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Introduction

Advances in medical technology and understanding over the last several decades have resulted in significant improvements in the survival of premature infants. Common ocular manifestations of prematurity include retinopathy of prematurity (ROP), strabismus, myopia of prematurity (MOP), and congenital or acquired infections. Ophthalmologists are most commonly consulted to do examinations for ROP which can lead to retinal detachment and blindness if not detected and treated in a timely manner. However, ocular examinations of the premature infant may also contribute to the diagnosis of developmental syndromes, chromosomal anomalies, sepsis, and coagulopathies. The immature eye differs in many respects from that of a child born at term and certainly can be much different than the adult eye. An understanding of these differences is important to the ophthalmologist, pediatrician, primary care provider, and the parents. This chapter will look at the differences in the structure and function of the immature eye, new evaluation techniques to identify these differences, and discuss the historical and current treatment considerations for ROP and other pathologies seen in the immature eye.

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Physical Characteristics

Definition

The physical characteristics of the developing eye and adnexal structures have been determined. These normal values may be helpful in the diagnosis of conditions such as hyper or hypotelorism, microphthalmia, or blepharophimosis. Awareness of the normal parameters is critical in the evaluation of infants with suspected birth anomalies.

Anterior Segment

External

The eyelids develop as a fused fold initially in the seventh week of gestational development. A number of very low birthweight (VLBW) premature infants are born with the eyelids either partially or completely fused. The critical time for eyelid opening has been cited to occur between 25.5 and 26.5 weeks gestational age. If the lids are fused at birth, studies have shown the average time to opening is 5.5 days [1]. There is generally no need to try to forcibly pry open the fused lids as they normally will open spontaneously, and without trauma, on their own. The fact that the lids were fused was previously considered a marker of non-viability for life and may have influenced some to apply more conservative resuscitation efforts for the child [2]. This is clearly no longer the case with more modern resuscitation techniques and standards.

Parents will often question the ophthalmologist regarding tear production in the premature infant, often citing that they have not noticed any tears when the baby cries. A study comparing the tear functions in premature versus term babies showed a statistically significant decrease in tearing and corneal sensitivity in the preterm infants. The authors urged that premature infants should be checked for the presence of dry eye complications [3].

Cornea and Intraocular Pressure

Corneal diameter and thickness are important determinants in the diagnosis of congenital glaucoma, with diameter being most important in the diagnosis of megalocornea, or microphthalmia. The infant's gestational age must be considered before considering a cornea to be abnormally large or small. A number of studies have been performed to determine corneal diameter in the preterm infant and its progression with advancing age [4–6]. Tucker et al. found corneal diameters between 6.2 and 9.0 mm in 70 infants of 25–37 weeks gestational age examined during the first week of life. The increases in corneal diameter with age were shown to parallel the linear increases in axial length of the eye [5]. Al-Umran et al. examined 127 premature infants between 27 and 36 weeks gestational age. The corneal diameters ranged from 7.75 mm in the youngest child to 10 mm in 34–35 week infants. They noted a positive correlation of corneal diameter to gestational age and birth weight [6]. Kirwan et al. in a study of 70 eyes of babies born at 31 weeks of gestation demonstrated an inverse relationship between corneal diameter and corneal thickness with advancing age. Horizontal diameter shows a progressive increase in size as the baby approaches term age and corneal thickness shows a progressive decrease (Table 2.1) [4]. Along with this remodeling process the corneal curvature of the infant eye is reduced. This has been reported to change from 65.83 diopters at 28 weeks post conception to 49.38 diopters at 42 weeks [7].

Central corneal thickness measured with an ultrasound pachymeter has been shown to be significantly greater in the premature newborn than in full term infants in the absence of any other ocular abnormalities. In a study of 33 patients with

central corneal thickness (CCT) measurements taken between 30 and 32 weeks and again at 39–41 weeks post conception, the CCT decreased from a mean of 691 μ m to a mean of 564 μ m [4]. Other studies have also shown the CCT to be thicker in the premature infant with a linear decrease as the child matures. Explanations offered for this remodeling process include better control of corneal hydration after the infant begins to open the eyes after birth. The hydration of the central cornea and the increased corneal thickness have also been suggested as the reasons premature corneas are often quite cloudy until the child approaches roughly 31 weeks post conceptual age [8].

Another important feature associated with central corneal thickness in premature infants relates to the accuracy of intraocular pressure measurements (IOP). Common devices used to measure IOP in premature eyes are the Tonopen (Reichert Technologies, Buffalo, NY, USA), the Icare tonometer (Kansas City, KS, USA and Helsinki, Finland), and the Perkins Tonometer (Haag-Streit USA and Reliance Medical products, Mason, Ohio). In a study of premature and term infants correlating IOP and central corneal thickness, Karahan et al. found that CCT did not affect IOP significantly in preterm infants and was only moderately correlated in full term infants [9]. In contrast, Uva et al. found that IOP measurements in premature infants using the Tonopen XL were slightly greater than in full term infants because of an increased CCT. They found the mean IOP in premature babies was 18.9 ± 3.7 mmHg with a mean CCT of 599 ± 36 μ m. In full term infants the IOP was 17 ± 2.6 mmHg with a mean CCT of 576 ± 26 μ m [8].

Anterior Chamber

The uses of ultrasound biomicroscopic measurements (UBM) have greatly enhanced the understanding of anterior chamber development in the preterm infant. This technology allows for accurate imaging and measurements of the anterior segment to be taken in premature eyes. This is particularly valuable when the media are not clear or a child is confined to an incubator and access with a portable slit lamp is nearly impossible. Anterior chamber depth can be measured as the axial distance from the corneal endothelial surface to the anterior surface of the lens. Also measurable are the trabecular-iris angle and iris thickness. In a study of 39 premature infants born from 25 to 39 weeks gestational age, Kobayashi et al. established normative values related to postconceptional age and birth weight for these measurements [10]. They found that each value showed a linear relationship with post conceptual age and birth weight. Therefore, the younger the child, the more shallow the anterior chamber depth, the narrower the trabecular-iris angle, and the thinner the iris tissue.

Table 2.1 Gestational age, central corneal thickness and horizontal corneal diameter at 30–32, 34–35, 37–38 and 39–41 weeks gestational age

Gestational age (weeks)	Central corneal thickness (μ m)	Horizontal corneal diameter (mm)
30–32		
Mean	691	8.0
SD	87	0.2
34–35		
Mean	648*	8.5*
SD	72	0.3
37–38		
Mean	605*	8.9*
SD	59	0.3
39–41		
Mean	564*	9.6*
SD	34	0.5

*Statistically significantly at $p < 0.05$

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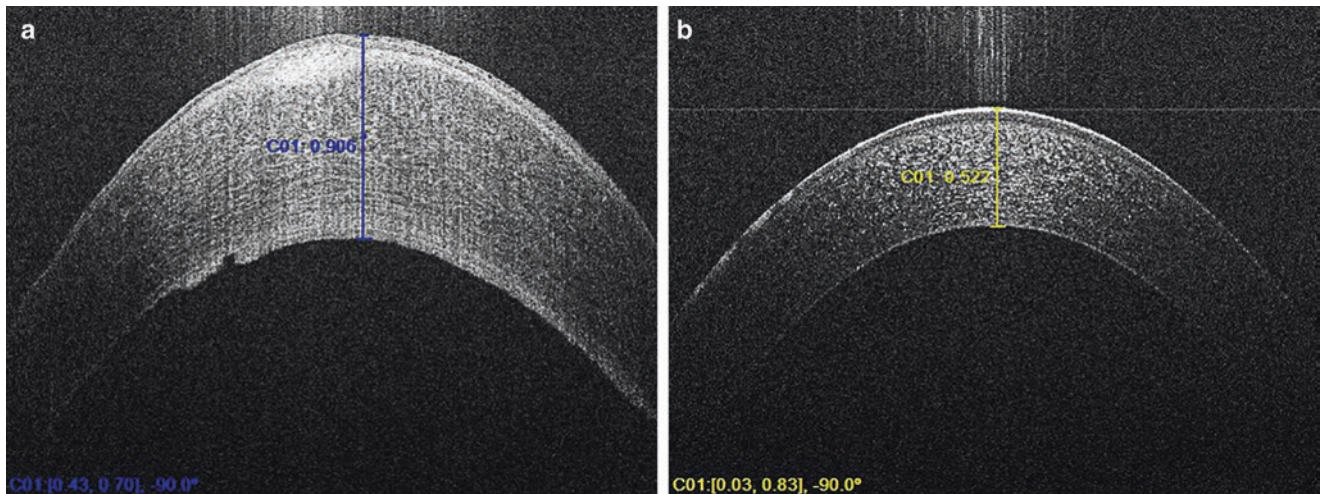


Fig. 2.1 (a) Hand-held spectral domain ocular coherence tomography (SD-OCT) (Biotigen, Inc, Morrisville, NC) image of a premature infant with a markedly thickened central cornea. (b) The normal cornea of the fellow eye is shown next to it

UBM has also been used to evaluate angle closure glaucoma in premature infants which has been noted to occur in the advanced stages of retinopathy of prematurity (ROP). In a report of three infants, high resolution UBM confirmed angle closure in the setting of advanced ROP with a retrolental membrane. After peripheral iridectomy, repeat UBM showed an open angle in each of these infants. The authors concluded that a pupillary block mechanism was the cause of the angle closure in these infants [11].

More recently, hand-held spectral domain ocular coherence tomography (SD-OCT) (Biotigen, Inc, Morrisville, NC) has been used to provide excellent quality images of the anterior segment in infants. As with UBM, this technology is particularly helpful when the cornea is cloudy and the direct view is compromised (see Fig. 2.1a, b).

Lens

Transient lens opacities can occur in premature infants. These were initially reported by McCormick and have later been confirmed by others [12]. Alden found 2.7 % of infants examined with a birth weight of less than 2500 g had opacities present. These transient opacities were distinguishable from neonatal cataracts by their appearance and clinical course. The lens changes were symmetrical, bilateral, and consisted of clear fluid vacuoles just anterior to the posterior lens capsule. The vacuoles were initially found in clusters corresponding to the apices of the posterior inverted Y suture of the lens. These progressed in varying degrees up to a total vacuolar opacification of the posterior subcapsular space. The onset of the lens opacities was estimated to be 16 ± 4 days post-partum and had a mean duration of 25 ± 30 days until

clearing. Resolution occurred in a manner opposite to the initial formation, with initial clearing centrally and the most prolonged retention of vacuoles at the lens apices [13].

The tunica vasculosa lentis may be a prominent feature in the examination of the preterm infant. It can be a contributory factor to the hazy view of the posterior pole seen in these patients. This represents a branching capillary network on the posterior lens capsule that extends anteriorly around the lens capsule. It has been suggested by Hittner et al. that the presence of this network between 27 and 34 weeks is a useful adjunct in accurately estimating the gestational age of a preterm infant [14]. Another consideration with persistence of the tunica is whether it may compromise transpupillary laser treatment for threshold ROP or perhaps predispose the child to cataract development. Paysse et al. reported a very low incidence of acquired cataract following diode laser treatment for threshold ROP. They indicated the mechanism for this cataract formation is unclear, but postulated it is more likely the result of thermal damage from absorption of laser energy by lens proteins or hemoglobin contained in a persistent anterior tunica vasculosa lentis. They reported an incidence of acquired cataract of only 0.003 % using diode laser therapy and suggested the incidence should be lower with diode than argon because of the reduced absorption of diode laser energy by hemoglobin [15]. In support of this hypothesis, other reports have shown an incidence of 1–6 % of cataract development after transpupillary argon laser photocoagulation in the setting of a persistent anterior tunica [16, 17]. Of note, there have been several reports of rapid resolution of the tunica vasculosa lentis after injection with bevacizumab, an anti-vascular endothelial growth factor medication that has been introduced into use for threshold ROP which will be discussed later in the chapter [18, 19].

Posterior Segment

Vitreous

The vitreous in the premature infant is often hazy, providing a less than optimal view of the peripheral retina. This is particularly true in infants less than 34 weeks gestational age, and is compounded by the premature corneal haze and the persistent tunica vasculosa lentis that have been discussed previously. By the end of the sixth to seventh month of gestation, the primary vitreous and hyaloid vasculature tend to atrophy and regress leaving a clearer secondary and tertiary vitreous gel. If this regression fails to occur, either partially or completely, this results in persistence of the fetal vasculature (PFV). In PFV, a fibrovascular stalk connects between the optic nerve head and the posterior lens capsule. A whitish fibrovascular membrane covers the posterior lens capsule to varying degrees and the eye may be microphthalmic with cataract development. If the membrane is large enough, it may result in traction on the ciliary processes and will pull them centrally toward the pupil. Angle closure glaucoma is a potential risk of this process.

