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Retinopathy of Prematurity: Recent Developments

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Drs Fleck and
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to this article. This
commentary does
contain a discussion
of an unapproved/
investigative use of a
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Objectives After completing this article, readers should be able to:

1. Describe the pathogenesis of retinopathy of prematurity (ROP).
2. Review the roles of oxygen and insulin-like growth factor-1 in the development of ROP.
3. Classify the clinical appearance of ROP.
4. Compare tools for screening examinations.
5. Delineate changes in treatment criteria and new treatments.

Abstract

Retinopathy of prematurity (ROP) is a disorder of retinal vascular development in preterm infants. It remains a major cause of childhood blindness worldwide. This review addresses advances in knowledge during the past 8 years. The pathogenesis has become clearer with animal experimental work and from clinical observations. Large clinical trials have informed better management, and new retinal digital imaging is likely to change the role of the ophthalmologist. New treatment modalities, such as vascular endothelial growth factor (VEGF)-blocking antibodies, are being assessed. Finally, a number of evidence-based clinical guidelines for the management of ROP have been published.

Introduction

Retinal vascular development is incomplete in preterm infants. Postnatal interference with normal development may lead to ROP. A number of significant developments in the field of ROP have been made since the excellent reviews written by Dale Phelps in *NeoReviews* in 2001. The understanding of the pathogenesis of ROP has changed, following laboratory and clinical studies of the role of insulin-like growth factor-1 (IGF-1) and of tissue oxygen values in ROP. Low concentrations of IGF-1 and relative hyperoxia in the early postnatal period lead to delayed retinal blood vessel growth. Later, increased concentrations of IGF-1 permit VEGF-induced angiogenesis as an acute event, represented as stage 3 ROP. The clinical classification of ROP has been

updated, with increased emphasis on the clinical significance of dilation and tortuosity of the posterior retinal blood vessels, known as “plus” disease. New retinal digital photograph technology, which is effective in detecting plus disease, now enables telemedicine ROP screening examinations by nonophthalmologists. The indications for laser treatment of ROP have been redefined by the Early Treatment of ROP (ETROP) study, with an emphasis on the presence of plus disease as the key criterion for treatment decisions. Intravitreal injections of anti-VEGF antibodies are being investigated as an alternative treatment. Finally, a number of new evidence-based clinical

Abbreviations

AP-ROP:	aggressive posterior ROP
BIO:	binocular indirect ophthalmoscope
ETROP:	Early Treatment of ROP
IGF-1:	insulin-like growth factor-1
ROP:	retinopathy of prematurity
SGA:	small for gestational age
VEGF:	vascular endothelial growth factor

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guidelines give robust direction to the organization of ROP screening and treatment programs.

Epidemiology

Many centers reported a decline in the incidence of ROP in the 1990s and early 2000s. In the Lothian region of southeast Scotland between 1990 to 2004, there was a significant increase in survival of infants whose birthweights were less than 1,500 g or whose gestational age was less than 32 weeks but a significant reduction in the number of infants treated for ROP. Chiang and associates reported a 20.3% incidence of any ROP in infants whose birthweights were less than 1,500 g born in New York State between 1996 and 2000, which was a similar incidence to that in Lothian at that time. However, the global picture has been mixed, and there has been an “epidemic” of sight-threatening ROP in “middle income” countries. An improved standard of neonatal care has led to improved survival of very low-birthweight babies, but highly sophisticated neonatal and ophthalmic care available in developed countries is not yet in place.

Pathogenesis

The current concept of the pathogenesis of ROP suggests that preterm birth interrupts the normal processes of retinal blood vessel development. The postnatal developing retina is exposed to a less stable and relatively hyperoxic oxygen environment. The normal physiologic hypoxia “drive” of angiogenesis is reduced. Local and systemic concentrations of growth factors, notably IGF-1, are low. Therefore, the process of retinal vascularization is delayed, and the peripheral retina remains avascular.

Understanding of the next steps in the pathogenesis has been improved greatly by laboratory and clinical work on the role of IGF-1 in retinal blood vessel development. Astrocytes in the peripheral avascular retina produce VEGF in response to tissue hypoxia caused by ischemia. However, VEGF is unable to trigger an angiogenesis response in the absence of adequate tissue concentrations of IGF-1. Preterm infants have low circulating concentrations of IGF-1, which increase with postnatal growth. When tissue concentrations of IGF-1 reach a critical threshold level, VEGF-signaled angiogenesis is permitted. Rapid-onset, excessive VEGF effects are seen in the retinal blood vessels. Extraretinal new vessels grow into the vitreous (stage 3 ROP), and the posterior retinal blood vessels become dilated and tortuous (plus disease). If the condition is untreated, a progressive gliosis of the retina and vitreous occurs, leading to retinal detachment and blindness (stage 4 and stage 5 ROP).

