely, or when daily insertion, removal, and disinfection is problematic. Extended wear increases the likelihood of accumulation of deposits, so it may be advisable to clean and disinfect lenses weekly, rather than encourage patients to wear them for the maximum schedule of continuous wear. Typically lenses are approved for two or four weeks of extended wear. There are higher water content hydrogel lenses approved for extended wear, however these are typically reserved for patients who are intolerant of silicone hydrogel lens or who require parameters that are unavailable in silicone hydrogel materials.

Contact Lens for Correction of Refractive Error During the Critical Period for Amblyopia

Aphakia

Congenital cataract is one of the major causes of visual impairment in infants. Removal of the cataract at an earlier age leads to increased visual acuity and contrast sensitivity while decreasing the risk for strabismus. Surgery should be followed immediately by full-time optical correction of the resulting aphakia. Prompt and aggressive contact lens management of an aphakic child can lead to excellent visual acuity outcomes (Chen et al. 2010; Bothun et al. 2013). Treatment of an aphakic child with a contact lens is associated with a lower cost of treatment as well as reduced stress upon the caregivers within the first 3 months of surgery (Carrigan et al. 2013; Celano et al. 2013).

A recent report from the Infant Aphakia Treatment Study compared the visual outcomes of infants optically corrected with contact lenses versus intraocular lenses following unilateral cataract surgery. The study concluded that there was no significant difference between the median visual acuity of operated eyes in children who underwent primary intraocular lens implantation and those left aphakic and treated with contact lenses. Significantly more adverse events and additional intraoperative procedures were noted in the intraocular lens group. For an infant younger than 7 months of age with a unilateral cataract, the authors recommend leaving the eye aphakic and correcting refractive error with a contact lens (Lambert et al. 2014).

Following optical correction of a unilateral aphakic eye, the sound fellow eye can be occluded with a high-plus contact lens to avoid the development of amblyopia. This form of optical penalization has the potential as an effective alternative to occlusive patching for those with compliance issues, however, more data is currently required to assess the long-term safety and visual outcome of this method (Saltarelli and Motley 2013).

Material Options for Aphakic Children

The choice of contact lens for aphakic children is limited due to the technical difficulties of producing high-plus lenses that are also highly oxygen permeable and therefore safe for the patient to wear. Extended wear lenses are the preferred modality for aphakic infants. Benefits include oxygen delivery to the cornea especially during sleep, ease of identification and handling, and infrequent need for replacement. The SilSoft (Bausch + Lomb, Bridgewater NJ) lens is currently the only extended wear contact lens approved by the FDA for the treatment of pediatric aphakia. It is manufactured in steeper base curves, higher powers, and smaller diameters appropriate for the infant eye. Indefinite wear of SilSoft is common up to the age of 3, with an average lens replacement of 5.6 lenses/eye/year. From the age of 3, deposit formation is the determining factor for refitting a child with silicone hydrogel, hydrogel, or rigid gas permeable

contact lenses (Aasuri et al. 1999; de Brabander et al. 2002; Saltarelli 2008). Hydrogel or silicone hydrogel lenses are relatively easy to fit in patients who have previously worn silicone lenses for infantile aphakia, with similar comfort allowing for rapid adaptation. However, soft lenses are prone to dehydration and are often rubbed out or fall out. High-plus hydrogel lenses also have low oxygen transmissibility, leading to corneal hypoxia and related complications. Aphakic children with moderate to high or irregular astigmatism may be best served by conversion to daily wear of RGP corneal lens or hybrid lenses to correct astigmatism fully thus reducing likelihood of astigmatic amblyopia. Gas permeable and hybrid contact lenses can provide high oxygen transmissibility and superior optics at high-plus powers. Either can be custom made for an optimal fit for better centration on the cornea of an aphakic infant or child.

Irregular Cornea

Pediatric corneal disease may result in an irregular corneal surface from infection, trauma, keratoconus, or prior surgery. Rigid gas permeable contact lenses offer optimal correction for visual rehabilitation and avoidance of amblyopia. Hybrid lenses are an option if tolerance or instability is an issue, but these patients must be monitored for tight lens syndrome and hypoxia. Partial correction with a toric or SiHy spherical lens may be preferable to no correction at all for patients who are intolerant of RGP lenses. Finally, scleral lenses and PROSE treatment are an option for children as young as age 6 with irregular corneas, with cooperation for daily insertion and removal of a soft lens a sign that there is capacity for cooperation for application and removal of scleral lenses or the devices used in PROSE treatment.

Corneal Irregularity After Trauma or Infection

Ocular trauma is common among the pediatric population and timely correction of any induced refractive error is especially important to avoid amblyopia in young children. Microbial infections, herpes simplex virus, and recurrent blepharoconjunctivitis are processes that can result in an irregular corneal surface, especially if treatment is delayed. Once the acute phase of the keratitis or trauma has resolved, rigid gas permeable lenses may be fitted to improve visual acuity and reverse or protect against amblyopia for children within the critical period. Rigid gas permeable lenses are ideal for a traumatized pediatric eye as they are safe, well tolerated, and inherently correct irregular astigmatism (Pradhan et al. 2014). However, if corneal insult results in only mild surface irregularities, then soft contact lenses might be better tolerated and can potentially yield excellent vision. Contact lenses with the highest oxygen permeability should be selected in these instances to promote ocular healing and reduce hypoxic complications. Traumatic aniridia, with photophobia and poor cosmesis may be best treated with a soft prosthetic contact lens. Due to the low oxygen permeability of these hydrogel lenses, wearing time should be limited. Scarring of the cornea after infection or trauma can be accompanied by neovascularization of the cornea, which can be exacerbated by contact lens wear, so children fitted with contact lens after infection or trauma must be followed closely. Fitting a contact lens to a scarred cornea can delay or avoid the need for penetrating keratoplasty, which is high risk in children (Smiddy et al. 1989; Kok et al. 1991; Kanpolat and Ciftci 1995).

Corneal Irregularity from Keratoconus or Other Corneal Ectasia

Kerataconus is a bilateral, corneal ectasia that is often asymmetric. Typical presentation is in the second decade with progression until the age of about 30–40 years before spontaneous stabilization. Young age is associated with faster disease progression and more severe forms of keratoconus, with an inverse relationship between age and severity. Early detection and close monitoring are therefore crucial in pediatric patients (Leoni-Mesplie et al. 2012). In the initial stages of keratoconus, many patients can be managed with toric soft contact lenses if the cornea

demonstrates regular astigmatism. As the disease progresses, RGP contact lenses are the primary choice to correct for refractive error as the regular surface of the hard contact lens and the tear lens that forms beneath it compensates for the irregular cornea. Specialty lenses including hybrid and scleral lenses and PROSE treatment should be considered if conventional fitting attempts fail, with the approach in adolescents identical to that for adults.