Retina

In 1986, Isenberg described the ophthalmoscopic appearance of the developing macula in a series of 129 premature infants [20]. He correlated the developmental changes in this region to the gestational age of the infant. At 34 weeks, pigment was first noted in the macular area. By 36 weeks, a complete annular reflex was present, and by 42 weeks in normal infants the macula appeared adult-like. The 37 infants in the study who developed retinopathy of prematurity showed a delay of 2 weeks in macular development in the later stages.

A number of studies have suggested that the presence of ROP, or premature birth alone, alters the development of

the central retina. Through the use of hand-held spectral domain ocular coherence tomography (SD-OCT), it has been shown the central retinal thickness is significantly increased in preterm infants than in age matched full term controls [21]. The thickest central retinal area was found in infants treated with laser for ROP (Table 2.2). More recent SD-OCT studies have documented the development of the human fovea after premature birth. The technology has evolved to the point that all retinal layers that in the past were only observed by histologic study, can now be seen in vivo with dramatic detail (see Fig. 2.2) [22]. At 31–33 weeks post conceptual age, the foveal thickness is greater than that found in the adult fovea. In the center of the fovea at this stage, ganglion cell, inner plexiform, and inner nuclear layers can be seen. As the retina matures in ensuing weeks, the inner retinal layers migrate in a centrifugal fashion toward the periphery and the foveal pit forms more succinctly. In conjunction with this migration, parafoveal inner retinal layers increase in thickness in contrast to the more peripheral retina. The majority of this migration of the inner retinal layers occurs between 31 and 42 weeks gestational age [22]. This increase in thickness is thought to result in the observation of a macular annular reflex by 36 weeks post conception, but the characteristic foveal light reflex generally is not visible until 42 weeks post conceptual age [20].

An interesting finding that has arisen from SD-OCT studies in premature eyes has been the presence of cystoid macular changes. These are generally not visible on examination of the retina by indirect ophthalmoscopy. Vinekar et al. in a study of 54 premature infants with ROP and 20 controls, demonstrated that no control eyes or eyes with stage 1 ROP showed any foveal edema or disruption of architecture in that region. In contrast, 29.1 % of eyes with stage 2 ROP showed cystoid foveal changes. When these eyes were re-imaged by SD-OCT at 52 weeks post conceptual age, 100 % of the eyes had normalized by this visit.

Table 2.2 Mean of OCT parameters

	Group I	Group II	Group III	Group IV	<i>P</i>
Total macular volume (mm ³)	7.1±0.3 (6.47–7.55)	6.9±0.4 (6.2–7.52)	6.7±0.33 (6.22–6.99)	7.1±0.3 (6.29–7.39)	0.095
Foveal thickness (μm)	220.4±39.1 (165–284)	198.6±23.6 (176–248)	190.7±28.9 (160–231)	164.7±16.7 (136–191)	0.002
Central retinal thickness (μm)	240.6±28.9 (201–286)	223.3±14.7 (208–253)	218.9±19 (191–248)	199.6±14.5 (171–221)	0.002
Inner retinal thickness (μm)	272.7±23.5 (210–291)	269.4±15.9 (244–295)	269.9±14.7 (249–291)	273.1±13.5 (256–295)	0.65
Outer retinal thickness (μm)	243.4±18.6 (198–267)	239.9±17.8 (210–264)	239.7±18.5 (217–279)	249.9±9.8 (235–262)	0.252

Data are expressed as the mean±SD (range). Results of Kruskal-Wallis H test, asymptomatic significance level for the four groups. All groups were compared with each other (10 eyes and 10 children/group). Significant differences (*P*) are italic

Group 1=Patients treated with laser for threshold ROP

Group 2=Patients with stage 1 or 2 ROP

Group 3=Patients with no ROP

Group 4=Age matched full term controls

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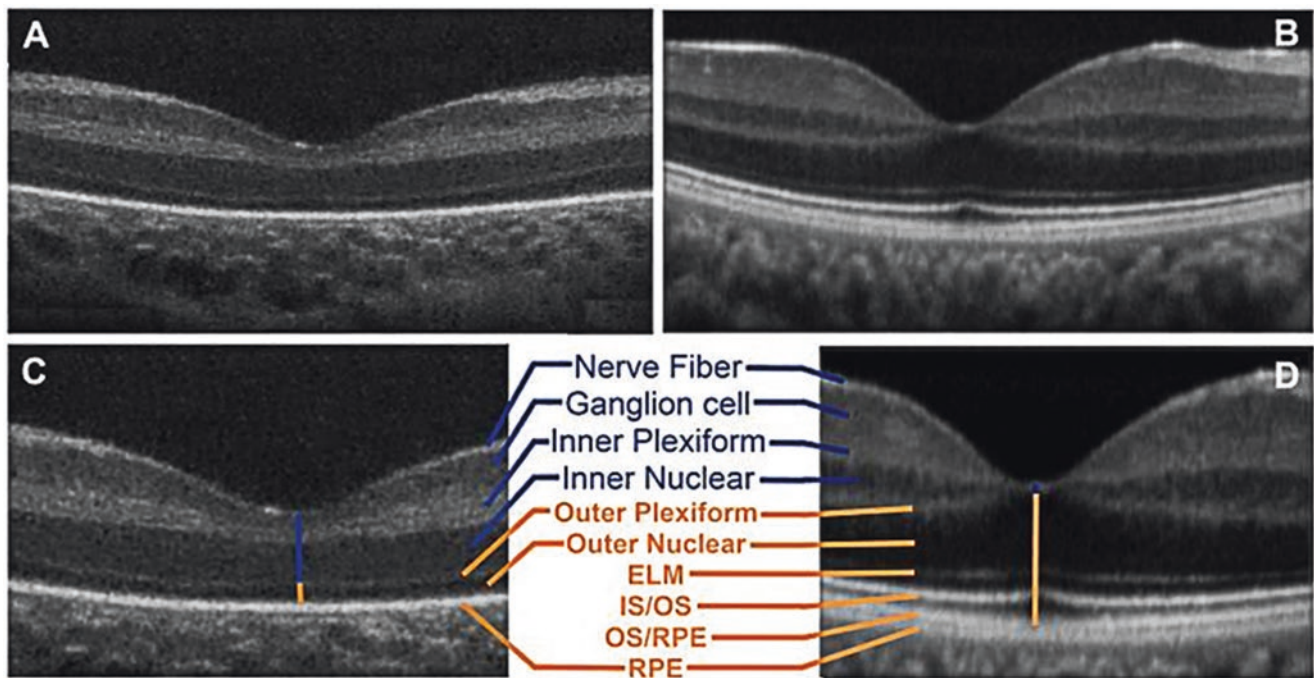


Fig. 2.2 Hand-held spectral domain ocular coherence tomography (SD-OCT) (Bioptigen, Inc, Morrisville, NC) cross sectional images of immature and mature retinas. On the left is the retina of a 31 week post conceptual age neonate born at 27 weeks and 1205 g. On the right is a 23

year old adult born at term. (Reprinted from Maldonado RS, O'Connell RV, Sarin N, Freedman SF, Wallace DK, Cotten CM, et al. Dynamics of human foveal development after premature birth. *Ophthalmology*. 2011;118(12):2315–25 [22]. With permission from Elsevier.)

The authors postulate that the macular edema noted in the more severe ROP could be due to several causes. The first is an increase in VEGF levels in this setting and the second is mechanical traction exerted on the macula by the more peripheral acting ROP process. They considered it less likely that the ridge found in stage 2 ROP exerted significant tractional forces on the macula [23].

Other studies done to assess the retina of formerly preterm children with ROP include fluorescein angiogram (FA) and electroretinogram (ERG). A smaller than normal foveal avascular zone has been documented in formerly preterm children. In children born before 30 weeks of post conceptual age, the normal remodeling of the avascular zone from a densely vascular area does not appear to occur fully. Of note, this smaller avascular zone does not correlate with visual acuity [24]. It should also be noted that the increased central macular thickness found in formerly premature infants discussed previously also did not correlate with visual acuity. Multifocal ERG studies have documented a significant reduction in amplitude and implicit time in children with a history of ROP as compared to age-matched controls. This is postulated to occur due to the impairment of the normal centrifugal movement of foveal cone nuclei and inner retinal cells in children with ROP. This arrest can result in the bipolar and amacrine cells remaining more central and causing the ERG findings [25].

Optic Nerve

During the second trimester of fetal development, the optic nerve contains about 3 million nerve fibers. During the third trimester, a number of the fibers are eliminated during the segmentation of inputs to the ipsilateral and contralateral lateral geniculate nuclei. An adult optic nerve is left with about 1 million nerve fibers. The optic nerve and optic tract are not completely myelinated at term birth and this process continues until roughly 2 years of age. The appearance of the optic disc is different in preterm infants, assuming initially an ovoid shape and over a period of several months normally becoming more round in shape. The optic nerve of a preterm infant often appears paler than that of an older child, regardless of racial or ethnic origins [26].

Optic Nerve Hypoplasia

Definition

An abnormally small optic nerve head that may appear pale or gray in color that may be surrounded by a peripapillary halo and bordered by a ring of either increased or decreased pigmentation. This process can be either unilateral or bilateral and may occur as an isolated event or be associated with midline brain defects.

History

The first case of optic nerve hypoplasia was described in 1877 by Briere. The first schematic drawing of the condition is attributed to Schwarz in 1915. The association of optic nerve hypoplasia with absence of the midline septum pellucidum was first described by Reeves in 1941. Dr. William Hoyt described in 1970 the association between optic nerve hypoplasia and growth hormone deficiency [27].

Epidemiology

Optic nerve hypoplasia is a common cause of congenital legal blindness. In 2007 the Babies Count Registry listed optic nerve hypoplasia as the third most common cause of blindness in infants. The first two were retinopathy of prematurity and cortical visual impairment. It was also attributed to be the most likely cause of blindness in children under the age of 3 years in the United States [28].

Systemic Manifestations

The most significant potential association with optic nerve hypoplasia is hypopituitarism. Infants manifesting this condition should be monitored carefully for associated endocrine abnormalities [29]. More recently, associations have also been established with hypothalamic dysfunction, developmental delay, and autism. Of note, these are all independent of septum pellucidum development. It is important to monitor these children carefully from an early age [30, 31].

Ophthalmic Manifestations

In a study of RetCam image analysis of the optic nerve in premature infants, Mcloone et al. sought to examine children with and without ischemic brain injury. These images were combined with serial cranial ultrasonography in order to date the brain injury in children with periventricular white matter damage. There is a well-established increased incidence of intraventricular hemorrhage (IVH) with decreasing gestational age. In the above study, 61 % of the 109 premature infants with birth between 24 and 33 weeks gestation demonstrated IVH. In this population, only the infants with grade 4 IVH had significantly more hypoplastic discs than the normal control group. The median age of injury for the patients in the Grade 4 IVH group was 26 weeks post conceptual age and this group represented 8.3 % of the study population. 44 % of infants in this group were noted to have hypoplastic discs [29]. The authors recommend that given the potential association of neurologic and visual complications, preterm infants with Grade 4 IVH be referred for eye evaluation even if they fall outside of normal ROP screening criteria. Jacobsen et al. have postulated that if early prenatal damage occurs to the periventricular white matter, prior to development of the supporting tissues around the optic nerve, then a smaller optic disc size may result. They also reported that a small optic disc area in a child with periventricular

leukomalacia or periventricular hemorrhage could predict the timing of the brain injury. A small optic disc area was only seen in children with white matter damage estimated to occur prior to 28 weeks of post conceptual gestational age. If the injury occurred after 28 weeks, they suggest that a normal sized optic disc would develop but it would have a large cup area and thin neuroretinal rim [32].