Treatment with laser ablation of the peripheral avascular retina leads to a rapid reduction of VEGF concentrations. Alternatively, injection of anti-VEGF antibodies into the vitreous leads to a similar reversal of the pathologic process.

Role of Oxygen

Laboratory studies in rat and mice pups have shown that both oxygen fluctuation and hyperoxia produce abnormal retinal blood vessel development. An abnormal oxygen environment alone, without any of the other abnormalities of physiology that occur in ill preterm infants, is sufficient to cause ROP. A number of case series clinical studies have reported a decrease in the incidence of severe ROP following the introduction of lower oxygen saturation targets.

A global group of multicenter randomized, controlled trials of reduced oxygen saturation therapy are underway at present. Each trial is designed to produce clinically significant outcomes in its own right, but the use of uniform interventions and outcome measures will allow planned meta-analysis of the trials, with very powerful results. Trials currently are underway in the United States, Canada, United Kingdom, Australia, and New Zealand. Infants are randomized to oxygen saturation ranges of 85% to 89% or 91% to 95%, using oxygen saturation monitors that are offset in a masked approach to produce one of the two ranges, while appearing to show the “normal” range of 89% to 92% to those undertaking clinical care of the infants.

Role of IGF-1

Intrauterine growth restriction, resulting in infants born small for gestational age (SGA), is a risk factor for the subsequent development of ROP. Poor postnatal weight gain is a risk factor for ROP in infants and in experimental animal models. Preterm infants, and especially SGA infants, have low serum concentrations of IGF-1. Fetal IGF-1 values normally increase rapidly during the third trimester. Preterm birth leads to a rapid decrease in fetal IGF-1 values due to loss of maternal sources of IGF-1. Clinical studies and experimental animal studies also show low IGF-1 values in association with poor nutrition, acidosis, low thyroxine concentrations, sepsis, and transient asphyxia.

IGF-1-deficient mice show retarded retinal blood vessel development. Retinal blood vessel endothelial cell response to VEGF is dependent on IGF-1. Low concentrations of IGF-1 prevent VEGF-induced activation of protein kinase B. Humans who have reduced growth hormone receptor function due to a gene defect (Laron

syndrome) show deficient retinal blood vessel development.

Low concentrations of IGF-1 in early postnatal preterm infants, therefore, appear to delay retinal blood vessel growth. Serum IGF-1 concentrations increase with neonatal development. Increased IGF-1 concentrations eventually allow VEGF-dependent angiogenesis to occur as a relatively acute event, resulting in the development of stage 3 ROP.

Serial serum IGF-1 concentrations have been measured in a cohort of preterm infants. The early postnatal mean IGF-1 values of infants who eventually developed severe ROP were low. Poor weight gain and reduced head circumference growth also were associated with low IGF-1 concentrations and the development of ROP.

IGF-1 concentrations gradually rise with postnatal growth. This increase is partly dependent on adequate nutrition. Infant IGF-1 concentrations, therefore, may be influenced by nutrition. Newborns fed human milk have higher serum IGF-1 concentrations compared with formula-fed controls. Early human milk contains available IGF-1 due to a low rate of proteolysis of IGF-binding protein II. Other forms of nutrition therapy also have been studied. Early elective insulin therapy can reduce hyperglycemia and increase IGF-1 concentrations in very low-birthweight infants. A number of approaches to the supplementation of early postnatal enteral and parenteral nutrition currently are being evaluated.

Both oxygen and growth appear to be important areas for the further development of strategies to prevent ROP.

Classification of Clinical ROP Appearances

It is important for the description of retinopathy to be standardized so that management strategies are applied uniformly around the world and particularly for infants in different clinical trials. An international group of ophthalmologists and neonatologists standardized the description in 1983 (The International Classification of Retinopathy of Prematurity), and it has changed little since. The degree of retinopathy is described in terms of stage, location, and extent. The presence of dilatation and tortuosity of the posterior retinal blood vessels or “plus” disease also is noted. The classification recently has been supplemented by the terms preplus disease and aggressive posterior ROP. An excellent teaching aid to the classification of ROP is available at www.boostnz.info/ROP.

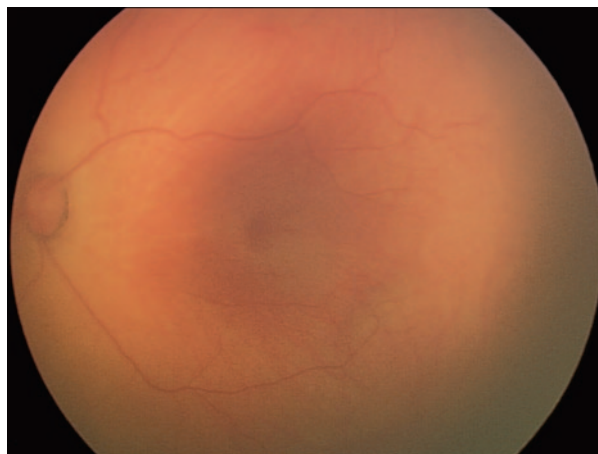


Figure 1. Normal immature retina, not fully vascularized.