High Refractive Error

High Spherical Refractive Error

In children with high power requirements, there are advantages to contact lenses over spectacles, including larger retinal image sizes in myopia and a normal field of view in hyperopia. Other benefits of contact lens correcting include elimination of induced prism, decreased aberrations, and elimination of large or heavy spectacle frames to maintain in place.

Anisometropia

For pediatric patients with high degrees of axial or refractive anisometropia, contact lenses effectively decrease aniseikonia thereby optimizing binocularity. Increased cortical fusion is essential in children to prevent the development of amblyopia, with earlier treatment associated with better outcomes. Contact lens treatment of anisometropia in children provides refractive error correction, reduces the likelihood of amblyopia, and relieves the patient of having disproportionate lenses and image magnification from spectacles (Winn et al. 1988; Roberts and Adams 2002).

High Cylindrical Refractive Error

Correction of regular astigmatism may be an indication for contact lenses in the pediatric patient. Rigid gas permeable lenses and hybrid lenses offer superior optics to toric soft lenses for moderate levels of astigmatism. Scleral lenses and PROSE treatment may be useful for higher levels of regular astigmatism in which spectacles or RGP or specialty lenses are not tolerated.

Contact Lenses for Myopia Control

Approximately 33% of the population in the United States in myopic, and some Asian countries report that up to 80% of children are nearsighted. Contrary to previous reports, soft contact lens wear in the pediatric population does not contribute to myopic progression when compared to spectacle wear (Horner et al. 1999; Walline et al. 2008). A Cochrane review investigating the interventions to slow the progression of myopia in children concluded that the most likely treatment to slow myopia progression thus far is topical use of anti-muscarinic agents (Walline et al. 2011). Potential side effects of available concentrations and lack of commercial availability of dilute concentration limits adoption of this approach. Recent evidence suggests that emmetropization in the human eye is modulated by hyperopic retinal defocus. Corneal reshaping or multifocal soft contact lenses with a distance center are promising options to reduce peripheral hyperopic defocus (Walline et al. 2011).

Overnight Orthokeratology

There are reports of suppression of axial elongation and slowed myopic progression through the practice of overnight orthokeratology (OOK), also known as corneal refractive therapy (CRT), using new RGP materials with very high oxygen transmissibility and new “reverse geometry” or centrally flat designs (Watt and Swarbrick 2007; Kakita et al. 2011; Cho and Cheung 2012; Santodomingo-Rubido et al. 2012a, b). There is excess risk of microbial keratitis with overnight wear of any contact lens, and there may be higher risk in young children. Small studies of orthokeratology in the United States and internationally demonstrate safety and effectiveness for myopia

correction in children (Walline et al. 2004; Mika et al. 2007; Koffler and Sears 2013; Santodomingo-Rubido et al. 2012a, b), but reports of infectious keratitis including infections with *P. aeruginosa* and acanthamoeba with poor visual outcomes have emerged.

There has been significant increase in contact lens-related microbial keratitis in children age 16 and younger in Taiwan, accounted for by cases associated with OOK (Lee et al. 2014). Of 138 pediatric patients with infectious keratitis seen at a single center in Hong Kong during a 5-year period, 32 patients wore soft contact lenses while nine were using RGP lenses for OOK (Wong, Lai et al. 2011). Daily wear of contact lenses may be a safer approach to myopia correction and myopia control in children.

Multifocal or Aspheric Contact Lenses

Evidence suggests that variations of distance center multifocal soft contact lenses can be effective in reducing hyperopic defocus, myopic progression, and axial length elongation in pediatric patients (Anstice and Phillips 2011; Sankaridurg et al. 2011; Walline et al. 2013; Lam et al. 2014). There is need for long-term randomized clinical data to fully assess the effectiveness and safety of soft multifocal contact lenses in young children in whom myopic progression has begun.

Orthoptics and Contact Lenses

Amblyopia

Amblyopia is the most frequent cause of visual impairment in the pediatric population. Treatment of amblyopia is usually undertaken with use of an occlusive eye patch but daily wear of an opaque contact lens can be an effective occlusion method for children with various practical and social impediments to patching. The advantages of occluding contact lenses for amblyopia are full-time occlusion and good patient compliance, with meaningful improvement observed in many children under 10 years of age (Eustis and Chamberlain 1996; Anderson et al. 2006; Michaud and Carrasquillo 2010). However, clinical judgment must be exercised when patching the sound eye with an occlusive contact lens as there is potential for increased risk of infection and patients lose the protective feature of spectacles.

Congenital Nystagmus

Contact lenses can partially suppress congenital nystagmus but the mechanism for this suppression remains uncertain. Thurtell et al. recommends correcting congenital nystagmus with a high-minus contact lens in combination with a high-plus spectacle lens. This impairs all other eye movements such that the patient must be stationary to achieve image stabilization and the field of view is limited. Due to these limitations they suggest contact lenses only for severe, intractable oscillopsia (Thurtell and Leigh 2012). Biousse's cross-over study of four patients with congenital nystagmus indicated that much of the clinical improvement observed with contact lenses resulted from an improved correction of their refractive error rather than from a true damping effect (Biousse et al. 2004).

Decorative/Occluding Lenses

Children with disfigured eyes, photobia, or color perception anomalies can benefit from a tinted or decorative contact lens. Tinted lenses can be utilized as an alternative treatment for the symptoms of cone dysfunction syndromes such as achromatopsia. These lenses have been shown to relieve photophobia and mild nystagmus while improving visual acuity and color perception (Rajak et al. 2006; Schornack et al. 2007). Decorative lenses are available in a wide range of prints and patterns to increase cosmesis in patients with coloboma or a disfigured eye. Occluding lenses can be used in amblyopia therapy or to decrease visual symptoms in children with severe diplopia, intolerable photophobia, albinism, or aniridia (Eustis and Chamberlain 1996; Astin 1998).