In a study by De Silva et al., optic nerve head dimensions were measured in 51 infants during routine ROP screening using the Retcam with either an 80 or 130° lens. Past studies were done using postmortem specimens and were subject to fixation and shrinkage artifact. The mean values obtained were horizontal disc diameter $1.05 \text{ mm} \pm 0.13$, vertical disc diameter $1.41 \text{ mm} \pm 0.19$, and mean disc area $1.17 \text{ mm}^2 \pm 0.26$. The infants studied ranged from 32 to 50 weeks post conceptual age and the authors found that the optic nerve head dimensions did not change significantly over this age range [33]. Other studies have also reported the optic disc parameters of premature infants such as optic disc area and cup-to-disc ratio did not correlate with birth weight or gestational age [30, 31]. The measurements taken of optic disc height and width were found to be larger than the values previously obtained from postmortem studies. Of note, De Silva et al. also reported a high proportion of eyes (23 %) to have a double ring sign classically ascribed to optic nerve hypoplasia. They suggest this may be a normal stage of disc development since their measurements would indicate the optic nerve enlarges by 50 % after birth to reach adult proportions. This growth largely abolishes the double ring sign in most and those that do not grow retain the double ring and are left with a hypoplastic nerve [33].

Refraction and the Premature Eye

History

Children with a history of prematurity, and particularly those that have had retinopathy of prematurity (ROP), have a higher incidence of myopia than their age matched counterparts. Another interesting finding that has been reported is that premature infants tend to have a higher degree of astigmatism, particularly in more severe cases of ROP [34, 35]. It remains a subject for debate as to which element(s) of the determination of refractive status are most responsible for the development of both myopia and astigmatism. A number of studies have been published over the last several years proposing several possible answers. These studies address axial length, corneal curvature, anterior chamber depth, lens thickness, and the impact of either laser or cryotherapy induced treatment changes as causative factors [36–41]. Other factors that have been implicated are bone mineral deficiency, temperature, lighting, and visual deprivation [42, 43].

Epidemiology

Quinn et al. have reported that in eyes with any stage of untreated ROP, and eyes treated with cryotherapy for threshold stages of the disease, the incidence of myopia increases during the first year of life [34]. Others have reported that myopia in preterm infants begins at about 6 months of age and severity increases between 6 months and 3 years of age [41]. The severity of the myopia is often linked to the severity and stage of the ROP that was present. Cross sectional and longitudinal studies have reported the rates of myopia in the pre-term population to be anywhere from 5 % to in excess of 80 % varying with the age at the time the examination was performed [44–46]. Choi et al. found in a study of 125 eyes that premature infants tend to initially develop myopia at the age of 6 months and progresses to the age of 3 years. The highest levels of myopia tend to develop in children that had cicatricial retinopathy, regardless of whether they received treatment with cryotherapy or not [41]. One common theme that emerges from most of these studies is that the myopia is not due to an increase in the axial length of the eye, but rather to factors related to the anterior segment of the eye such as the cornea, anterior chamber depth, and lens.

Ophthalmic Manifestations

The normative refractive status of full term infants is generally a moderate state of hypermetropia. This tends to persist for the first several years of life with a steady decline in hyperopic refraction through the childhood years as the emmetropization process proceeds. In premature eyes, there are several factors that may contribute to the development of myopia, which may be mild to severe. In a study comparing highly myopic eyes in preterm children with a history of ROP to an age matched group of patients with high myopia born at term without any ROP, Garcia–Valenzuela et al. found that increases in lens thickness and attendant power are the primary factors causing high myopia in ROP eyes. This finding was not related to stage of ROP attained or treatment of threshold ROP [47]. This finding led them to support a theory of altered anterior segment development for the resultant high myopia. They also found only a minimal increase in axial length as compared to age matched norms (mean of 23.36 ± 1.71 mm vs. 22.21 ± 0.80 mm). In the full term group with high myopia, the cause was primarily axial length with the mean value measured at 27.02 ± 1.87 mm. They advocate comparing the ratio of lens thickness/anterior chamber depth between ROP and full term highly myopic eyes to highlight the difference in anterior structures between the two groups. The eyes with ROP had a ratio 50 % higher than full term or normative eyes [47].

Fielder et al. proposed that myopia associated with prematurity was a result of the preterm cornea not appropriately flattening in the setting of the cooler environment outside of the womb [42]. Hittner et al. reported decreased anterior chamber depth in myopic eyes that had cicatricial changes secondary to ROP [48]. Laws et al. found that axial length was inversely related to increasing stage of ROP with the higher the stage reached, the lower the axial length recorded. This remained true after correction for gestational age, sex, birth weight, and head circumference. They also found that infants reaching threshold stage 3 disease had a shorter axial length than stage 3 infants not receiving treatment. In both cases, the growth in axial length was found to be linear [49]. Yang et al. found that laser treated eyes for threshold ROP showed a significantly thicker lens and shallower anterior chamber depth than full term control infants [50]. A reasonable conclusion is that the myopia associated with prematurity has an arrested development of the anterior segment structure as its root cause and is nonaxial in nature. Its cause seems to be more related to a steeper cornea and a thicker lens with associated shallower anterior chamber depth. Findings from the Early Treatment of Retinopathy of Prematurity Study (ETROP) would also indicate that the increased myopia in patients treated with laser is not due to any direct effect of the laser on the retinal periphery, but rather due to the severity of the ROP [51]. In a follow on report regarding the progression of myopia to ages 4–6 years, the ETROP group found that approximately 2/3 of eyes of children that had high risk pre-threshold ROP will likely be myopic into the early school-age years. The proportional increase in high myopia noted in earlier age groups was not noted to continue between ages 3 and 6 years [52].

Another potential refractive outcome in the premature infant with ROP is the development of astigmatism. In a cross-sectional study of 24 consecutive preterm children treated with diode laser for threshold disease at age 9 years, Yang et al. sought to assess the prevalence of astigmatism in this group. They matched their results with 1021 full term controls from a national survey in Taiwan, Republic of China. They found that the laser treated eyes had a mean astigmatism of 3.47 ± 1.92 diopters, with a mean spherical equivalent of -4.49 ± 3.76 diopters. Age matched controls showed a mean of 0.08 ± 0.9 diopters, with a mean spherical equivalent of -0.44 ± 1.48 diopters. 98 % of the eyes studied showed astigmatic changes, the majority of which were with-the-rule with greater steepening in the vertical meridian. They found the astigmatism to be corneal in origin and reported a statistically significant steeper vertical corneal meridian and flatter corneal meridian than those found in the control group. Their hypothesis was that there is an incomplete postnatal development of the cornea, anterior sclera, and anterior segment in this population at the age of 9 years [53]. In an ETROP study report,

Davitt et al. reported that by age 3 years, over 40 % of eyes with high-risk pre-threshold ROP will develop astigmatism of greater than or equal to 1.00 diopter and 10–20 % of these eyes will develop more than 2.00 diopters. There was no evidence that earlier treatment of this population, or the presence of stage 1 disease or plus disease significantly influenced the development of astigmatism. The majority of the astigmatism was with the rule in nature [51].

Ocular Infections in the Premature Infant

Definition

An ocular infection can be considered to be located anywhere on the surface of the eye, on the surrounding ocular adnexa, such as the lids or periocular skin, or inside the eye in the form of endophthalmitis. A series of infections with the collective acronym TORCH infections can have potentially devastating clinical and ocular manifestations. This acronym stands for Toxoplasmosis, Other (syphilis, Varicella Zoster), Rubella, Cytomegalovirus, and Herpes Simplex Virus. These infections, with the exception of Herpes Simplex, will be addressed in another chapter of this text.

History

Ophthalmia neonatorum or conjunctivitis of the newborn has been a public health concern that has been recognized for over 100 years. In late nineteenth century Europe, the prevalence of this condition exceeded 10 %, with blindness occurring in about 3 % of affected infants. About 50 % of the children in schools for the blind during this era were there due to ophthalmia neonatorum infection. In an 1881 paper, Crede' published the impact of using a 2 % silver nitrate solution in reducing the number of cases of this disease dramatically. He realized that the majority of infections resulted from transmission of *Neisseria gonorrhoea* as the child passed through the vagina at birth. His discovery led to a dramatic reduction in the disease throughout Europe [54]. In the modern era, silver nitrate has been largely supplanted in developing countries by erythromycin or tetracycline ointment. These antibiotics are far less irritating, seldom produce a chemical conjunctivitis, and also provide better coverage for *Chlamydia trachomatis*, the number one cause of ophthalmia neonatorum in developed countries today. Prophylaxis is recommended by the American Academy of Pediatrics and required by state law in many states, but is not being done automatically in other developed nations such as the United Kingdom [55]. Another option for prophylaxis worldwide, but not CDC approved in the United States, and one which is highly cost effective, is the use of povidone iodine 2.5 %.

The cost of a 5 cm³ container of this substance is \$0.10, as compared to erythromycin ointment at \$0.74 [54]. Drug shortages of erythromycin in the United States in 2009 led to the use of alternative, unproven antibiotic substitutes [56].

Epidemiology

The duration of hospitalization for a newborn infant is inversely related to the gestational age at birth. The average length of stay for newborn infants born at 26 weeks is roughly 2 months. This population of extremely low birth weight infants generally undergoes a number of invasive procedures and is commonly exposed to mechanical ventilation, including high frequency jet and oscillation, continuous positive airway pressure devices (CPAP), endotracheal suctioning, prolonged use of central venous lines, and nasogastric tube feedings. This places them at high risk for the development of infections, a number of which can affect the eyes from either exogenous or endogenous sources. In a study of two Neonatal Intensive Care Units (NICU) over a 2 year period and involving almost 3000 premature infants, conjunctivitis was found in 5 % of patients. An association was established between low birth weight, the performance of an eye examination, and respiratory support measures as a predictor for the development of conjunctivitis. The respiratory support measures implicated included nasal cannula delivered CPAP, endotracheal intubation, and mechanical ventilation [57]. Common pathogens isolated are identified in Table 2.3 with

Table 2.3 Organisms causing conjunctivitis in neonatal intensive care unit patients

Organism	Total no. of isolates ^a
Coagulase-negative <i>Staphylococcus</i>	38 (25) ^b
<i>Staphylococcus aureus</i>	29 (19)
<i>Klebsiella</i> spp.	16 (10)
<i>Pseudomonas aeruginosa</i>	13 (8)
<i>Enterococcus</i> spp.	13 (8)
<i>Escherichia coli</i>	12 (8)
<i>Serratia marcescens</i>	12 (8)
<i>Enterobacter</i> spp.	10 (6)
<i>Streptococcus</i> spp.	9 (6)
Other Gram-negative bacilli	11 (7)
Diphtheroids	3 (2)
Yeast	4 (3)
Culture not obtained	33 (21)
Total	203 (131) ^a

^aIncludes 44 cases with >1 organism isolated

^bNumbers in parentheses, percent of cases

Reprinted from Haas J, Larson E, Ross B, See B, Saiman L. Epidemiology and diagnosis of hospital-acquired conjunctivitis among neonatal intensive care unit patients. The Pediatric infectious disease journal. 2005;24(7):586–9 [57]. With permission from Lippincott, Williams & Wilkins

the most common pathogen being coagulase negative *Staphylococcus Aureus*. These results are consistent with previous studies published in the literature [58–60]. Another important factor to consider is the potential colonization of bacteria among mothers and infants which could contribute to the development of ocular infection in vulnerable preterm infants. Studies have shown that between 1–4 % of mothers and infants are colonized with the potentially serious Methicillin Resistant *Staphylococcus Aureus* (MRSA). This organism may be vertically transmitted from mother to child during vaginal birth [61]. An important consideration is that in some cases of conjunctivitis in a premature infant, the causative organism may lead to a significant keratitis or endophthalmitis, and may also result in a life threatening systemic infection. Conjunctivitis in a preterm infant warrants a thorough evaluation with cultures and bloodwork.

Ophthalmic Manifestations

Bacterial conjunctivitis in the preterm infant is generally heralded by a purulent discharge from one or both eyes accompanied by ocular redness and possible lid swelling. The discharge may be less copious than that observed in an older child with a similar infection due to the immature immune system. Gonococcal conjunctivitis is a notable exception and normally presents with a hyperpurulent discharge even in the preterm infant. The most frequent cause found in the United States and other developed countries is *Chlamydia trachomatis*. This is a sexually transmitted pathogen normally acquired by the child during the delivery process. The incubation period is generally 5–14 days after delivery and it may present either unilaterally or bilaterally. Children born to infected mothers have a 30–40 % chance of developing conjunctivitis [62]. Unfortunately, according to the 2012 Red Book, there is no effective agent to date to prevent the vertical transmission of *Chlamydia* from infected mother to her infant. Infections can range from mild to severe with the mildest forms presenting with a clear discharge with thickening and erythema of the palpebral conjunctiva. More serious infections can result in a thicker discharge with pseudomembrane development or corneal involvement in the form of clouding or pannus [63].