Stage

In the absence of retinopathy, the retina of the very preterm infant merges imperceptibly from vascularized centrally to avascular peripherally (Fig. 1). Although ROP affects the entire retina, abnormalities are particularly striking at the junction of the posterior vascularized retina and anterior avascular retina.

Stage 1 ROP: A flat line of demarcation occurs between the vascular and avascular retina.

Stage 2 ROP: The line of demarcation acquires volume to become a ridge. Tufts of new vessels may appear on the posterior edge of the ridge, but these vessels still are within the retina (Fig. 2).

Stage 3 ROP: Neovascularization can be seen within the ridge, and extraretinal vascularization extends out of the retina (Fig. 3).

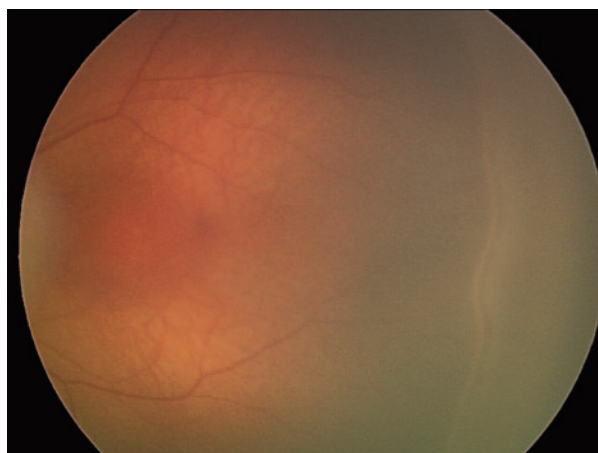


Figure 2. Stage 2 ROP, indicated by the development of a ridge between the vascular and avascular retina.

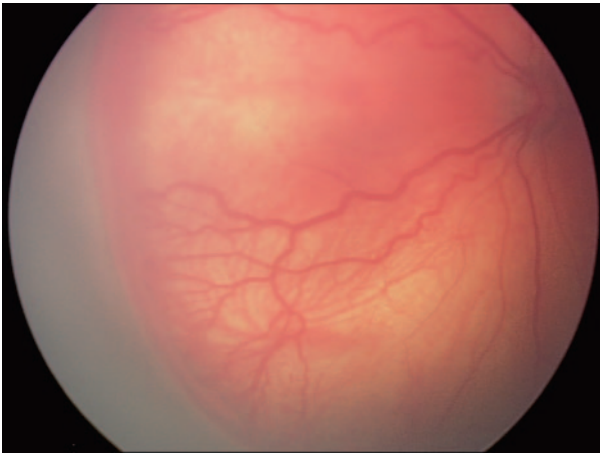


Figure 3. Stage 3 ROP, showing neovascularization within the ridge and extraretinal vascularization out of the retina. Courtesy of Professor Michael O'Keefe, Dublin, Ireland.

Stage 4 ROP: Partial retinal detachment occurs, which may be extrafoveal or foveal.

Stage 5 ROP: Eventually total retinal detachment may occur (with resulting complete blindness).

The appearances of stages 0 through 3 ROP are summarized in Figure 4.

Extent

The extent of disease is described as total clock hours (of the worst stage involved).

Location

The retina is divided into three zones (Fig. 5). Zone I, which is most posterior, consists of a circle with a radius of twice the distance from the optic disc to the center of the macula, centered on the optic disc. Zone II extends

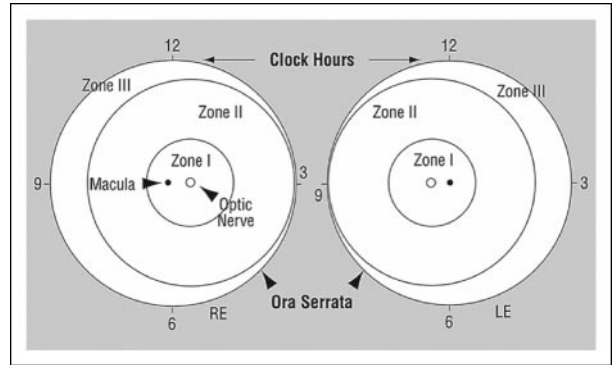


Figure 5. ROP zones. Reprinted with permission from An international classification of retinopathy of prematurity. *Pediatrics*. 1984;74:127–133.

from zone I forward to the anterior edge of the retina (ora serrata) on the nasal side of the eye, centered on the optic disc. The ora serrata is closer to the optic disc on the nasal side than on the temporal side of the eye. Zone III is the retina anterior to zone II (only present on the temporal side).