Ocular Surface Disease

Therapeutic Lenses for Pediatric Ocular Surface Disease

There is a role for contact lens in the management of ocular surface disease (OSD) in children. Categories of OSD in which contact lenses can be useful for support of the ocular surface include

- Stevens–Johnson syndrome
- Chemical, radiation, or thermal injury
- Congenital corneal anesthesia syndromes
  Hereditary sensory and autonomic neuropathy
  Goldenhar syndrome
  Mobius syndrome
- Acquired corneal anesthesia syndromes
  HSV keratitis
  Tumor or vascular malformation
  After surgery for tumor or vascular malformation
- Exposure keratitis
- Atopic, vernal, and allergic keratoconjunctivitis
- Chronic ocular Graft-Versus-Host Disease
- Persistent Epithelial Defect
- Ectodermal dysplasia

The benefits of therapeutic lenses in ocular surface disease can be attributed to high oxygen transmission, mechanical support of the corneal epithelium and the epithelial-mucin interface, protection from adverse environment, protection from abnormal or dysfunctional lid margins, and relief of pain. Therapeutic soft lenses, scleral lenses, and PROSE treatment can be useful in the management of ocular surface disease in children. Patient cooperation is typically the limiting factor in whether therapeutic lenses are an option in the pediatric age group. Because of low cost, universal fit, and wide availability, silicone hydrogel lenses are typically the initial choice for therapeutic or bandage lenses in the acute setting. Alternatively, large diameter RGP lenses and PROSE treatment are good options for long-term management of pediatric patients suffering from chronic ocular surface disease in that they offer correction of the irregular astigmatism that often accompanies ocular surface disease and are associated with lower risk of microbial keratitis. Patients with neutrophic corneas might be considered good candidates as the lack of corneal sensation eliminates the aversive responses that are typical with attempted contact lens insertion in children. Typically, patient cooperation for soft lens insertion and removal is necessary before one can consider large diameter RGP lenses or PROSE treatment, as cooperation for daily application and removal is required for these latter options. Extended wear, with its attendant risks, an exchange for new or disinfected lenses, periodically by caregivers or physician, in office or under anesthesia, is an option only for therapeutic soft lenses.

Soft Contact Lenses for Therapeutic Use (Bandage Lenses)

Soft contact lenses dispensed or prescribed for therapeutic use are sometimes referred to as bandage lenses. “Bandage lens” is a term that distinguishes such a lens from one that used to correct refractive error. Typically lenses that have been FDA-approved for this purpose are labeled “for therapeutic use.” Hydrogel lenses are an option for therapeutic use, but the lower low Dk of these materials may contribute to hypoxia, hypercapnia, and acidosis of the cornea predisposing to infections, infiltrates, and neovascularization. Silicone hydrogel materials, because of higher oxygen transmission, are theoretically a better choice for bandage lenses, although if there is poor retention of silicone hydrogel bandage lens in standard diameters, hydrogel lenses which come in very large diameters may be considered. Some patients accumulate excessive deposits in silicone hydrogel lenses and hydrogel might be considered if excessive deposits prove to be a problem. The effectiveness of silicone hydrogel lenses has been reported in a series of pediatric patients with

a broad spectrum of ocular surface disease (Bendoriene and Vogt 2006). Cautious use of bandage contact lenses, along with other supportive therapies, is recommended as helpful in preventing progressive corneal damage in pediatric patients presenting with corneal breakdown in congenital corneal anesthesia (Ramaesh et al. 2007). The concomitant use of prophylactic antibiotics is controversial, with potential for acquired resistance possibly outweighing any advantage against infection. It is our practice to use prophylactic antibiotic only when therapeutic lens is being used in the presence of a geographic epithelial defect. Formulations of choice are moxifloxacin or polymyxin-trimethoprim drops twice daily until defect is healed.

Scleral Lenses and PROSE Treatment

There has been increased appreciation of the value of large-diameter RGP lenses (cornea-scleral, mini-scleral, and scleral lenses) in the management of ocular surface disease in the last decade; there are few reports of experience with these modalities in pediatric patients. PROSE treatment has been shown to be a successful treatment option for pediatric patients especially after failure of conventional therapy in a broad range of ocular surface and refractive disorders in children (Gungor et al. 2008). The devices used in PROSE treatment vault the cornea entirely and bear on the sclera; they are filled with saline at the time of insertion Fig. 9.1 and must be applied and removed daily. There are recent reports of the effectiveness of PROSE treatment in patients including children with the chronic sequelae of Stevens–Johnson syndrome (SJS) (Ciralsky et al. 2013; Papakostas et al. 2014). In chronic SJS, a PROSE device protects the ocular surface from blink-related trauma from tarsal conjunctival and lid margin abnormalities, alleviating pain and photophobia, and improving visual acuity and visual function. PROSE treatment has been reported to improve long-term ocular health and visual function of children and adults with vernal keratoconjuctivitis (Rathi et al. 2012).

Fig. 9.1 PROSE device being filled with sterile saline prior to application. Information on PROSE network sites can be found at www.bostonsight.org

Case Study—Therapeutic Lens Options in Pediatric Ocular Surface Disease

Stevens–Johnson syndrome (SJS) and its most severe form, Toxic Epidermal Necrolysis (TEN), are acute blistering disorders of the skin, and mucous membranes that commonly result in significant scarring of the ocular surface and eyelids. The result can be painful, blinding, and debilitating with children often affected. Repairing the damage caused to the eyelids and ocular surface can be challenging and fraught with complications.

This 7-year-old Male was referred for consideration of PROSE treatment for support of the ocular surface and stabilization of pannus 2 years after hospitalization for TEN. At the time of referral, there was forniceal shortening, cicatricial lagophthalmos, exposure keratitis, trichiasis, distichiasis, and inferior pannus with keratinization OU. Multiple lid procedures had been undertaken OU, including mucous membrane grafting to lid margins OS only. Topical regimen

was loteprednol drops BID and vitamin A ointment at night. Daily disposable hydrogel lenses were worn on an extended wear basis for comfort with weekly replacement. The patient was correctable to 20/20 in each eye. Figure 9.2a is image of OD at presentation with hydrogel soft contact lens in place. Theessels appeared inactive, so a recommendation was made to switch to daytime only wear of a higher Dk SiHy lens, with substitution of ointment for lens wear at night, to reduce any hypoxic challenge that might trigger progression of vessels. Daily disposable SiHy lenses were substituted when that option became available. Eventually, the topical steroid was eliminated from the regimen. Figure 9.2b shows the OD with a soft contact lens in place 18 months after initial referral, when patient was referred again for consideration of alternative treatment options for OS. Improved clarity of inferior pannus OD with extended wear of higher Dk soft lens is notable. This repeat evaluation was sought after a tuft of corneal neovascularization was noted inferiorly OS, Fig. 9.3a, and introduction of topical anti-VEGF therapy was being considered. It was decided to optimize surface support prior to treating the vessels themselves. Topical steroid was resumed and PROSE treatment was undertaken with the objective of eliminating any contact with cornea that might induce breakdown and activate neovascularization. Figure 9.3b reveals stabilization of fine pannus with inactive vessels after 3.5 years