Gonococcal conjunctivitis is also a sexually transmitted pathogen acquired by the infant during vaginal delivery. Classically this presents as bilateral hyperpurulent conjunctivitis with significant lid edema, chemosis, and potential formation of membranes or pseudomembranes. Its ocular consequences may be more severe with progression to corneal ulceration or perforation if not treated promptly. The organism is able to penetrate intact epithelial cells and multiply rapidly inside of them. The onset of the infection is usually within 48 h of vaginal delivery. In the modern era, this

organism represents less than 1 % of the cases of neonatal conjunctivitis [59].

Another potentially serious bacterial pathogen in the preterm infant is *Pseudomonas aeruginosa*, which tends to colonize in water saturated respiratory equipment. Although *Pseudomonas* is a less common cause of conjunctivitis, it is capable of progressing rapidly to corneal ulceration or perforation if not treated promptly. An outbreak in seven ventilated infants at a NICU in Brazil suggests that the conjunctivitis may have occurred from spread from endotracheal tube aspirates. The same strain of *Pseudomonas* was isolated from the respiratory tract of two of the infected infants [64]. In an outbreak of this organism in a pediatric hospital involving 30 patients, 70 % of the patients were preterm infants in the NICU. All of the patients except one had respiratory care interventions prior to the onset of conjunctivitis. These included endotracheal tube, tracheostomy placement or suctioning of the respiratory tract. The authors stressed the need for caution and protection around the eyes when performing these measures [65].

Other organisms, both gram positive and negative, have been identified as causative agents in conjunctivitis in the preterm infant. Common gram positive organisms are *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Streptococcus viridans*. These collectively make up 30–50 % of the reported cases [66]. Common gram negative organisms isolated, in addition to the previously mentioned *Pseudomonas aeruginosa*, are *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Haemophilus influenzae*. Very low birth weight infants with commensurate early gestational age in the NICU with signs of conjunctivitis should generate immediate concern for a possible gram negative etiology. Chen et al. reported the incidence of gram negative isolates causing conjunctivitis as 38 % in a NICU setting [67].

Viral conjunctivitis is another potential issue for the preterm infant. Most herpetic infections in the preterm infant are secondary to vertical transmission of HSV-2 transmitted to the infant during birth. This infection generally occurs within the first 2 weeks after birth and may affect one or both eyes. Clinical signs may be subtle and include lid edema, bulbar conjunctival injection, and a watery discharge. Typical dendrites are seldom noted but geographic ulceration of the cornea may be seen. Herpetic infection may also result in a retinopathy causing necrosis, vasculitis, and hemorrhage. Those with retinitis will often develop a cataract and the virus can often be isolated from these lenses [68]. Ocular signs may be the initial or only manifestation of herpetic infection although serious systemic disease can result, as will be discussed in the next section. If a mother with an active genital herpetic infection delivers vaginally, there is a 40–60 % chance the child will be infected [69]. In about 60 % of infections in the preterm infant, the mother will show no signs of active herpetic infection [70].

Another potential viral pathogen of the preterm infant is adenovirus. In an outbreak in a NICU in Israel, the virus was found in seven premature infants who had undergone an eye examination 4–7 days previously. Three of the infected infants went on to manifest systemic respiratory symptoms. The temporal relationship of the eye exams to the outbreak suggests direct inoculation of the infants by ophthalmic instruments or transmission by the involved personnel. Several of the affected children had underlying pulmonary disease and were being treated with steroids which likely exacerbated the course of the illness [71]. Respiratory related pathology is a very common finding in the preterm infant. The need for aseptic techniques using separate sterile instruments for each child in the NICU during exams cannot be overemphasized.

More serious ocular infections are also a very real threat in the premature infant. Endophthalmitis may result from both exogenous and endogenous sources. It has been reported that 80 % of neonatal endophthalmitis comes from endogenous sources [72]. In the cases of exogenous spread, conjunctivitis was the initial presenting sign. These infections are generally nosocomially acquired, often from contaminants from suction devices, nasal CPAP devices, or respirators. Typical exam features in the NICU are a red eye, a compromised red reflex, and corneal clouding. *Pseudomonas aeruginosa* has been identified as an exogenous source agent of neonatal endophthalmitis and has been reported to be the causative agent in more than 75 % of invasive eye infections in this population. Preterm infants are particularly vulnerable to infection by this organism [73]. Gaili and Woodruff reported a case of a preterm infant who initially became ill on day 12 of life and intravenous antibiotic treatment was begun, but there were no signs of ocular infection at that time. She was started on nasal CPAP. By day 21, the eye became “sticky”, and by day 22 there was a frank purulent discharge coming from one eye and the cornea became cloudy. A culture of the conjunctiva was positive for *pseudomonas aeruginosa*. Despite intensive intravenous and topical therapy, the eye perforated and was lost. They postulate an initial corneal epithelial injury that likely occurred via the CPAP apparatus and progressed rapidly [74]. Figueirdo et al. describe a similar case of *pseudomonas aeruginosa* endophthalmitis in a preterm infant born by caesarean section. In this instance, the infant initially developed septicemia and shortly thereafter developed a red eye with discharge, a cloudy cornea and hypopyon. Blood cultures subsequently revealed *pseudomonas aeruginosa*, but conjunctival cultures were negative. The mother’s wound cultured positive for the same organism. As in the first case, despite aggressive intravenous and topical therapy, the ocular infection progressed and the eye perforated and was lost [75]. These cases underscore the importance of aggressive treatment of ocular infections in the preterm infant. If the organism is fulminant, as in

the case of *pseudomonas*, morbidity is very high and the infection can be life threatening.

Other forms of endophthalmitis can also occur in the preterm infant. Group B streptococci (GBS) are a major pathogen causing bacterial infection in this age group. Endophthalmitis from this pathogen is unusual in the neonate, but has been reported [76]. Most of the cases are associated with both sepsis and meningitis from the organism and tend to occur weeks later than the onset of the systemic infection, even with appropriate intravenous antibiotic therapy. Group B streptococcal meningitis interferes with the normal blood flow autoregulation to the eye and may contribute to an increased risk of retinal pathology in this group [77].

Another form of endophthalmitis to which the preterm infant is susceptible is *Candida*. This is also a rare occurrence but the visual consequences are often devastating. It is almost always associated with a septicemia due to the *Candida* organism and is spread to the eye endogenously. Systemic candida infection has been reported to occur in 1.6–12.9 % of premature births, particularly in very low birthweight children [78–80]. Of note, there are a number of reported cases of endogenous *Candida* endophthalmitis in premature infants secondary to the organism remaining sequestered in the lens [81–83]. The endophthalmitis often presents after resolution of the systemic candidemia and is thought to be potentially due to the regression of the fetal hyaloid artery between 24 and 32 weeks post conceptual age. This permits the transmission of the fungus to the lens initially with subsequent sequestration. A cataract that may develop in this setting may actually represent a fungal abscess within the lens [84]. Fungal endophthalmitis may lead to necrotic retinal detachment and glaucoma, in addition to cataract.

Systemic Manifestations

A number of ocular infections in the preterm infant can be associated with serious systemic illness and may result in serious morbidity or mortality. Premature infants who contract a *Chlamydia* infection during the birth process have a 10–20 % chance of developing pneumonia related to this organism [85]. This generally results from an infection in the nasopharynx or aspiration of infected secretions from the mother during birth. The presentation is generally a respiratory distress with low grade fever and cough that may progress to apnea requiring ventilator support. The infection typically occurs around 3–6 weeks after birth but has been reported between 1 and 19 weeks of chronologic age [86].

Sepsis of early or late onset is not an uncommon occurrence in the preterm infant. Infant birth weight is inversely related to the risk of developing sepsis. Organisms that can

cause ocular infection that can also result in sepsis include Group B streptococcus, *Staphylococcus aureus*, Coagulase negative staphylococcus, *Klebsiella pneumoniae*, *Haemophilus Influenza*, *Candida albicans*, *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Neisseria gonorrhea* [87].

Although intrapartum prophylaxis has significantly reduced early onset of GBS infection, late onset GBS sepsis is still common in the preterm infant. Most reported cases of associated endophthalmitis are associated with later onset disease and generally occur 1 week to 3 months after birth [76, 88]. The early onset infections are generally vertically transmitted from an infected or colonized mother during the birth process. The later onset infections are either acquired from colonized mothers, staff, or equipment in the NICU. With the increased survival rates of preterm infants, the burden of potential infection remains higher than ever. If a preterm child becomes septic, pediatricians often recommend a daily eye exam for early identification of ocular disease, and prompt ophthalmology consultation for any ocular signs [87].

Candida is a major cause of sepsis in the NICU in infants born less than 1500 g. Rates have been reported between 1.6 to 12.9 % in this population of infants, and morbidity and mortality rates approach 25 % [80]. The sources of systemic candidiasis are mostly endogenous, and infections are associated with total parenteral nutrition solutions and indwelling intravenous lines [89, 90]. Some authors suggest that candida sepsis should be strongly suspected after the third week of NICU admission in infants on mechanical ventilation and who have undergone treatments with multiple classes of antibiotics for other infections [91]. The general colonization rate for candida in infants who have been in the NICU environment for 1–3 months may be as high as 50 %, with the GI tract often being an early area affected [92]. Once the empiric or confirmed treatment for candida sepsis is begun, the ophthalmologist is often consulted to check the eyes for evidence of candida endophthalmitis.

Meningitis is another potential systemic complication of infections in the preterm infant that can also affect the eye. The potential organisms involved are those previously described that may result in sepsis. Meningitis is usually of later onset in this population, between 1 week and 3 months after birth. The most commonly identified organism causing meningitis in the premature infant is GBS, which is involved in about 50 % of cases. E-coli is the next most common pathogen, implicated in 20 % of cases, with *Listeria monocytogenes* next at 5–10 % [93, 94]. Another potential causative organism in neonatal meningitis worthy of mention is the *Herpes simplex* virus. The impact of a meningitis infection in these infants is significant. In a large study of 1500 babies with neonatal meningitis, 8 % had motor deficits, to include cerebral palsy, 7.5 % had learning difficulties, 7.3 % suffered from seizures, and 25.8 % had hearing impairments [95].

Diagnosis

The diagnosis of ocular infection in the premature infant may be more challenging than in the adult patient. Due to the increased susceptibility of the immature immune system, a healthy suspicion of a possible coincident systemic infection must be kept in mind. For a suspected conjunctivitis, the suggested evaluation would include a conjunctival swab for culture and sensitivity, a conjunctival scraping for gram and giemsa stain, polymerase chain reaction (PCR) testing for *Chlamydia*, chocolate agar plating for *Gonococcus* or *Haemophilus*, blood agar for other bacterial species, and PCR for suspected Herpes infection. In the setting of any associated illness, blood cultures should also be performed immediately. Blood cultures should include both aerobic and anaerobic varieties, with results usually available within 36–48 h.

In the setting of a suspected endophthalmitis, organisms may be identified through vitreous culture, either from a biopsy or retrieval from a vitrectomy specimen. Most commonly the diagnosis is established by blood cultures. In a review of endogenous bacterial endophthalmitis, blood cultures were positive with the offending organism in 94 % of cases, and vitreous samples were positive in only 56 % [76]. To evaluate for fungal etiology, routine cultures can be ordered but are often low yield. More recently, the use of pan-fungal PCR testing has improved the yields on these cultures [96].

Management

In treating conjunctivitis in the preterm infant, initial treatment should be presumptive based upon initial gram stain or giemsa stain results. Consideration should be given to the potential for maternal infection and potential transmission of *N. gonorrhea*, *Chlamydia*, *Herpes*, or Group B streptococcus. Examination and culture of the parents may be necessary if suspicion is present. Time honored initial treatment of the conjunctivitis is the use of erythromycin ointment for gram positive organisms or topical gentamicin or tobramycin for gram negative organisms. It is also important to initially start intravenous antibiotics to cover for potential *Neisseria gonorrhea* infection or *Chlamydia* infection pending the return of culture results. The use of topical antibiotics alone is inadequate for the treatment of either of these forms of conjunctivitis and generally should not be used once the diagnosis is confirmed. Typical intravenous regimens would include either penicillin G or ceftriaxone to cover the *Neisseria gonorrhea* and erythromycin to cover *Chlamydia* [97].