The retinal blood vessels grow out from the optic disc between 16 and 40 weeks' gestation. When the blood vessels are confined to zone I, retinal blood vessel development is very immature. Retinopathy in zone I has a much worse prognosis than retinopathy observed more peripherally.

Preplus Disease

Increased dilation and tortuosity of the posterior retinal vessels are very significant indicators of ROP activity (Fig. 6). The outcome of the ETROP treatment trial has emphasized the central place of plus disease when mak-

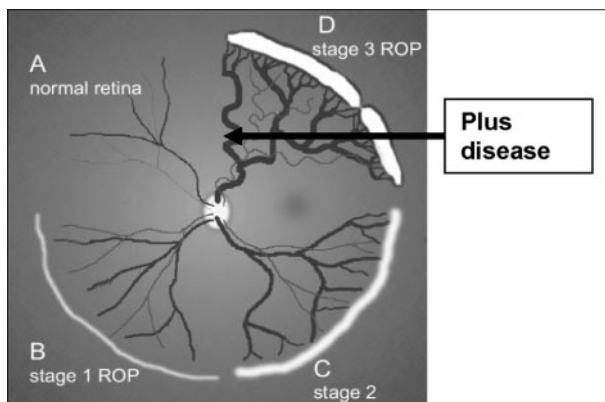


Figure 4. ROP stages. Reprinted with permission from the United Kingdom Guidelines for the Screening and Treatment of Retinopathy of Prematurity.

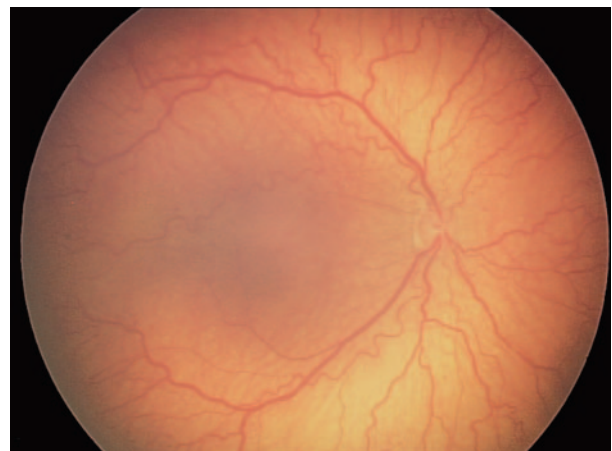


Figure 6. Plus disease, as indicated by tortuosity of the posterior retinal vessels.

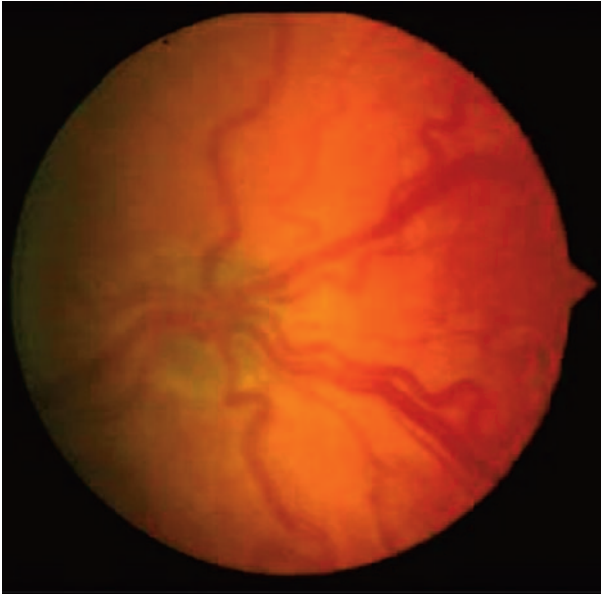


Figure 7. Plus disease standard reference photograph. Reprinted with permission from An international classification of retinopathy of prematurity. *Pediatrics*. 1984;74:127–133.

ing treatment decisions; detailed analysis of ROP stage and extent has become relatively less important. Increased dilation and tortuosity of the posterior retinal vessels is compared with a standard reference photograph (Fig. 7). If changes of at least this severity occur in at least two retinal quadrants, a diagnosis of plus disease is made. Preplus changes are vascular abnormalities of the posterior retina that are insufficient for the diagnosis of plus disease, but that cannot be considered normal (Fig. 8). Iris vascular engorgement, poor pupillary dilation (rigid pupil) with dilating eye drops, and vitreous