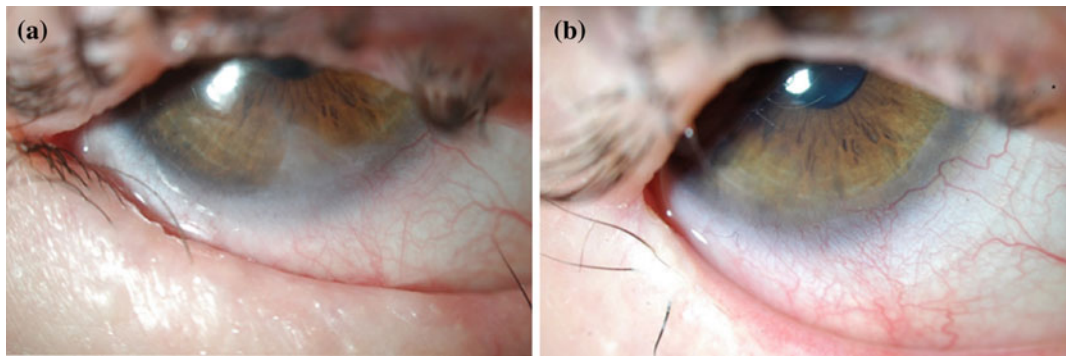

Fig. 9.2 **a** Right eye of 7 year old male at time of referral, 2 years after hospitalization for TEN. There is daily disposable soft contact lens in place which was being worn on a weekly replacement extended wear basis. **b** Right eye 18 months later after switch to daytime only wear of higher Dk silicone hydrogel lens. Note improved clarity of inferior pannus. Topical steroid was eliminated at some time during the prior year

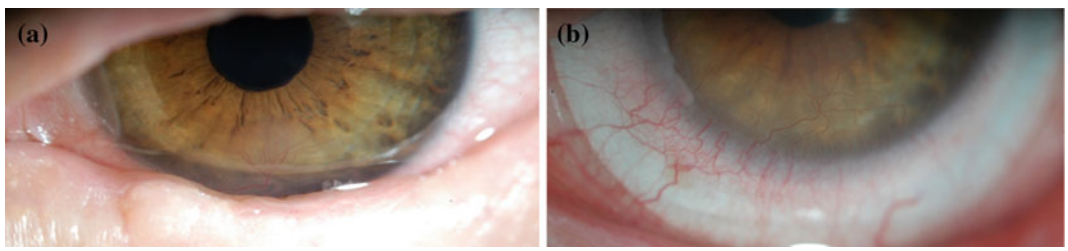

Fig. 9.3 **a** Left eye at this same 18 month visit referred for new development of inferior neovascular pannus despite switch to daily wear only of higher Dk silicone hydrogel lens. Topical steroid was resumed and PROSE treatment was undertaken to eliminate any mechanical contact between contact lens and cornea that might contribute to inflammation and neovascularization. **b** Left eye in PROSE device 3.5 years later, age 12, with continuation of very low dose soft steroid. There has been no progression of vessels or pannus. Vision remains 20/20 in each eye in PROSE devices

of daily wear of PROSE device, with no anti-VEGF treatment undertaken. Five years after presentation vision is 20/20 in each eye with daily wear of PROSE device OU and regimen of loteprednol gel and vitamin A ointment QHS.

Summary

Contact lenses play an important role in the management of eye disease in children. Contact lenses are useful when there is high refractive error or irregular cornea during the critical period for amblyopia, especially in unilateral cases. Contact lenses can be considered as an alternative to spectacle correction, if patients or their caregivers can manage insertion and removal, and if they are able to comply with instruction in lens care and hygiene. Contact lenses can also be very useful in the management of ocular surface disease in the pediatric age group. Ophthalmologists caring for children with corneal disease should be aware of advances in the field of contact lens and be familiar with various contact lens options for the pediatric population.

Compliance with Ethical Requirements Deborah S. Jacobs and Aaron C. Barrett declare that they have no conflict of interest. Deborah S. Jacobs, M.D. is a full-time salaried employee of Boston Foundation for Sight, 501(c) 3. She has no proprietary or financial interest in any contact lens or prosthetic device. No human or animal studies were carried out by the authors for this article.

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Corneal Diseases in Children: Amblyopia Management

10

Melanie Kazlas

Introduction

Vision in children with corneal disorders needs to be monitored closely by an experienced pediatric eye specialist. Although amblyopia is defined as decreased vision in one eye during childhood in an eye that is structurally normal, children with corneal opacities often have overlying amblyopia. Visual deprivation from the opacity impairs visual development at the cortical level. Once the opacity is eliminated or improved, amblyopia treatment is essential to achieve the best acuity for the child. Even if corneal surgery is not contemplated, amblyopia overlying a partial opacity should be treated to achieve at least some improvement in the child's vision.

The word amblyopia is derived from the Greek words, ambly, meaning dull, and ops, meaning vision. In verbal children, the definition of amblyopia includes a minimum of a two-line difference in acuity.

Amblyopia affects children worldwide and is one of the most common preventable causes of vision loss in children. The prevalence of amblyopia in the United States is as high as 5% (Ehrlich et al. 1983). The prevalence of amblyopia in various ethnic and racial groups was studied in the Vision in Preschoolers Study (VIP). A cohort of 4040 3 to 5-year olds from Head Start programs across the Unites States was examined. Prevalence of amblyopia among all groups, which included African American, American Indian, Asian, Hispanic, and non-Hispanic white, was similar, with a range of 2.98% in Asians to 5.44% in non-Hispanic white children (Ying et al. 2014).

Pathophysiology of Amblyopia

1. The development of normal visual acuity is contingent on the visual cortex receiving excellent, high-grade visual input from each eye. The temporal period over which this learning process occurs is called the "critical period of visual development." This period spans the time from birth to about age 10. During this time, if there is absent visual input, such as from a dense central corneal opacity, blurred visual input, such as from induced astigmatism from an off-axis corneal lesion, or uncorrelated input, such as from a sensory strabismus secondary to poor input in the setting of a corneal opacity, then amblyopia results. Pioneering work, conducted by Dr. David Hubel and Dr. Torsten Wiesel, provided the foundation for why addressing visual deprivation early in life is so important. These Nobel prize-winning visual physiologists conducted experiments on kittens simulating various types of visual deprivation such as suturing a lid shut to simulate a dense

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opacity, administering atropine to one eye to simulate blur from anisometropia, and severing an extraocular muscle to simulate strabismus. Hubel and Wiesel conducted single electrode recordings from the visual cortex, isolating responses from the amblyopic and normal eyes in response to viewing grating images (Wiesel and Hubel 1963). They found profound attenuation of signal from the cortical cells receiving input from the amblyopic eye and postmortem analysis of the lateral geniculate nucleus and ocular dominance columns in the visual cortex revealed diminution of cells receiving input from the amblyopic eye. The earlier in the experimental animal's life the induced amblyopia, the more profound the changes in the electrode recordings and measured visual behavior. However, recent work in kitten and mouse models by Mitchell and Bear suggest that visual cortex plasticity can be revived, even into adulthood. Their work reveals an active inhibition of cortical and subcortical pathways of the amblyopic eye by the fellow eye, inhibitory influences which may be lifted pharmacologically or environmentally (Cooper and Bear 2012; Duffy and Mitchell 2013).