Longer duration of stay in the NICU may predispose the infant to other pathogens that may cause conjunctivitis. Gram positive organisms, to include Methicillin Sensitive *Staphylococcus Aureus* (MSSA) and *Enterococcus* have

been reported in higher frequency with greater duration of stay. Gram negative organisms such as *Pseudomonas aeruginosa* and *Serratia marcesans* were more frequently cultured after the first 10 days of admission, presumably from nosocomial transmission [98]. These organisms, with the potential exception of MRSA (see next paragraph), can be effectively treated with topical fourth generation fluoroquinolone preparations. These medications have shown very low resistance patterns to most gram positive and gram negative isolates to date. This potent class of antibiotics tends to kill the organisms quickly, thus reducing the potential for bacterial mutation [99].

Bacterial conjunctivitis caused by Methicillin Resistant *Staphylococcus Aureus* (MRSA) has also been reported in the neonate. A common practice in a number of NICU's is to take weekly pharyngeal and skin swabs to test for colonization of MRSA. These infants are typically not symptomatic, but colonization may be associated with a nasolacrimal duct obstruction. In these cases, it is possible that the parents or staff is also colonized and they should be checked accordingly [100, 101]. Current guidelines suggest treating MRSA infections with agents other than fluoroquinolones when possible. This is due to the high in-vitro resistance rates that MRSA have shown to these agents [102]. Other options in this setting would be topical vancomycin, a topical polymyxin B- trimethoprim combination, and topical chloramphenicol, although the latter is seldom used in the United States and carries with it the potential complications of bone marrow hypoplasia and aplastic anemia.

The treatment of endophthalmitis, in the immature infant needs to be aggressive in nature. It is usually endogenous in origin, associated with sepsis, and often has a poor visual outcome. The diagnosis may be established from blood culture results or vitreous sampling. Treatment is generally with intravenous antibiotics and possibly intravitreal antibiotics. The normal blood ocular barrier is usually broken down in the setting of endophthalmitis, allowing reasonable absorption of intravenous antibiotics into the eye. Initial treatment involves empiric broad spectrum antibiotics for presumed bacterial infections. These generally include vancomycin and ceftazidime or amikacin, and arguably dexamethasone. Some favor the administration of steroids and others do not. The dosage of vancomycin for a preterm infant is a 15 mg/kg loading dose, followed by 10 mg/kg/day. The infusion is generally given over a 1 hour period and dosing can be effectively adjusted using serum creatinine concentration and desired trough levels as a guide [103]. The dosage of ceftazidime in this age group is 25–100 mg/kg/day in two divided doses.

Some preterm infants may have a persistent endophthalmitis or even develop endophthalmitis while on appropriate intravenous therapy with blood levels in the therapeutic range. This has led to the recommendation to combine intravitreal antibiotic

injection with intravenous antibiotic use. Vitreous biopsy can be achieved at the time of injection of intravitreal vancomycin and ceftazidime. This provides excellent initial gram positive and gram negative coverage and can be modified accordingly dependent upon gram stain and culture results. The normal dose of intravitreal vancomycin is 1.0 mg/0.1 mL and for ceftazidime 2.25 mg/0.1 mL [104, 105].

Vitrectomy is another treatment option in this age group but remains controversial. While it can relieve the bacterial burden in the vitreous, these children are often very ill and may not be well enough to undergo the surgical procedure [76]. It may be best advised for those infants who are not as ill systemically, those who may have developed a retinal detachment in the process, those with infections with particularly aggressive organisms, or in cases where the fundus cannot be visualized. Modern 25 gauge vitrectomy instruments may make this challenging surgery marginally safer.

The treatment of fungal endophthalmitis can often be initiated based upon the characteristic white appearance of the retinochoroiditis with overlying white vitreous condensations. This is a rare infection but accounts for many ocular consultations in the NICU in children with systemic involvement. Intravenous therapy with amphotericin B is a common approach, but this medication has relatively poor ocular penetration and can be toxic to the renal system. Less toxic alternatives include fluconazole with a usual dose of 200–400 mg/day for *Candida* species [106]. Intravitreal injection of amphotericin B or voriconazole are a possible adjunctive treatment approach, and vitrectomy may need to be considered if the infection remains unresponsive to treatment [107]. Recommended intravitreal dosage of amphotericin B is 5–10 µg/0.1 mL and Voriconazole 50–100 µg/0.1 mL.

Retinopathy of Prematurity

History of ROP

In 1941, Dr. Paul Chandler encountered the first two cases of retrolental fibroplasia in Boston, Massachusetts. These two cases were the forerunners of the epidemic now referred to as retinopathy of prematurity (ROP) [108]. Between 1942 and 1945, Dr. Theodore L. Terry collected 117 additional cases of ROP and determined that the pathology occurred in premature infants who initially had normal eyes. The changes associated with retrolental fibroplasia occurred a number of weeks after birth [109]. Husband and wife ophthalmologists, William and Ella Owens concluded that postnatal development of the vascular abnormality seen in ROP was caused by neovascularization beginning 2.5–3.5 months after birth [108, 110]. Secondary to these findings, weekly examinations of the interior of the eye soon became routine for ophthalmologists at large research institutions around the world.

Initially, multiple factors were considered in the pathogenesis of ROP including infection, anemia, vitamin deficiency, and oxygen supplementation. In the 1950s, Patz and colleagues reported an association between supplemental oxygen use and the exponential increase of ROP and resulting blindness worldwide [111, 112]. As a result of the Cooperative Study undertaken to determine the effect of oxygen on ROP, neonatal units started limiting the use of oxygen delivered to pre-term newborns and the morbidity and mortality of these infants exponentially increased [113–115]. In the 1970s, advances in medical technology improved the ability to save the most premature and low birth weight infants, and the incidence of ROP again increased exponentially [116]. Over the years, numerous multi-center trials have been performed to study the treatment outcomes and pathogenesis of ROP.

Pathogenesis of ROP

Understanding of the pathogenesis of ROP requires a basic understanding of ocular embryology. The retinal vasculature begins its development around 16 weeks post conception. The vessels begin at the optic nerve and spread circumferentially, reaching the nasal ora serrata around the eighth month of gestation and is completed at the temporal ora serrata at 40 weeks gestation. In full term infants, the retinal vasculature is mature; however, in pre-term infants, the amount of mature retina is highly dependent on how prematurely the infant is born. The risk of normal development of the retinal vasculature depends on the gestational age of the infant: the younger the infant, the higher the risk.

The relationship between ROP and oxygen exposure has been well elucidated over the years. Researchers are now able to explain the relationship of oxygen and ROP on a molecular level. It is known that angiogenesis is controlled by oxygen tension in many tissues; however, the retina appears to be more at risk when a breakdown of oxygen control occurs. The relationship between retinal and choroidal circulations is suspected to be the reason behind this vulnerability [117]. When a premature infant is placed on supplemental oxygen, a rise in oxygen tension occurs, which in turn reduces the level of cytokines, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF-1), required for blood vessel formation [118]. Therefore, the formation of normal retinal vasculature stops. Secondary to the inner retina's interaction with the choroidal circulation, which continuously maintains a high level of oxygen, the retinal vessels constrict and irreversibly close [119]. This is referred to as the hyperoxic stage. The next stage, hypoxia, occurs when the premature infant is taken off supplemental oxygen. Because of the fall in oxygen levels in the retina, angiogenic factors (VEGF and Erythropoietin) are

up-regulated and neovascularization occurs [119]. These new vessels may resolve spontaneously with adequate oxygenation; however, in severe cases, contraction of the new vessels places traction on the retina leading to retinal detachment and permanent vision loss.

The angiogenic factors most notable for their role in the pathogenesis of ROP include VEGF and IGF-1. As mentioned previously, VEGF is down regulated during hyperoxia causing retinal blood vessels to become irreversibly obliterated. VEGF is then up-regulated during hypoxia and promotes the formation of new blood vessels that contribute to the pathology seen in ROP [120]. With this knowledge, it is not surprising that anti-VEGF agents, such as bevacizumab, have been used with success in the treatment of ROP [18, 121–123]. This topic is discussed further in the section titled Treatment of ROP.

IGF-1 is also an important player in the development of normal retinal vasculature and in the pathogenesis of ROP. A deficiency of IGF-1 early in life causes abnormal retinal vascular development and contributes to the development of ROP. IGF-1 appears to contribute to ROP independent of oxygen related factors, such as VEGF [124].

Other factors such as Hypoxia-inducible factor 1 α (HIF-1 α), Placental growth factor (PlGF), and Erythropoietin (Epo) have also been implicated in the pathogenesis of ROP, although their roles are not as well understood. HIF-1 α is responsible for controlling the formation of VEGF. It is down regulated during hyperoxia and increased production occurs when oxygen levels return to normal. Therefore, HIF-1 α is important in both phases of ROP [120]. PlGF is similar to VEGF and shares many of the same biochemical properties; however, it has not been sufficiently studied in the pathogenesis of ROP and normal angiogenesis [120]. Epo is released during hypoxia and increases angiogenesis, as well as the number of erythrocytes. Studies have shown that a deficiency of Epo contributes to the first phase of ROP [125]. Current studies are evaluating the role of genetic factors, nitric oxide, apelin, adenosine, β -adrenergic receptors, inositol, and omega-3 fatty acids in the prevention and treatment of ROP [120, 126, 127]. Additionally, studies conducted in mice and several infants in utero suggest that increased light exposure decreases the risk of severe ROP [128]. Additional studies are underway to determine role of light exposure in ROP.

Oxygen Therapy and ROP

As mentioned previously, the role of oxygen therapy in the pathogenesis of ROP is well known. Michelson, Ashton et al., and Patz were the first to describe the effects of oxygen therapy on the developing retina in animal models [111, 112, 129, 130]. At that time, high oxygen levels alone were

believed to be responsible for the vascular attenuation seen in the developing retina. Since then, further studies have revealed that the duration of supplemental oxygenation is most strongly responsible for the development of ROP [115]. The incidence of ROP has remained high over the years and this can be attributed in large part to advancing technology that has enabled neonatologists to save extremely low birth weight infants. The availability of these advanced technologies varies throughout the world and accounts for the variability reported on the incidence of blinding ROP, reported as 10 % in the United States and 20 % or more in developing countries [131, 132].

After evidence that high levels of oxygen therapy were responsible for the epidemic of blinding ROP, neonatologists began to limit oxygen therapy for preterm infants. It quickly became apparent that insufficient oxygen therapy was devastating to the survival of preterm infants [113]. Studies in animal models suggested that oxygen therapy later in the course may reduce severe ROP by reducing the release of angiogenic factors responsible for the disease. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial studied this hypothesis. STOP-ROP tested whether higher oxygen saturation levels (96–99 % S_{pO_2}) as compared to lower levels (89–94 %) would decrease the progression to threshold ROP [133]. The study found that the group with higher oxygen saturations did not significantly reduce the number of infants requiring treatment for threshold ROP, nor did it increase the number of infants progressing from prethreshold to threshold disease [133].

Owen and Hartnett reviewed the recent studies published on the current role of oxygen therapy in ROP. They found these studies show no agreement in the appropriate target range for oxygen levels in premature infants [134]. The reasons cited for the inconsistencies found between the studies include differences in neonatal populations enrolled, as well as potential differences in NICU technology to monitor oxygen saturations. Some studies included infants from areas outside the United States, which strongly add to the potential variability in neonatal care and technology [164]

Classification of ROP

The classification of ROP follows criterion set forth by the International Classification of ROP (ICROP), a consensus statement published by a group of international ROP experts in 1984. The criterion was expanded in 1987. This system classifies ROP in regards to the location, extent, and severity of disease based on retinal landmarks, clock hours of diseased retina, and stage of neovascular response, respectively.