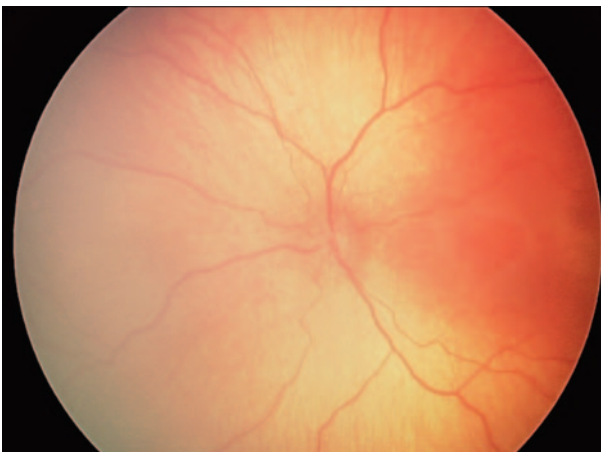


Figure 8. An example of preplus disease.

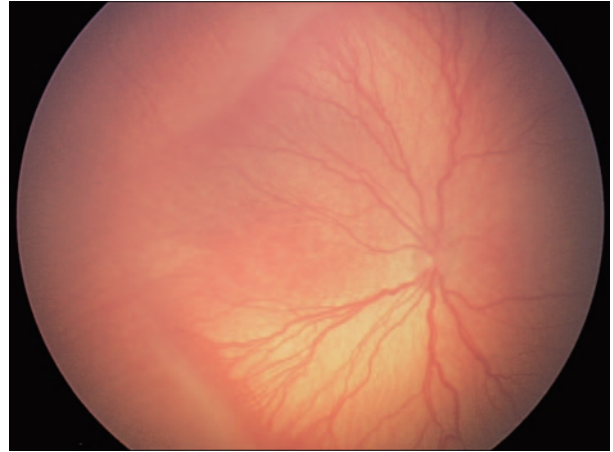


Figure 9. An example of aggressive posterior ROP. Courtesy of Professor Michael O'Keefe, Dublin, Ireland.

haze may occur as part of plus disease in more severe cases.

Aggressive Posterior ROP

The rapidly progressive and severe form of ROP, previously known as “rush” disease, now is termed aggressive posterior ROP (AP-ROP) (Fig. 9). AP-ROP occurs in zone I and in posterior zone II. It is deceptively featureless and may appear as a flat network of neovascularization within the retina. The most prominent feature is severe plus disease. AP-ROP does not have the appearance of classic ROP and does not progress through stages 1 to 3. Urgent treatment is required, and the prognosis following treatment is more uncertain than in other forms of ROP.

Screening Examination of the Retina

With current management, blindness due to ROP in extremely preterm infants is largely preventable. Most infants born at less than 28 weeks' gestation develop some degree of ROP. In most, the disease is mild and regresses spontaneously. However, a small proportion of infants, even up to 32 weeks' gestation (and if SGA at even greater gestations), develop potentially severe retinopathy, with the danger of visual impairment or possible total blindness. Screening of infants at risk can monitor the progress of retinopathy, and timely intervention has a good chance of preventing progression and preserving vision.

Observational clinical studies and resulting evidence-based clinical guidelines are now well developed. Guidelines may be used to inform the most effective and efficient program of screening examinations for each

infant, including the timing of the first screening examination, the time intervals between subsequent screening examinations, and the criteria for proceeding with retinal treatment or discontinuing screening examinations when the risk period has passed. Screening examination programs vary, depending on the gestational age of the infant at birth, whether ROP develops, and the form of ROP that develops. In addition, screening guidelines are specific to the health-care setting, with relatively more mature infants at higher risk of developing sight-threatening ROP in health-care environments in which highly sophisticated neonatal care is not available. The logistics and administrative processes of ROP screening programs also are of great importance; blindness can follow a simple administrative error in failing to arrange appropriate ROP screening for an infant. In addition to oral communication, parents should be given written information about the screening process prior to the first eye examination of their baby.

The binocular indirect ophthalmoscope (BIO) has been used for ROP examinations for many years. Viewing is improved with the use of an eyelid speculum and scleral indentation. Local anesthetic eye drops are instilled, and comfort care techniques such as administering sucrose solution, nesting, swaddling, or the use of a pacifier should be considered during the examination.

The use of BIO for ROP screening examinations has some limitations. The technique is technically challenging, and ophthalmologists trained in the technique may not be easily available to some neonatal nurseries. Documentation of the retinal appearances is by written description, supplemented with sketch diagrams, leading to inevitable variation in the subjective analysis of ROP appearances by different ophthalmologists. The chart used to document ROP screening retinal examination indicates the zone, stage, and extent in terms of clock hours of any ROP and the presence of any preplus or plus disease (Fig. 10). The examiner recommends the timing of the next examination.