Diagnosis of Amblyopia

Key aspects of a vision screening program include testability, (the likelihood a child will be able to complete the test), reliability, (the likelihood that the same result would occur on repeated testing), and accuracy, (the likelihood of the test giving the correct answer). Age appropriate methods of determining vision include preferential looking techniques, using commercially available Teller Acuity cards, in preverbal infants and toddlers. This method tests resolution acuity, not recognition acuity. This method is based on the premise that a child would rather view black and white stripes as opposed to a gray background (Fig. 10.1). The infant or toddler orients himself to view the black and white stripes by moving the eyes or turning his head. The observer looks for the child's response via a peephole in the center of the card. When a child does not consistently orient to the side of the card with stripes, the previous card is taken as the threshold and notated on the exam sheet in cycles per degree at the measured distance, typically 38 or 55 cm, or in the Snellen equivalent. One drawback of the preferential looking technique is over estimation of visual acuity and absolute visual acuities maybe misleading to the parent. However, the exam sheet provides expected values based on age with 95 and 99% confidence intervals derived from clinical studies of healthy children. This method is most useful to follow comparative visual behavior in a preverbal child undergoing amblyopia treatment.

Fixation preference, introduced by Dr. Kenneth Wright in the 1990s, is performed by observing which eye a child fixates with while a 10 prism diopter base down prism is held over either eye. However, a study in 2009 concluded that using fixation preference was a poor surrogate to determine if a child had amblyopia, with low sensitivity in anisometropic and strabismic amblyopes (Cotter et al. 2009).

Older children, age 3–5 years, can often perform a matching game using HOTV optotypes or LEA symbols (Fig. 10.2). In 2001, the Pediatric Eye Disease Investigative Group (PEDIG) determined that a single HOTV optotype with surround bars had a high testability, reliability, and accuracy in determining visual acuity in children age 3–6 (Homes et al. 2001). The crowding phenomenon is characteristic of amblyopic vision. Patients with amblyopia have difficulty resolving optotypes that are placed close to each other. This phenomenon occurs because of abnormalities in the receptive fields in the visual cortex. Thus, using a single optotype to assess vision will likely overestimate visual acuity and amblyopia will likely be missed. Testing with linear optotypes or a single optotype with crowding bars surrounding the optotype are methods to address this issue.

Literate children can perform Snellen visual acuity testing based on level of development, with children as young as age 2 occasionally able to identify the letters of the alphabet.

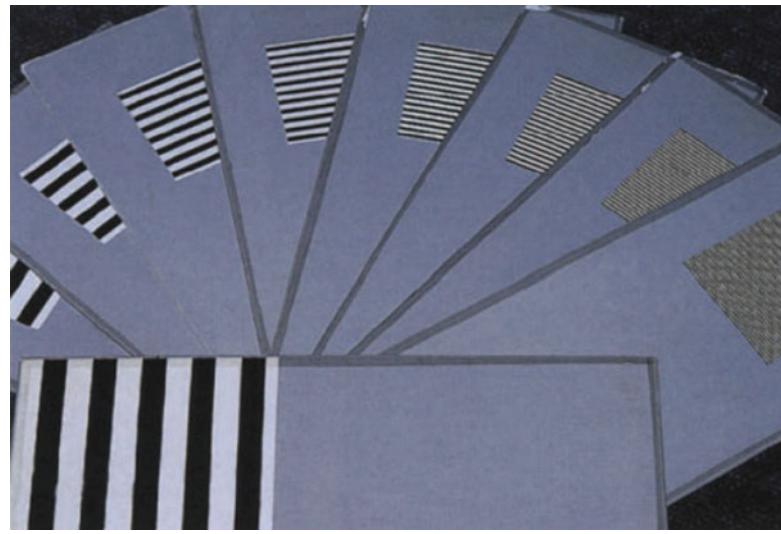

Fig. 10.1 Teller acuity card. Reproduced from Quinn et al. (2002) © Springer Science +Business Media, New York 2002

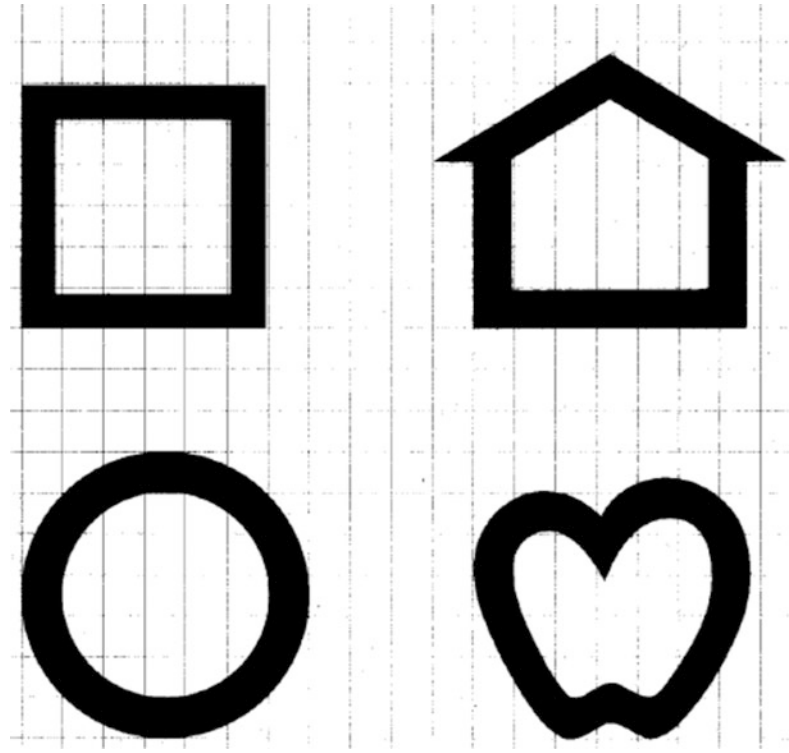

Fig. 10.2 LEA symbols. Reproduced from Gräf et al. (2000) © Springer-Verlag 2000

Familiarity with all these methods is crucial for the examiner to diagnose amblyopia and monitor a child's progress with treatment. It is essential to test a child's vision using an occlusive patch. Numerous children who pass a school or pediatrician's vision screening eventually come to the attention of a pediatric ophthalmologist with amblyopia who "passed" because the unaffected eye was not sufficiently occluded during testing.