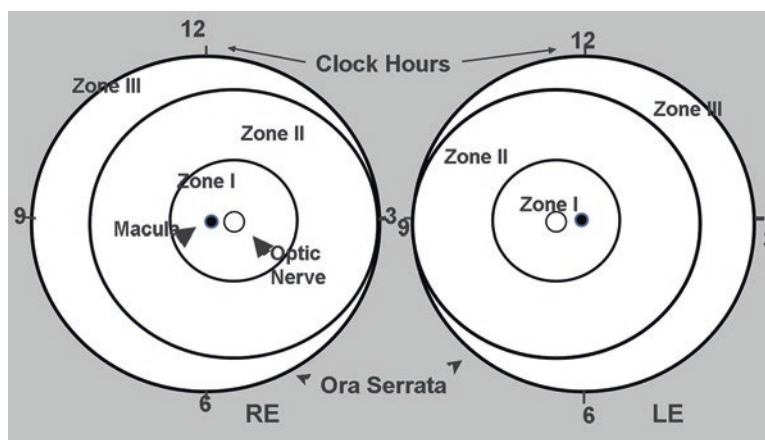
Location of disease is defined by three concentric zones surrounding the optic disc. Zone I is the innermost zone and its radius is twice the distance from the optic disc to the center of the macula, with the optic disc being the center of the circle. Zone II extends from Zone I to the nasal ora serrata (3 o'clock in the right eye and 9 o'clock in the left eye) and along the same line of curvature temporally. Zone III is the temporal crescent of retina anterior to Zone II [135] (see Fig. 2.3).

The extent of disease is recorded as clock hours of diseased retina. Each clock hour, for example from 12 o'clock to 1 o'clock, subtends 30° [135]. When the examiner is looking at the patient, the 3 o'clock position is nasal in the right eye and temporal in the left eye. The 9 o'clock position is temporal in the right eye and nasal in the left eye. The more clock hours of retina involved, the worse the retinal disease.

The severity of disease is classified in stages of abnormal retinal vasculature. In premature infants without ROP, the junction between vascular and avascular retina is very discrete. As ROP begins and advances, this junction becomes more apparent, and the observer can assign the pathology seen into one of the five stages of ROP. The highest stage seen in the eye is the stage assigned to that eye. This is an important distinction because different stages can be seen in different locations within the same eye.

Stage 1, the vascular-avascular junction is described as a white demarcation line. Often times, abnormal branching of vessels can be seen leading up to the demarcation line [136]. In stage 2, the demarcation line develops height and width and becomes a ridge extending above the retina. Tufts of neovascularization may be seen posterior to the ridge and on the

Fig. 2.3 Standard retinopathy of prematurity (ROP) classification zones and their location relative to the optic nerve head. (Reprinted from International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991–9 [136]. With permission from the American Medical Association.)



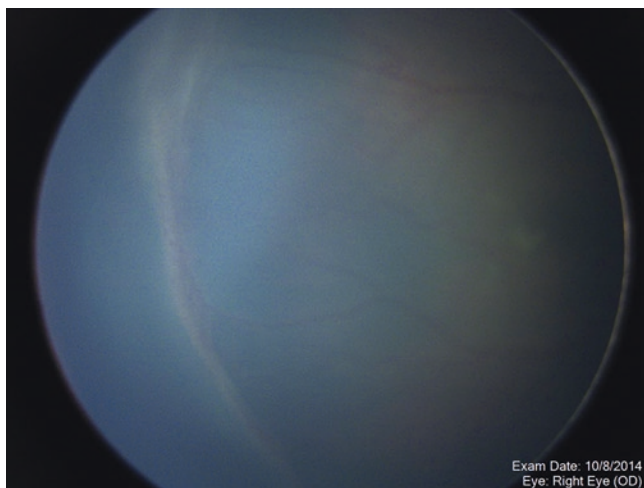


Fig. 2.4 Stage 3 retinopathy with prematurity (ROP) demonstrating an elevated ridge with neovascularization posterior to the ridge in zone 2

surface of the retina. This vascular tissue, called “popcorn”, is not consistent with stage 3 neovascularization. Stage 3 refers to fibrovascular proliferation involving the ridge that extends into the vitreous. The severity of stage 3 can be classified into mild, moderate, or severe disease, depending on the extent of fibrovascular tissue extending into the vitreous [135]. Contraction of the neovascular tissue can lead to retinal detachment, which is diagnostic for stage 4 ROP. Stage 4 is divided into two groups: extrafoveal (stage 4A) and foveal (stage 4B) retinal detachment [135]. If there is a total retinal detachment, this is classified as stage 5. As mentioned previously, retinal detachments in the setting of ROP are tractional and usually funnel shaped. Stage 5 can be divided into groups based on the appearance of funnel (see Fig. 2.4).

In addition to changes at the vascular-avascular junction, changes in the posterior pole vessels can aide in determining the severity of ROP. Plus disease refers to venous dilation and arterial tortuosity of the posterior pole vessels. Additionally, plus disease can worsen to include findings such as poor pupillary dilation, iris vascular engorgement, and vitreous haze [135]. A standard photograph depicting the minimum amount of venous dilation and arterial tortuosity to diagnose plus disease is used commonly in practice and has also been evaluated in several multi-center ROP trials [133, 137, 138]. If qualifying vascular dilation and tortuosity is present in two or more quadrants, the diagnosis of plus disease is made (see Fig. 2.5).

In 2005, the ICROP criteria were revised. Several important additions were made during this revision to include descriptions of pre-plus disease and aggressive, posterior ROP (AP-ROP) [136]. Pre-plus disease is defined as the observation of venous dilation and tortuosity that does not meet the criteria of the standard photograph for plus disease. These findings indicate a risk for progression to plus disease

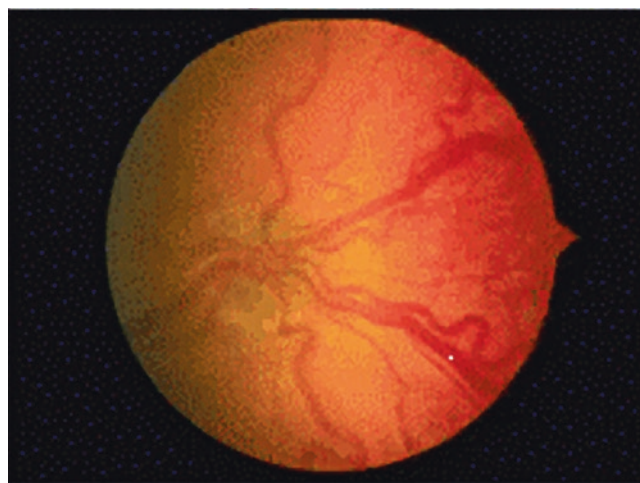


Fig. 2.5 Standard photograph of Plus Disease. (Reprinted from International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991–9 [136]. With permission from the American Medical Association.)

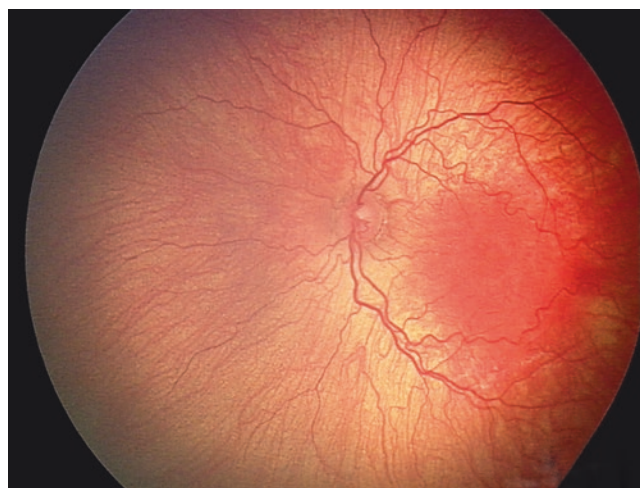


Fig. 2.6 Aggressive posterior retinopathy of prematurity (APROP) in zone 1 prior to laser treatment

and treatable ROP. AP-ROP (previously called rush disease) is a severe, rapidly progressive form of ROP that is seen in a very posterior location, usually zone I, and displays a prominence of plus disease and ill-defined extraretinal fibrovascular pattern. Plus disease is seen in all four quadrants, and it is often difficult to distinguish between the retinal veins and arteries secondary to significant dilation and tortuosity of both [136]. APROP may be easily overlooked by an inexperienced observer because the vascular-avascular junction may be relatively featureless, displaying only a flat neovascular network. APROP extends circumferentially and a circumferential vessel is often seen [136]. If left untreated, APROP often leads to stage 5 ROP (see Figs. 2.6 and 2.7).

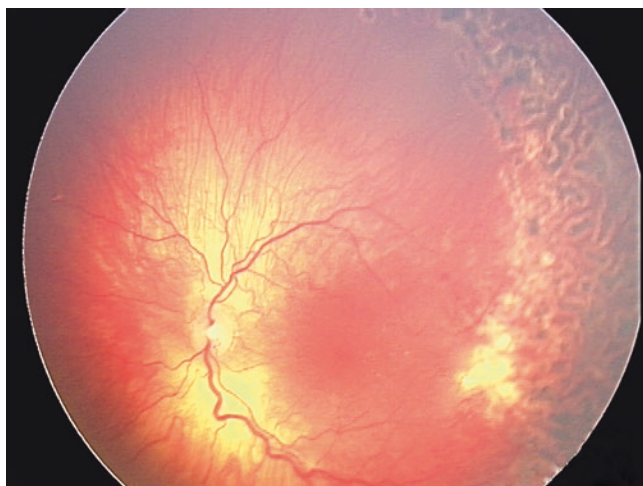


Fig. 2.7 Aggressive posterior retinopathy of prematurity (APROP) in zone 1 after laser treatment

The proper documentation of ROP follows a standardized format for describing the zone and stage of disease. The zone is documented using Roman numerals I, II, or III. The stage uses numerical notation, stages 0–5. If plus disease is noted, a “+” can be placed next to the stage or plus disease can be written instead. If pre-plus disease is noted, this distinction can be written next to the ROP stage. For example, zone two, stage three with plus disease is written zone II, stage 3+.

In addition to describing the zone and stage of ROP above, a standardized drawing method is also used. The extent and stage of disease is drawn on a standard cartoon of the posterior pole depicting zones I, II, and III. For stage 0, the posterior pole vessels are drawn extending from the optic nerve and ending at the clinically observed vascular-avascular zone. Stage 1 is drawn as a single line for the amount of clock hours it is observed. Stage 2 is drawn as double lines and stage 3 is drawn as three lines with “x” depicting the area of neovascularization.

Screening Guidelines

The American Academy of Pediatrics, American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus have published standard guidelines for American hospitals to follow regarding the screening of immature infants for ROP. The confidence of these guidelines in detecting severe ROP is 99% [139]. The goal of a hospital screening program is to identify the few premature infants that will require treatment for ROP from the larger number of at risk infants. In following these parameters, the goal is to decrease the amount of exams required to diagnose treatable ROP and to minimize the hospital resources required to examine a larger number of

Table 2.4 Recommendations for timing of first eye exam in premature infants

Gestational age at birth (weeks)	Age at examination (weeks)	
	Postmenstrual	Chronological
22 ^a	31	9
23 ^a	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4

^aThis guideline should be considered tentative rather than evidence-based for infants with a gestational age of 22–23 weeks because of the small number of survivors in these gestational age categories

Reprinted from Coats DK and Reddy AK. Retinopathy of Prematurity. In Pediatric Ophthalmology. Berlin Heidelberg. Springer-Verlag; 2009 [200]

infants. This is also important because ROP examinations can be stressful and potentially harmful for the premature, sick infants [139].

The current guidelines recommend screening of all infants born at 30 weeks estimated gestational age (EGA) or earlier or infants weighing <1500 grams (g) at birth. Additionally, infants with EGA of more than 30 weeks or those with a birth weight between 1500 and 2000 g with an unstable clinical course as determined by the attending neonatologist should also be screened. Screening should be performed with indirect ophthalmoscopy after pupillary dilation and topical anesthesia to reduce any discomfort the exam may cause. One retinal examination is sufficient only if it unequivocally shows full vascularization of the retina in both eyes. Many ophthalmologists that screen for ROP prefer a second exam confirming the presence of full vascularization before discharging the patient from examinations.

The guidelines for initiating screening examinations for ROP was developed by the evidence gathered in the Cryotherapy for Retinopathy of Prematurity study (CRYO-ROP) and later confirmed by the Light Reduction in ROP study [137, 140]. Because the onset of severe ROP correlates better with postmenstrual age (gestational age at birth plus chronologic age), this is used over postnatal age when determining the appropriate time for initiating screening examinations. In other words, the youngest infants at birth take the longest to develop serious ROP [141]. The initial eye examination should take place at 31 weeks postmenstrual age or 4 weeks chronological age, whichever is later (see Table 2.4).