Digital camera technology is capable of retinal imaging in preterm infants. This new technology has been evaluated as an alternative to BIO examination screening. Retinal images may be viewed and analyzed at leisure, and sequential retinal examination appearances may be compared over time. Wide-field corneal contact camera systems (Figs. 11 and 12), noncontact narrow-field systems, and indirect ophthalmoscope video cameras have been evaluated. A number of studies have emphasized the telemedicine use of retinal images on an international scale. Nurses and neonatologists are capable of using digital cameras to perform ROP screening. Digital

Stage 1:	Stage 2:	Stage 3:	Stage 4/5:	Laser:	AP-ROP:	
—	==	***	••••	××××	AAA	
Date:	R		L			
Postmenstrual Age:						
Follow-up:						
Examiner:	Zone:	Stage:	Preplus: Y / N	Zone:	Stage:	Preplus: Y / N
Comments:			Plus: Y / N			Plus: Y / N

Figure 10. Example of a chart that may be used for the documentation of ROP screening examinations. Reprinted with permission from the *United Kingdom Guidelines for the Screening and Treatment of Retinopathy of Prematurity*.

imaging examinations appear to cause similar or less systemic distress to infants than BIO examinations.

Several studies have compared the performance of digital imaging and indirect ophthalmoscopy in ROP screening. Digital imaging appears to be as effective as



Figure 11. Wide-field camera in use for ROP screening examination. (The camera was not in contact with the infant at the time of the photograph).



Figure 12. Wide-field camera in use for ROP screening examination. (The camera was not in contact with the infant at the time of the photograph).

BIO in detecting severe forms of ROP, including those that require treatment. The reported sensitivity and specificity of digital image-based diagnosis, compared with the gold standard of expert observer indirect ophthalmoscopy diagnosis, has been remarkably consistent. Although the detection of mild peripheral forms of ROP is limited by poor visualization of the peripheral retina with camera systems, with 82% to 85% sensitivity in the detection of any stage of ROP, performance is much better for sight-threatening ROP that may require treatment. The appearances that are of most diagnostic significance, namely, plus disease, and forms of retinopathy that occur in the more posterior retina are well demonstrated with camera systems. A number of studies, including the recently completed multicenter PhotoROP study, have demonstrated a sensitivity of 100% in the detection of sight-threatening, treatment-requiring ROP.

At present, camera systems appear to be at least as satisfactory as the BIO in detecting ROP that requires treatment. The only situation in which the BIO currently retains an advantage is the detection of peripheral ROP in the presence of normal posterior retinal vessels. This form of ROP does not require treatment, but knowledge of its presence or absence is of value in making decisions as to when the ROP screening program may be discontinued in an individual infant. Our current practice is to use the digital camera system for most ROP screening examinations, employing the BIO for the examination anticipated as being the final screening examination.

Digital images also allow quantitative image analysis of retinal appearances, rather than relying on the subjective interpretation of expert readers. The presence of plus disease was an important criterion for treatment decisions, as defined by the CryoROP study. The findings of the ETROP study have emphasized further the priority of plus disease. Interobserver variation of classification of plus disease is relatively high, which may contribute to the variation in reported rates of ROP treatments in different hospitals. The quantification of plus disease by image analysis is, therefore, an important goal of software development. A number of software programs have been developed to quantify blood vessel dilation and tortuosity, and this approach is likely to be adopted more widely in the near future.

Future ROP screening examinations likely will be performed by neonatal nurses or doctors, using digital camera systems that analyze and quantify the retinal appearances in real time. The role of ophthalmologists will change to that of off-site telemedicine readers, particularly when borderline treatment decisions are required, and subsequently as experts in laser ablation treatment. The approach is likely to follow that already adopted in diabetic retinopathy screening and treatment programs.

Treatment Criteria

The CryoROP was a landmark study that demonstrated the effectiveness of retinal cryotherapy treatment of ROP that had reached “threshold” severity. However, treatment of ROP at this stage of severity had a significant failure rate. The question was asked as to whether earlier treatment of milder “prethreshold” ROP disease severity might produce better outcomes. The ETROP multicenter trial randomized infants who had prethreshold disease to either immediate treatment or to a wait-and-see policy, with treatment if threshold disease developed. The outcome showed benefit from early treatment. The severity of ROP that requires treatment, therefore, has been redefined. The threshold degree of severity defined by the CryoROP study has been replaced by “type I ROP” defined by the ETROP study.

Type I ROP consists of:

- Zone I, any stage of ROP with plus disease
- Zone I, stage 3 ROP without plus disease
- Zone II, stage 2 or 3 ROP with plus disease

In practice, treatment decisions almost always are based on the presence or absence of plus disease. The extent (number of clock hours) of ROP no longer is used as a criterion for treatment. For these reasons, the em-

phasia when performing screening examinations has shifted to examination of the posterior retina, looking for plus disease in zone I and posterior zone II.