Table 10.1 Amblyopia risk factor criteria

Age, months	Anisometropia	Hyperopia	Astigmatism	Myopia
12–30	>2.5D	>4.5D	>2.0D	>−3.5D
31–48	>2.0D	>4.0D	>2.0D	>−3.0D
>48	>1.5D	>3.5D	>1.5D	>−1.5D

All ages: Manifest strabismus >8 PD or Media opacity >1 mm
D (diopter) PD (prism diopter)
From 2013 American Association for Pediatric Ophthalmology and Strabismus Vision Screening Committee. Used with permission

2. There are other characteristics of amblyopic vision that are important to be familiar with in order to understand the full impact of amblyopia on a patient. These attributes include impaired contrast sensitivity and abnormal motion processing. Stereopsis is reduced in amblyopic patients. Even reading fluency, defined as speed and accuracy of oral reading, is compromised (Repka et al. 2008).

Anisometropia and strabismus comprise 90% of the causes of amblyopia. Cycloplegic retinoscopy must be performed to determine if there is a significant difference in refractive error between the eyes. Guidelines from the most recent AAPOS publication can help the clinician identify refractive and strabismic risk factors for amblyopia (Table 10.1).

Role of Strabismus in Amblyopia

If visual deprivation is severe enough, ocular alignment instability, or sensory strabismus, may result. This is an additional impediment to visual rehabilitation of the affected eye with a corneal opacity. The gold standard of identifying strabismus is the cover uncover test. This requires the cooperation of the child to fixate an accommodative target at distance and near. Observe the uncovered eye for movement. If there is movement, there is a tropia, which if constant, and with a strong fixation preference, could indicate risk for development of amblyopia. Strabismus may seem to be present by Hirschberg light reflex test, but may represent an abnormal angle kappa. Angle kappa is defined as the angle between the pupillary and visual axis. The corneal light reflex is displaced temporally with a negative angle kappa, giving the appearance of an esotropia. The corneal light reflex is displaced nasally with a positive angle kappa, which gives the appearance of an exotropia. Occasionally, immature facial features, such as a narrow pupillary distance, epicanthal folds, and a flat nose bridge give the appearance of esotropia, but this is an illusion or pseudostrabismsus. Use specific clinical methods of strabismus determination such as the Hirschberg light reflex test or cover test to determine if this is the case. The Bruckner test is also useful in identifying a manifest strabismus. Observe the red reflex with the direct ophthalmoscope. The fixating eye will have a darker red reflex and the deviated eye will have a brighter or lighter red reflex because light is reflected from a less pigmented area of the retina or even from the optic nerve, depending on the direction of strabismus.

Role of Refractive Error in Amblyopia

Recognizing significant refractive error is a key element in the visual rehabilitation of children with corneal opacities. Glasses are often the first line of treatment. Prescribing glasses in children is an art. A cycloplegic refraction is essential to provide the most accurate prescription. If there is significant hyperopic anisometropia, for example, subtract equal amounts of hyperopia to reflect the natural accommodation of the child in the undilated state. However, if there is a significant esotropia along with a significant refractive error, give all the hyperopic correction, or at most subtract 0.5 D of hyperopia from each lens. If the child with a corneal condition is also

pseudophakic, base your refraction on the child's age. For infants and toddlers, whose visual interactions occur mainly in the near and intermediate range, aim for 2.5–3D of additional hyperopia in the pseudophakic eye. For the child over age 2, correct for infinity in the distance part of the lens and add a bifocal to the affected eye. For young children, avoid prescribing progressive addition lenses since young children have a difficult time finding the ideal head position for various viewing distances.

3. Contact lenses are an ideal approach to ameliorating the irregular astigmatism induced by many corneal disorders. A knowledgeable pediatric optometrist is essential to obtain a good fit and educate the child and parents about proper handling and care of the contact lens. Irregular astigmatism from corneal scarring arises from irregular refraction of light by the scarred area and light scatter by the opacity with concurrent light sensitivity, reduced contrast sensitivity, and impaired visual acuity. Spectacles cannot address this irregular refraction. Rigid gas permeable lenses or hybrid lenses reduce irregular astigmatism and promote visual clarity by providing a regular refracting surface. Also, the tear film between the irregular cornea and back of the lens contributes to improved focus. However, in one study, the success of long-term wear of gas permeable lenses in patients less than 6 years of age was only 50%, likely due to loss of the lens or lens discomfort (Kanpolat and Ciftci 1995). A scleral contact lens, also known as a PROSE lens, (Prosethetic Replacement of the Ocular Surface Ecosystem, Boston Foundation Fight for Sight, Needham, MA), is helpful in promoting visual clarity and comfort in patients with scarred corneas. However, tear film debris accumulates, and a recent study found improved vision is reduced after 4 h of use, requiring frequent rinsing and replacing, which can be a challenge in young children (Rathi et al. 2012).

Treatment of Amblyopia

If optical correction is not sufficient to achieve excellent visual acuity, then amblyopia therapy is indicated. Current standard of care is to penalize the dominant or sound eye either by patching or use of atropine. Optical penalization by use of a blur lens, a Bangerter foil, or even an occluder contact lens may be appropriate for certain children.

4. The Pediatric Eye Disease Investigative Group (PEDIG), a consortium of private and university-based pediatric ophthalmologists, have conducted multicenter randomized prospective clinical trials since its inception in 1997 to further our understanding of amblyopia and to provide an evidence-based approach to optimal treatment (Repka and Holmes 2012). The first Amblyopia Treatment Study (ATS) compared visual acuity outcomes in children age 3–6 with moderate amblyopia (20/40–20/100) who were randomized to patching at least 6 h a day or to daily atropine. The improvement in vision was similar in both groups (3.16 lines in the patching group and 2.84 lines in the atropine group), but children who patched achieved their final best acuity sooner than those who received atropine (Beck 2002). Until publication of the ATS, many ophthalmologists administered occlusion therapy concurrently with glasses for anisometropic amblyopia. However, this study demonstrated that children with moderate to severe anisometropic amblyopia (20/40–20/250) improved visual acuity by >2 lines in 77% and resolved amblyopia in 27% by wearing glasses alone. The average response time to best visual acuity was 10 weeks and some study subjects continued to improve even up to 30 weeks after initiating wearing glasses (Cotter 2006). Full time occlusion versus patching the dominant eye 6 h a day was examined in severe amblyopes (20/100–20/400). Both treatment groups had improvement of visual

acuity by an average of just over 4.5 lines at the 4-month study conclusion (Beck 2003).