Follow-up examinations should be recommended based on retinal findings encountered on examination. Follow-up of 1 week or less is normally recommended for the following findings: (1) zone I, stage 1 or 2 or (2) zone II, stage 3.

Table 2.5 Recommended follow up intervals for premature infants with or at-risk for Retinopathy of Prematurity

ROP severity	Recommended follow-up
Stage 1 or 2 ROP: zone I	1-week or less follow-up
Stage 3 ROP: zone II	
Immature vascularization: zone I—no ROP	1- to 2-week follow-up
Stage 2 ROP: zone II	
Regressing ROP: zone I	
Stage 1 ROP: zone II	2-week follow-up
Regressing ROP: zone II	
Immature vascularization: zone II—no ROP	2- to 3-week follow-up
Stage 1 or 2 ROP: zone III	
Regressing ROP: zone III	
Plus disease zone I or II	The presence of plus disease in zones I or II suggests that peripheral ablation, rather than observation, is appropriate

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The patient should be re-examined in 1–2 weeks with the following findings: (1) zone I, no ROP (immature vascularization); (2) zone II, stage 2; or (3) zone I with regressing ROP. Two week follow-up is recommended for the following: (1) zone II, stage 1 or (2) zone II with regressing ROP. Follow-up of 2–3 weeks is recommended for the following: (1) zone II, no ROP (immature); (2) zone III, stage 1 or 2; or (3) zone III with regressing ROP. The parameters for treatment of ROP are discussed later in the chapter [141] (see Table 2.5).

It should be noted that there are several factors that can make the ROP examination difficult and may require further examination for better visualization. These factors include poor dilation, normal haze of the premature cornea, persistent tunica vasculosa lentis (most often related to early post-conceptual age), vitreous flare or vitreous hemorrhage. It is important to document these findings as they often prevent an adequate screening examination and may warrant repeat examination sooner than otherwise necessary. It is also important to consider that some of these findings, including poor pupillary dilation, persistent tunica vasculosa lentis, vitreous haze, and vitreous hemorrhage, can be associated with active, severe ROP.

Age and retinal findings guide the decision regarding cessation of ROP examinations. Findings that suggest that the examinations can be stopped include the following: (1) zone III retinal vascularization without previous zone I or II disease; (2) full vascularization; (3) postmenstrual age of 45 weeks and no prethreshold disease (zone II, stage 3 or any zone 1 ROP) or worse ROP is present; (4) regression of ROP with absence of abnormal vascular tissue capable of progression or reactivation. If the infant is less than 35 weeks

postmenstrual age, confirmatory exams, even in the presence of the above findings, may be warranted [139, 142].

Most ROP screening programs arrange for the examining ophthalmologist to examine infants in the neonatal unit once weekly [143]. The neonatologist and neonatal nurses are responsible for identifying infants meeting the screening guidelines outlined above and communicating this with the ophthalmologist and his/her staff. Many large ROP screening programs have a specific ophthalmology nurse or technician responsible for maintaining this list in the ophthalmology office. This person often accompanies the ophthalmologist during weekly ROP exams, as well. It is equally important that the neonatal and ophthalmology staffs communicate regarding which infants need continuing examinations. This can become problematic if the infant is discharged home or transferred before the follow-up examination date [143]. If either of these events occurs, it is the responsibility of the neonatologist and ophthalmologist to ensure that the baby is screened either as an inpatient at the new facility or as an outpatient in the ophthalmology office and for communicating previous findings and appropriate timing of repeat examination.

It is crucial to ensure that parents are informed of scheduled ROP examinations and to keep them updated regarding their child's ROP status. Ensuring that the parents understand the basics of ROP and the potential consequences, if left untreated, often helps in maintaining appropriate follow-up, especially when the patient is discharged from the hospital. Providing this information both verbally and in writing is helpful, and all encounters with the parents should be documented in the patient's medical record. However, parents of premature infants often feel quite overwhelmed and come into contact with many providers. Special family situations in which multiple caregivers are responsible for the child's care and in the setting of multiple births, it is difficult for parents and caregivers to remember to schedule and keep follow-up appointments for ROP screenings [143]. Often, significant follow-up efforts on the part of the ophthalmology staff are required to ensure that screening and treatment is occurring as necessary. In some cases, when multiple appointments are missed or are not occurring at timely intervals despite the staff's efforts to arrange for the patient to come to clinic, social services or even law enforcement may be required to become involved to ensure the appropriate care is received.

The medicolegal risk for those who examine and treat ROP is high. Even with the best of screening programs as described above, ROP can still be a blinding disease [144]. These risks can be minimized with good training, diligent screening programs, and effective communication with the families of at risk patients.

Treatment of ROP

The CRYO-ROP study defined the criteria for threshold, or treatable, ROP, which is defined as five or more contiguous or eight cumulative clock hours of neovascularization (stage 3) in zones I or II with plus disease. Prethreshold disease is a term used for ROP that has a high risk for meeting threshold criteria. With the revision of the ICROP criteria, the number of clock hours involved became less important and plus disease became a requirement for treatment (except for zone 1, stage 3 disease) [145]. The terms threshold and prethreshold are not commonly used today and have been replaced with the terms type I and type II ROP [109]. Type I ROP (high-risk prethreshold) is defined as any one of the following: (1) zone I, stage 3 without plus disease; (2) zone I, any stage with plus disease; or (3) zone II, stage 2 or 3 with plus disease. Type II ROP (low-risk prethreshold) includes any one of the following: (1) zone I, stage 1 or 2 without plus disease or (2) zone II, stage 3 without plus disease. The ET-ROP study found that patients have a more favorable outcome if treated prior to developing threshold disease. The recommendation now is that patients with type I ROP be treated within 48–72 h of diagnosis [138, 143]. If AP-ROP is detected, treatment may be warranted emergently.

Traditionally, cryotherapy was the preferred treatment for type I ROP. However in recent years, laser photocoagulation has replaced cryotherapy as the treatment of choice. The proposed mechanism of action for laser photocoagulation is that ablation of the peripheral retina decreases the stimulation for neovascularization by destroying the retinal tissue responsible for cytokine production that induces neovascularization. Treatment of the peripheral avascular retina is accomplished with transpupillary diode or argon laser. Spots are typically placed in a nearly continuous pattern, 1–1.5 spot sized widths apart [146]. Each laser technique is associated with complications many of which are undesirable, including decreased peripheral vision, intraocular bleeding, high myopia, macular dragging, cataract formation, and/or retinal detachment. It has been established that cataract formation is more common with argon laser [15, 17]. Laser photocoagulation can be performed in the neonatal intensive care unit or in the operating room with sedation or general anesthesia. Often times, general anesthesia with intubation is required for precise laser treatment, which is a major disadvantage in the eyes of neonatologists, ophthalmologists, and parents. The decision regarding anesthesia and location of treatment ultimately depends on the medical status of the infant, preferences of the treating ophthalmologist and neonatologist, and hospital protocols. Another major disadvantage of laser is that ROP may continue to progress for at least a week following successful laser treatment. The reason for this is that VEGF is already present in the vitreous prior to laser, thus it continues to stimulate neovascularization [121]. Only the formation of additional VEGF is halted with laser treatment.

Secondary to the lasting side effects and undesirable outcomes of laser photocoagulation, there have been many efforts to find a less destructive and more effective treatment. This is especially important in cases of zone I, posterior zone II, and AP-ROP, when laser treatment causes permanent damage to the posterior retina [121]. Recently, the use of anti-VEGF agents, popular in the treatment of other retinal disorders including wet macular degeneration and diabetic retinopathy, have been used as an off label treatment for type I ROP. The appeal of treatment with anti-VEGF agents is that it inactivates VEGF already present in the vitreous. The most widely used anti-VEGF agents include bevacizumab (Avastin®) and ranibizumab (Lucentis®). Bevacizumab is a complete antibody, rather than an antibody fragment like ranibizumab, giving it less ability to penetrate retinal tissue and less potential to escape the eye [121]. Additionally, the newest anti-VEGF agents, known as VEGF traps (Eylea®), have been used with some success in animal models [147].

The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) study demonstrated that bevacizumab was a successful intervention for eyes with zone I and posterior zone II, stage 3+ disease, and potentially superior to laser therapy for zone I retinopathy [121]. However, the BEAT-ROP trial was not powered to evaluate safety, and few studies have investigated the global effects of bevacizumab in the pediatric population, so the effects of a VEGF-antagonist on the developing child remain largely unknown.

One of the major advantages of anti-VEGF therapy is that it is delivered directly to the vitreous through intravitreal injection at the bedside without sedation or anesthesia. Often, only a single injection is required to stop angiogenesis. As mentioned previously, the use of this less destructive treatment is desirable when severe posterior disease is present and in cases of AP-ROP [122]. Studies have shown that even after treatment with anti-VEGF, vascularization of the peripheral retina continues, which is vastly different from the ablative effects of laser treatment. Additionally, myopia is not a common side effect of anti-VEGF therapy. Lastly, earlier treatment may be justifiable with anti-VEGF therapy as opposed to laser because of its lack of irreversible damage to the retina [121, 148].

There are also controversies regarding the disadvantages of anti-VEGF therapy. As mentioned previously, the major concern is potential ocular and systemic complications when using these drugs in neonates. With multiple centers of rapid blood vessel growth, such as the brain, lungs, and kidneys, premature infants may be more vulnerable to the systemic effects of anti-angiogenic therapy. It is known that anti-VEGF causes serious systemic side effects when used in repeated, large doses in cancer patients; however, the drug is given as a single, low dose intravitreal injection to premature infants with ROP [121]. Recent evidence suggests that bevacizumab may enter the systemic circulation after intravitreal injection; adults treated with intravitreal bevacizumab dem-

onstrated significantly lower blood VEGF levels than those not treated with the medication even 1 month after injection [149]. In a study of infants previously treated with laser, bevacizumab levels were measured in the serum 2 weeks after intravitreal administration, and reported that the serum concentration of bevacizumab increased from 946 to 1214 ng/mL from 1 to 2 weeks after a 0.5 mg intravitreal injection. Additionally, a significant negative correlation between serum concentration of bevacizumab and VEGF was found [150]. A recent case study of 13 patients suggested that systemic development up to age five is preserved after intravitreal bevacizumab, but the authors noted that their study was limited by its small patient number and lack of a control group [151]. The Pan-VEGF Blockade for the Treatment of Retinopathy of Prematurity study (BLOCK-ROP) attempted to evaluate the safety and tolerability of bevacizumab in newborns with APROP by assessing two doses of anti-VEGF therapy. However, the study was cancelled in first phase secondary to lack of patient enrollment. A randomized, controlled trial evaluating the safety of anti-VEGF therapy is warranted to answer these lingering questions regarding long-term safety and systemic outcomes in neonates.

Another potential disadvantage of anti-VEGF therapy is that it is not beneficial for stage 4 or 5 ROP. While anti-VEGF is quite beneficial for decreasing angiogenesis, it has no effect on fibrosis and may accelerate retinal detachment by triggering contraction of the fibrovascular tissue [152]. Local complications of intravitreal injections include infectious and traumatic events. If the injection is given too anteriorly, there is risk of injuring the lens which may lead to cataract formation. Additionally, retinal tears and detachments may occur, but the risk is decreased by using a smaller gauge, shorter length needle [152]. Good sterile technique and administration of topical antibiotics for 1 week following the procedure decrease the risk of infection. Lastly, there are concerns that retinal development may be adversely affected in eyes treated with bevacizumab. Histopathology on a pair of premature, infant eyes that were examined 20 weeks following intravitreal injection revealed that all layers of the retina had developed normally and inner retinal vessels had advanced beyond the vascular-avascular junction noted at the time of injection [153].

Recurrence of disease can be seen with any of the aforementioned treatments. After laser treatment, recurrent disease has been noted to occur as soon as 1 week following the procedure and up to 55 weeks post menstrual age [152]. Treatment for recurrence after laser includes repeat laser treatment with or without vitrectomy and/or anti-VEGF injection. It is important to note that there is a risk that the anti-VEGF agent may escape the eye more rapidly in an eye previously treated with laser, thus necessitating multiple injections. Recurrence of disease after anti-VEGF tends to occur later than that seen with laser treatment, usually between 1 month after injection and up to 70 weeks

post-menstrual age [152]. Therefore, it is very important for infants treated with anti-VEGF agents to be followed for a longer period of time. Treatment for recurrence after anti-VEGF injection includes additional injections, if discovered prior to the development of fibrovascular traction, or laser therapy with or without vitrectomy.