Treatment

BIO-delivered diode laser ablation of the peripheral avascular retina has become the usual method of treating ROP; cryotherapy is used rarely. The aim is to produce almost confluent burns of all areas of the avascular retina anterior to the ROP ridge, extending to the ora serrata. Careful primary treatment, ensuring complete cover of the retina and avoiding untreated “skip” areas, reduces the risk for required retreatment. Good treatment conditions, with a stable, well-sedated or anesthetized infant, facilitate high-quality primary treatment.

An entirely new approach to ROP treatment is under investigation. Intravitreal injection of anti-VEGF antibodies is used widely in ophthalmology for the treatment of neovascular forms of age-related macular degeneration and diabetic retinopathy. Pilot studies of intravitreal injection of anti-VEGF antibodies, with or without laser therapy, have given promising results as a new form of therapy for ROP. A multicenter trial is underway. The injections are administered under sterile conditions through the sclera adjacent to the cornea into the vitreous. A volume of 0.025 mL is used, and a single injection appears to be sufficient in most cases. The attraction of this form of therapy is that normal retina is not subjected to laser ablation, with permanent scarring and some reduction of the peripheral visual field. Because acute ROP is a transient phenomenon, a single injection provides an effect of adequate duration. The approach is “physiologic,” with the temporary high concentrations of intraocular VEGF blocked during the transient stage when permanent sequelae can occur. Potential problems with this form of treatment include intraocular hemorrhage, retinal tear with retinal detachment, cataract, and intraocular infection (endophthalmitis). Intravitreal injections are more invasive than laser therapy, and this new approach should be viewed with caution, pending the outcome of treatment trials. Long-term follow-up is required to assess whether this form of treatment modifies ocular growth, resulting in altered refractive outcomes (myopia), or modifies development of the normal retinal vasculature.

Clinical Guidelines

A number of evidence-based clinical guidelines have been published. These give confidence and direction to the organization of ROP screening and treatment pro-

grams. We refer primarily to the American Academy of Pediatrics (AAP) guidelines published in 2006. However, useful additional information and tools are available within the 2008 United Kingdom guidelines. Following is a summary of current American Academy of Pediatrics guidelines:

Which infants should have ROP retinal screening examinations? Infants whose birthweights are less than 1,500 g or gestational ages are 30 weeks or less. Additional candidates include selected infants whose birth-

Table 1. Time of First Eye Examination

Gestational age at birth (weeks)	Age at first examination (postnatal, weeks)
23	8
24	7
25	6
26	5
27	4
28	4
29	4
30	4
31	4
32	4

Who? <1,500 g or <32 weeks' gestation.
When? 31 weeks postmenstrual age or 4 weeks postnatal age.

Table 2. Timing of Follow-up Screening Examination

1 Week or Less

Zone I, stage 1 or 2 ROP
Zone II, stage 3 ROP

1 to 2 Weeks

Zone I, no ROP
Zone I, regressing ROP
Zone II, stage 2 ROP

2 Weeks

Zone II, stage 1 ROP
Zone II, regressing ROP

2 to 3 Weeks

Zone II, no ROP
Zone III, stage 1 or 2 ROP
Zone III, regressing ROP

ROP=retinopathy of prematurity

Table 3. **Division of Responsibilities**

Responsibilities of the Neonatal Nurses

- Inform parents that ROP screening is being performed.
- Inform parents if their infant has ROP, with updates on progression.

Responsibilities of Neonatal Physicians

- Ensure that a clear process is in place to identify infants who require ROP screening and ensure that these infants are referred automatically to the screening ophthalmologist.
- When treatment is required, ensure that transfer or other arrangements occur in a timely manner.
- When planning hospital discharge or transfer at a time when ROP screening is ongoing, communicate with the screening ophthalmologist to determine current ROP status and when the next eye examination is needed. Liaise with the receiving physician to ensure that the current ROP status and the timing requirement of the next eye examination are understood. Ensure that a specific arrangement is in place for the next eye examination BEFORE discharge or transfer.

Responsibilities of Screening Ophthalmologists

- Document the findings of each retinal examination, with a clear decision as to whether treatment is needed; further examination is needed, and the appropriate timing of this examination; or screening examinations may be discontinued. If a further examination is needed, schedule this.
- Ensure that a clear system is in place for the follow-up examinations of referred infants. Ensure clear communication with the neonatal unit staff about the timing of your visits and ensure that a colleague substitutes for you during periods of absence. You are responsible for infants referred to you until screening has been discontinued or until the infant is discharged or transferred (with specific follow-up arrangements in place).
- Ensure that arrangements are in place for any longer term ophthalmic follow-up that may be required after discharge from the ROP screening program.
- Inform parents when treatment for ROP is required. Inform parents of the reasons for treatment and the risks involved if treatment is not performed. Discuss the possibility of a poor visual outcome despite optimal treatment. Give information about treatment arrangements. Document these discussions.
- Ensure that timely arrangements for treatments are in place.