Atropine is a powerful anti-cholinergic eye drop that is an important treatment option for children either as a first-line treatment or for those who are non-compliant with patching. Atropine is most efficacious in moderate amblyopes with visual acuity better than 20/100. The regimen of atropine penalization, whether daily or just on the weekend, was studied in a cohort of children younger than 7 with visual acuity in amblyopic eye of 20/40–20/80. Visual acuity improved by an average of 2.3 lines in each group at the 4-month study conclusion. Occlusion amblyopia, in which the sound eye suffers reduced visual acuity during treatment, is rare but needs to be monitored for especially in children receiving atropine penalization therapy. Check the vision, which is blurred from atropine from cycloplegia, by performing a refraction. Then place the correcting lens in front of the dominant eye. If the vision in the dominant eye does not improve to better than the amblyopic eye, or close to 20/20, then occlusion amblyopia is likely. Discontinue treatment and closely follow the patient to ensure restoration of acuity in the previously dominant eye (Repka 2004).

Intuitively, it may seem that patching while performing a near activity that requires concentration and integration of visual and fine motor skills, such as a video game, would be more effective in improving visual acuity. This assumption was investigated in a study that randomly assigned near activities or distance activities during 2 h a day of patching the dominant eye. There was no difference in best-corrected visual acuity at the conclusion of the study between the two groups (2008).

The effect of age on response to amblyopia treatment was examined in a meta-analysis of prior studies. Visual cortex plasticity appears to diminish with age and amblyopia treatment appears to be more effective when instituted at a younger age (Homes et al. 2011). However, older children do respond to treatment as demonstrated in this ATS of children 7–17 years old with residual amblyopia or never before treated amblyopia (20/40–20/400). All participants were given optimal optical correction and then randomized to continued wear of optical correction alone or optical correction and amblyopia treatment. All participants in the treatment group patched the dominant eye 2–6 h a day and in the younger, 7–12-year old, group they also received daily atropine 1%. The study determined who were responders, defined as a participant who achieved greater than or equal to two lines of visual acuity improvement, or non-responders. In the 7–12 year olds, 53% were responders in the treatment group and 25% were responders in the optical correction only group. In the older cohort, about one quarter of participants in the treatment and optical correction group were responders. However, for participants in the older group who never received amblyopia treatment in the past, 47% were responders in the treatment group versus 16% in the optical correction only group. These findings emphasized that ophthalmologists should offer at least optimal optical correction to all older children with amblyopia and offer amblyopia treatment even to teens, especially if they never received amblyopia treatment in the past (Scheiman 2005).

Adherence to the prescribed treatment is critical to improving the vision in the amblyopic eye. In 2006, a paper in IOVS conducted a randomized trial in which the intervention group received educational material about patching and age appropriate incentives like stickers and the control group receive only a picture to color. Compliance with patching, which was objectively assessed with an occlusion-monitoring device, was greater in the group that had an educational component (Loudon et al. 2006) Maximal improvement of vision occurs 6–12 months after initiation of treatment but often needs to be maintained throughout the critical period. Patching regimens greater than or equal to 6 h a day should be weaned to minimize regression, or loss of best-corrected visual acuity. According to one study, there was a fourfold reduction in the incidence of regression when patching was gradually reduced. Additional risk factors for recurrence of amblyopia include excellent visual acuity at time of treatment

cessation, number of lines of improved vision, and history of prior regression. Excellent eye alignment or stereopsis did not appear to have a protective effect (Holmes et al. 2007).

With conventional monocular amblyopia treatment, visual input to the dominant eye is either eliminated (patching) or blurred (atropine and Bangerter foil). The potential for deleterious effects on binocular vision with monocular treatment has led to the development of binocular treatments for amblyopia. The concept involves the child wearing anaglyphic goggles while playing a video game. The dominant eye sees figures on the computer screen with attenuated contrast and the amblyopic eye sees figures at 100% contrast, a scenario that allows for binocular integration of the images and successful video game play. As the vision improves in the amblyopic eye, the contrast is modulated to eventually equal that of the dominant eye. Birch and colleagues recently published results supporting the efficacy of this treatment in a group of children with anisometropic amblyopia (Li et al. 2014).

Childhood Corneal Opacities

Recently, the nomenclature for describing congenital and neonatal corneal opacities has been revised (Nischal 2015). Advances in anterior segment imaging and genetic analysis have allowed a more accurate classification of corneal disorders in children. Prior to this revolution in imaging and genetics, the mnemonic "STUMPED" (Sclerocornea, Trauma, Ulcer, Metabolic, Peter's anomaly, Endothelial disorder, Dermoid) was used, but as Nischal pointed out in his recent paper, these terms are misleading as to the pathophysiology of these lesions. A more comprehensive classification to reflect recent advances in anterior segment imaging and genetics, allows improved phenotype/genotype correlations which hopefully will lead to more accurate descriptions of natural history, response to treatment, and visual prognosis in these disorders. The mechanisms through which a child with a corneal disorder can suffer from amblyopia include visual deprivation from the opacity itself, regular astigmatism, irregular astigmatism, and sensory strabismus. Congenital or neonatal corneal disorders can be categorized as congenital nontraumatic, acquired nontraumatic, and acquired traumatic. A complete discussion of congenital corneal opacities can be found in Chap. 6 (Robert and Colby).

The literature contains studies comprised of children with corneal disorders, who are at risk and treated for amblyopia. Inherent in such studies is an inability to discern the contribution of amblyopia to visual dysfunction from the corneal opacity itself.

The demographic and clinical characteristics of 116 cases of ocular dermoids were studied. There were 21 cases of corneal or limbal dermoids. The prevalence of amblyopia was 14% (3/21). The authors identified astigmatism greater than 1.5 diopters as a risk factor. No conclusions were drawn about whether surgical resection facilitated amblyopia treatment or improved visual outcome (Rocio Arce Gonzalez et al. 2013). The issue of type of surgery and timing of surgical intervention was examined in a paper that examined preoperative and postoperative characteristics of 46 consecutive patients who underwent surgery for solid epibulbar dermoids and subconjunctival dermolipomas. Forty one percent of patients, all of whom had epibulbar dermoids, had amblyopia. In corneal dermoids that did not occlude the visual axis, a significant correlation was found between tumor volume and preoperative visual acuity, which was positively correlated with postoperative visual acuity. Visual acuity significantly improved postoperatively in patients whose corneal dermoids were operated, improving from 0.21 to 0.35. Note that the authors used the decimal system of visual acuity notation in which the reference distance is eliminated. For example, 20/20 is 1 and 20/200 is 0.1 in this system. Interestingly, hyperopia and astigmatism were unchanged after excision. Most epibulbar dermoids were excised with lamellar excision (26 eyes) and the remainder with lamellar keratoplasty or eccentric sclerocorneoplasty.