The treatment of late-stage ROP (stages 4 or 5) differs from that of acute phase disease. As mentioned previously, in late-stage ROP tractional disease is present making laser and anti-VEGF injection unsuitable for treatment. Surgery for stage 4 and 5 retinal detachments includes vitrectomy with or without scleral buckle. Many retina specialists advocate the treatment of stage 4a ROP; however, there are concerns that intervention may cause more harm in addition to the potential medicolegal consequences. It is well known that stage 5 detachments have universally poor outcomes; therefore, earlier intervention is often desired for stage 4a and 4b ROP [154]. Several studies have shown success with vitreoretinal surgery for stage 4a ROP in regards to stopping detachment progression and visual outcomes [155, 156].

Evaluation Modalities

The standard evaluation modality for ROP screening still remains binocular, indirect evaluation and treatment of ROP [157]. However, advancements in imaging technology, along with a shortage of trained or willing ophthalmologists in both the United States and the developing world, have employed the use of telemedicine in ROP screening. The photographic screening for retinopathy of prematurity (photo-ROP) determined that remote use of digital fundus images is a useful adjunct to standard indirect ophthalmoscopic exams of the retina [158]. Since then, various digital photographic systems have been studied as screening tools for the documentation of ROP for telemedicine purposes and have been found to be useful in the detection of clinically significant ROP [158–171]. Additional studies evaluating software providing analysis of posterior pole vessel diameter and tortuosity have also shown promising results in diagnosing plus disease and reducing interexaminer variability of this diagnosis [160, 172–175]. This technology may also prove to be beneficial in predicting the need for treatment of severe ROP prior to the clinical diagnosis of plus disease [176].

One of the primary limitations for broad implementation digital imaging for ROP is cost of the imaging system, especially in the developing world [177]. However, considering the alternative cost of employing additional medical staff, this alternative may be more cost effective. Additionally, the technology is portable, so it could be used for multiple regional hospitals, making this option more cost effective [177]. Other barriers to widespread implementation include limited internet access, parental and staff acceptance, liability, and lack of insurance coverage and reimbursement [178].

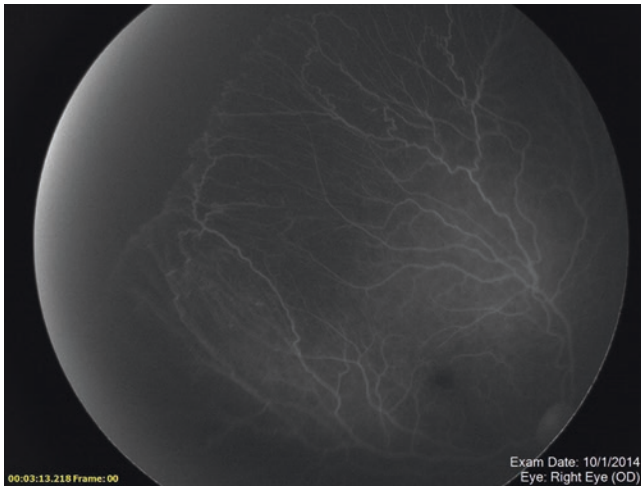


Fig. 2.8 Intravenous fluorescein angiogram in a premature infant at 37 weeks post conceptual age 7 days after treatment with intravitreal Bevacizumab for threshold retinopathy of prematurity

Similar to ROP programs within a single institution, it is equally, if not more important to have designated office staff to manage the telemedicine program and to ensure examinations and referrals are occurring as needed. Communication between neonatologists, ophthalmologist, and patient caregivers remains of utmost importance.

Advancements in imaging technology have provided additional modalities to allow ophthalmologists to monitor changes in the retina over time. These modalities include intravenous fluorescein angiography (IVFA), spectral domain optical coherence tomography (SD-OCT), and ultrasonography. IVFA has allowed researchers to compare the extent of retinal vascularization in eyes treated with laser compared to those treated with anti-VEGF therapy. We know that laser therapy permanently ablates the peripheral retina but little is known about the effects of anti-VEGF on the peripheral vasculature. The BEAT-ROP trial concluded that peripheral vascular development continued after injection with intravitreal anti-VEGF agents. However, further research following IVFA studies after anti-VEGF therapy suggest that while the peripheral retinal pathology does resolve, the peripheral retina may remain incompletely vascularized with leakage at the vascular-avascular junction [179–181] (see Fig. 2.8).

Ultrasonography can be used as an adjunct screening tool in ROP to document changes overtime. Several investigators successfully documented all stages of ROP with ultrasonography; however, earlier stages are difficult to detect [182]. This technology may be useful in patients with poor pupillary dilation or hazy media, and as well as an initial screening tool in telemedicine programs or developing countries with a shortage of qualified examiners [182–184]. Recent studies have determined the utility of SD-OCT in demonstrating subclinical retinal pathology in ROP [184]. Changes documented in foveal architecture are felt to represent foveal

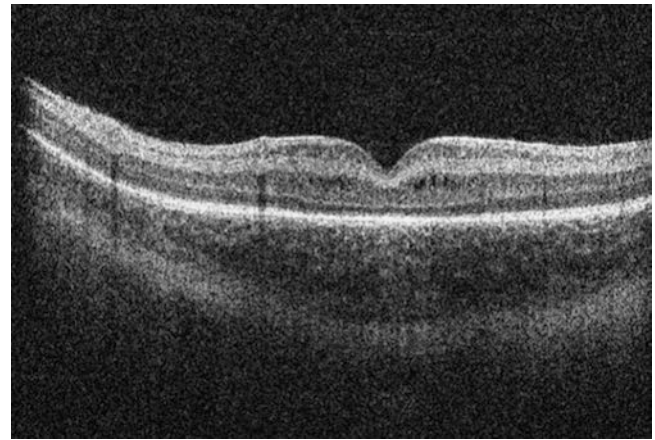


Fig. 2.9 Spectral domain optical coherence tomography (SD-OCT) of the foveal region (Bioptigen, Inc, Morrisville, NC) in a premature infant at 35 weeks post conceptual age

pathology seen in older ROP survivors [23]. These changes include retention of inner retinal layers and absent foveal depression, although these changes may not correlate with visual acuity. Instead, photoreceptor maturation may be a better indicator of final visual outcome in these patients [185] (see Fig. 2.9).

Additional ROP Studies

In addition to the ROP studies previously mentioned in the text, there are other ROP studies worthy of mention and reference. The use of beta blockers in treatment of ROP was evaluated by the safety and efficacy of propranolol in newborns with Retinopathy of Prematurity study (PROP-ROP). Newborns receiving systemic propranolol showed less progression to stage 3 ROP and required fewer laser and anti-VEGF treatments. However, serious adverse effects including hypotension and bradycardia were encountered in these infants [186]. The PINT ROP, WIN-ROP, and CHOP ROP studies evaluated and validated clinical prediction models, including postnatal weight gain to determine the risk of severe ROP. Future implications of the algorithms developed by these studies may allow ophthalmologists to reduce the number of ROP screening examinations on preterm infants [187–189].

Cataracts Unique to Premature Babies

Since the establishment of routine ophthalmologic examination in premature infants in 1996, it became apparent that a significant number of the smaller premature babies develop transient lens opacities [12, 13]. Described first by Dr. McCormick, the cataracts always exhibited bilateral symmetry and appeared to consist of vacuoles in the poste-

rior cortex near the lens capsule and to lie in relation to the posterior inverted Y suture. McCormick described seven infants born with clear lenses on the first, second, and third day of life who developed cataracts between the eighth and fourteenth days of age and persisted for between 10 and 18 days. McCormick attributed the lens vacuoles to a non-specific metabolic disturbance since they appeared to be completely reversible [12]. Alden, Kalina and Hodson noted transient cataracts in 2.7% (19 of 692) babies examined in a single NICU neonatal intensive care unit from January 1, 1969 and August 1, 1971. The lens opacities which were observed were similar to those described by McCormick and according to these authors were sufficiently characteristic to prevent confusion with any other type of cataract. They noted that the resolution occurred in a manner opposite to formation, with initial clearing centrally and most prolonged retention of the vacuoles at the apices of the posterior lens suture. Interestingly, after a case-control analysis the authors concluded that the time taken to regain birth weight was longer in the patients with cataracts (18 ± 7 days) than in the control infants (12 ± 6 days) ($p < 0.05$). These authors suggested an osmotic factor as the most likely etiologic agent [13].

Another unique category of cataracts infants is the development of *Candida* lens abscesses in premature infants with history of neonatal candida sepsis. Isolated infections of the neonatal lens can occur in the absence of endophthalmitis. It has been hypothesized that these lens abscesses are initiated when fungal organisms spread hematogenously to the neonatal lens via a patent tunica vasculosa during episodes of candidemia. After regression of the tunica vasculosa lenticis, the fungal organisms become effectively sequestered from the immune system surveillance and exposure to systemically administered anti-fungal agents. The lenticular opacity may be evident at variable times after neonatal *Candida* sepsis/fungemia and onset can be delayed for months. Treatment regimens for lens abscesses have consisted of lensectomy, anterior vitrectomy, and intravitreal injection of antifungals in addition to systemic treatment. Cultures should be obtained of the aqueous, the lens/vitreous aspirate or any associated anterior chamber membranes. The prognosis for functional vision is poor in these eyes [81, 83, 190–192].

Endogenous bacterial endophthalmitis in preterm babies can also present with leukocoria. This can be confusing for the treating pediatrician or neonatologist but should be readily recognized by the examining ophthalmologist because of the location of the opacity behind the lens. In these cases, vitreous inflammation can result in dense white vitreous opacities that produce the grey-white reflex. Endogenous endophthalmitis can be initially misdiagnosed and can result in poor visual prognosis if the treatment is delayed. Treatment generally involves vitreous biopsy and culture with intravitreal administration of antibiotics. Vitrectomy may be required to clear the visual axis. Secondary cataract

formation is common post-vitrectomy and also secondary to the significant intraocular infection and inflammation. Early systemic antibiotic therapy remains the cornerstone of treatment. Vitrectomy can be therapeutic [76, 88, 105].

Bilateral transient cataracts have been reported in a preterm newborn during treatment with linezolid therapy and relieved 1 week after the discontinuation of the therapy. Linezolid is the first member of the oxazolidinone antibiotic therapy, indicated for serious infections caused by resistant organisms (vancomycin resistant enterococcus (VRE), methicillin resistant *S. aureus* (MRSA), methicillin resistant coagulase negative staphylococci and penicillin resistant *S. pneumoniae*) in infants and child. Treatment with linezolid had been associated with reversible thrombocytopenia developing after the second week of therapy as a side effect reported in children. A premature baby born at 26 weeks gestation had a screening ROP exam that revealed avascular zone 2 without plus disease at 31 weeks of corrected age. This baby was diagnosed with late onset sepsis on day 40 because of apnea and fever. Although treated with vancomycin and meropenem, VRE was isolated on blood culture on day 47. Thereafter, vancomycin was discontinued and linezolid (10 mg/kg/day, twice daily) was started. Routine ROP examination was performed on day 50, and vacuoles located in the peripheral portion of the lens close to the posterior capsule were observed, on the third day of linezolid treatment. The cataracts were also evident on day 13 of linezolid therapy. Follow-up blood cultures were negative on Day 18 of therapy and thereafter linezolid was discontinued. There was regression of the cataracts, with no sign of cataract on the eye examination performed 1 week later [193].

As described earlier, laser ablation remains effective therapy for proliferative retinopathy of prematurity. However, phthisis bulbi secondary to anterior segment ischemia following laser photocoagulation for threshold ROP has been reported [194, 195].

Cataracts have been reportedly consistently among infants treated for threshold ROP with laser photocoagulation [16, 196–198]. Cataract formation was not common in the earlier era when threshold ROP was treated with cryotherapy [199].

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The Eye in Pediatric Systemic Disease

Levin, A.V.; Enzenauer, R.W. (Eds.)

2017, XII, 837 p. 182 illus., 118 illus. in color.,

Hardcover

ISBN: 978-3-319-18388-6