Responsibilities of Treating Ophthalmologists

- Inform parents of the reasons for treatment and the risks involved if treatment is not performed. Discuss potential complications of treatment. Discuss the possibility of a poor visual outcome despite optimal treatment. Give information about treatment arrangements. Document these discussions.
- Ensure that treatments are performed in a timely manner.

ROP=retinopathy of prematurity

weights are 1,500 to 2,000 g or whose gestational ages are more than 32 weeks and have unstable courses, those requiring cardiorespiratory support, or those believed to be at high risk.

When should the first screening examination be performed? The onset of ROP is related more closely to gestational age than postnatal age. Significant retinopathy almost never occurs before 31 weeks gestational age. Table 1 is evidence-based, and following suggested guidelines should detect prethreshold disease with 99% confidence, before the point at which treatment may be needed.

When should the next ROP screening examination be performed? Table 2 provides guidelines for the timing of the follow-up examination.

When should ROP be treated? Type 1 ROP, as defined by the ETROP study, should be treated. Treatment should be performed within 72 hours of the decision to treat. The following types of disease should be treated: zone I, any stage of ROP with plus disease; zone I, stage 3 ROP without plus disease; and zone II, stage 2 or 3 ROP with plus disease.

When should screening examinations be discontinued? Examinations can be discontinued when the retina is fully vascularized; when vascularization has progressed into zone III, without prior ROP; when ROP has regressed; and at 45 weeks postmenstrual age, when prethreshold disease is absent. The last two criteria are dependent on the judgement of an experienced examiner.

Who is responsible for what? Clear lines of communication, responsibility, and accountability are vital in the management of ROP. Blindness may occur due to simple errors. Documentation is important. Each unit must have a clear written policy of which all staff are aware. The scheme in Table 3 is suggested but may be varied to suit local circumstances.

Suggested Reading

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American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the normal vascularization of the retina.
- Know the risk factors, pathophysiology, and approaches to prevention of retinopathy of prematurity.
- Know the incidence, clinical features, and course of retinopathy of prematurity and the staging of severity according to the international classification.
- Know the treatment and outcome of retinopathy of prematurity in relation to severity and therapy.



NeoReviews Quiz

5. Retinopathy of prematurity (ROP) is a disorder of retinal vascular development in preterm infants. Several risk factors have been identified in the pathogenesis of ROP from animal experimental work and human clinical observations. Of the following, the *single* risk factor that can cause ROP independently in the absence of other abnormalities in preterm infants is:
 - A. Abnormal oxygen environment.
 - B. Fungal sepsis.
 - C. Hypothyroxinemia of prematurity.
 - D. Intrauterine growth restriction.
 - E. Postnatal malnutrition.

6. A 6-week-old preterm infant has evidence of ROP. The ophthalmologic examination reveals a ridge between the posterior vascular retina and the anterior avascular retina. There are no extraretinal blood vessels. Of the following, the *best* designation for the stage of ROP in this infant, based on the International Classification of Retinopathy of Prematurity, is:
 - A. Stage 1.
 - B. Stage 2.
 - C. Stage 3.
 - D. Stage 4.
 - E. Stage 5.

7. A new designation representing a rapidly progressive and severe form of ROP, called aggressive posterior ROP (AP-ROP), has been added to the International Classification of Retinopathy of Prematurity to identify cases that may warrant urgent treatment. Of the following, the *most* prominent feature of AP-ROP disease is:
 - A. Anterior zone II retinal location.
 - B. Dilation and tortuosity of posterior retinal vessels.
 - C. Fixed pupillary dilation with eye drops.
 - D. Four clock hours of retinal involvement.
 - E. Neovascularization confined within the retina.

8. The onset of ROP is more closely related to gestational age than postnatal age. Of the following, the *best* postmenstrual age for the first retinal screening examination for detecting prethreshold ROP is:
 - A. 28 weeks.
 - B. 29 weeks.
 - C. 30 weeks.
 - D. 31 weeks.
 - E. 32 weeks.

9. The retinal screening examinations for ROP can be discontinued when the retina is fully vascularized or when vascularization has progressed into retinal zone III without prior ROP. Of the following, the *best* postmenstrual age for the last retinal screening examination to confirm full vascularization of the retina in the absence of prethreshold ROP is:
 - A. 37 weeks.
 - B. 38 weeks.
 - C. 40 weeks.
 - D. 42 weeks.
 - E. 45 weeks.

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