The impact on vision from corneal lacerations without an intraocular foreign body in a cohort of children less than 7 years of age was studied. Wound size was measured and ranged from 1 to 10 mm, but the location of the laceration was not specified. Only one patient had associated retinal injury. The authors emphasize that excellent visual function can be achieved with attention to instituting amblyopia treatment. Seventy percent of patients achieved 20/40 visual acuity or better. They note that because of young age at presentation, an initial visual acuity, which in adult studies is a prognostic factor for final visual acuity, cannot be obtained. However, aggressive treatment of secondary traumatic cataracts and refractive error should be instituted in all cases (Segev et al. 2007).

Vigilance is required in infants who develop corneal opacities in the setting of infectious and non-infectious keratoconjunctivitis. In a study of infants who had presumed epidemic keratoconjunctivitis in the first year of life, seven had persistent unilateral corneal opacities, significant astigmatism, and sensory strabismus. Despite amblyopia treatment, 57% (4/7) remained amblyopic (Gu et al. 2011). Nischal and colleagues note that amblyopia was a confounding factor in 48% of their patients who had severe blepharokeratoconjunctivitis (Jones et al. 2007).

Children with mucopolysaccharidosis, a rare inborn error of metabolism, need to be monitored for amblyopia. Mucopolysaccharidosis (MPS) I or Hurler's syndrome is a lysosomal storage disease which results in the accumulation of glycosaminoglycans in various tissues, including the cornea, because of a deficiency or absence of the enzyme, alpha-L-iduronidase. Treatment, such as hematopoietic stem cell transplant or enzyme replacement, is especially effective in improving life expectancy if administered before age 2. Corneal opacities can improve, but are rarely eliminated with treatment. In one study of children with treated MPS-I-Hurler, all had high hyperopia (>5D), which was determined to be secondary to short axial length and reduced corneal power (Fahnehjelm et al. 2012).

Amblyopia Following Keratoplasty

If corneal surgery is indicated to facilitate visual rehabilitation and promote amblyopia therapy, the choice of technique is important. A large retrospective review studied the indications, graft survival, and visual outcomes in primary full thickness penetrating keratoplasty (PKP) in children. Historically, corneal grafts have a higher rate of failure in children because of allograft rejection and glaucoma. One hundred sixty five penetrating keratoplasties were performed in 134 children 12 years of age or younger. The indication for surgery was congenital opacities in 130 eyes (78.8%), acquired traumatic opacities in 18 eyes (10.9%) and acquired nontraumatic opacities in 17 eyes (10.3%). The authors stress the hardship of the postoperative regimen on the family. Penetrating keratoplasty performed on eyes with congenital hereditary endothelial dystrophy (CHED) had the best visual outcome and were more likely to attain ambulatory vision of better than 20/200. Worse visual outcomes occurred in children with unilateral non-CHED opacities (59 unilateral vs. 18 bilateral). Children with CHED more often had bilateral surgery (13 vs. 9) Unilateral or very asymmetric opacities creates more of a competition at the cortical level with more pronounced amblyopia (Al-Ghamdi et al. 2007). In another large retrospective study of PKP's, Huang and associates studied graft survival and visual acuity outcomes in a cohort of 47 children less than age 14 who underwent 106 PKP's. Median follow up was 4.4 years and the indication for surgery was congenital opacities (61%), acquired nontraumatic opacities (21.7%) and acquired traumatic opacities (16.7%). Age at time of surgery or diagnosis was not associated with graft survival, which overall was 54% at one year. The only independent predictor of graft failure was

pretransplant and/or posttransplant glaucoma. Visual acuity outcomes at last visit were not encouraging, with about 10% of patients with congenital opacities and about 7% of patients with acquired opacities achieving better than 20/100 vision (Huang et al. 2009).

For congenital and acquired endothelial dysfunction that results in a visually significant opacity of the cornea, selective endothelial replacement is an option. The group of potential patients is small, mainly comprised of those with congenital hereditary endothelial dystrophy (CHED) and corneal decompensation after traumas or pseduophakia. Diseased endothelium is stripped from the host and healthy donor Descemets is inserted via a small scleral incision that is positioned over the diseased area and tamponaded with an air bubble. Advantages over pediatric penetrating keratoplasty include rapid visual rehabilitation, on the order of 6–12 weeks instead of 6–12 months (Colby 2008). No sutures need to be removed and postoperative astigmatism is reduced because the anterior layers of the cornea are not disturbed. A recent review highlights the advantages of endothelial keratoplasty as an alternative to penetrating keratoplasty in children. Endothelial grafts clear more quickly, thereby facilitating earlier amblyopia rehabilitation (Anwar et al. 2012). However, the procedure can be technically challenging.

Superficial corneal opacities may be ameliorated with the use of phototherapeutic keratectomy (PTK) with the excimer laser. One retrospective study examined five children, three with band keratopathy, one with an opacity after EKC and one with anterior basement membrane dystrophy. Optical treatment zone was 8 mm in four patients and 7 mm in one patient. Mean visual acuity improved from 1.22 logmar to 0.64 logmar. There was a slight hyperopic shift. PTK is less traumatic to perform than lamellar or penetrating keratoplasty and postop healing is faster resulting in improved corneal transparency (Kollias et al. 2007).

For pediatric patients who have failed or are at high risk for graft failure, the Boston keratoprosthesis is an option, although there is limited long-term follow up and risk of complications is high (Lee et al. 2015).

Conclusions

Medical or surgical treatment of a corneal opacity during childhood is only the first step in optimizing the visual acuity of the child. The visual deficit suffered by these children is compounded by impaired visual experience at the cortical level. The ensuing amblyopia needs to be recognized and promptly treated. This requires close collaboration of the cornea specialist with an experienced pediatric ophthalmologist. The onset of the corneal opacity, the location of the opacity, the natural history of the particular corneal condition, and successful medical and surgical management are all determinants of final visual outcome. However, extra diligence and attention to the treatment of amblyopia in these children will ensure an even better visual acuity that will last a lifetime.

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