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# Update on the Diagnosis and Management of Retinopathy of Prematurity

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**Retinopathy of prematurity (ROP) is a disease affecting the immature retina. Infants born at low gestational age (GA) and low birth weight (BW) are at the highest risk for developing this disease. Although most cases of ROP regress spontaneously as the infant matures, a small, but significant number develop severe ROP that can lead to cicatricial changes in the retina, tractional retinal detachment, and eventual blindness. With advances in neonatal care, babies at increasingly smaller gestational age and birth weight are surviving and, therefore, the number of infants at risk of developing severe ROP is rising. ROP is a significant cause of preventable blindness in infants in the developed world. As a result, it is imperative that adequate screening programs are implemented to detect and treat this potentially blinding disease. This issue of *Ophthalmology Rounds* focuses on recent changes in the classification, screening guidelines, and treatment recommendations for ROP, and provides a summary with reference images for ophthalmologists involved in the care of premature infants.**

ROP was first described by Terry in 1942.[1] Shortly thereafter, the association between ROP and the excessive use of oxygen was established.[2-4] These findings led to careful monitoring of the amount of extra oxygen given to premature infants to allow adequate blood oxygen saturation levels. However, ROP has not been eradicated. Although oxygen has a central role in the pathogenesis of ROP, there are many other factors involved that are beyond the scope of this article.

## The natural history of ROP

Retinal vascularization starts during the 4th month *in utero*; before that, the thin immature retina receives its nutrients from the underlying choroid. The process of vascularization involves vasculogenesis and angiogenesis. Vessels grow from the optic nerve towards the periphery of the retina. Normally, retinal vessels reach the nasal ora serrata first and the temporal ora serrata later. When an infant is born prematurely, the peripheral retina is avascular. If the normal process of peripheral retinal vascularization is disrupted, ROP develops.

A multicentre study of cryotherapy for ROP (CRYO-ROP) has provided valuable information about the natural course of the disease.[5] This study was conducted in 23 centres in the USA and involved >4000 infants with BWs <1251 g who were enrolled over almost 2 years. Overall, ROP was diagnosed in almost 66%. The highest risk of developing ROP was associated with the lowest BWs, ranging from 90% in those with BWs that were <750 grams to 47% in those whose BWs ranged from 1001 to1250 grams. Around 6% of the infants who developed ROP reached "threshold" and underwent treatment.[6]

The incidence of ROP in neonatal nurseries is variable in different countries. In middle-income countries – in spite of improvements in the survival rates of preterm babies – limited health resources result in lower standards of neonatal care and ROP is found in babies with greater ranges in GA and BW. Thus, ROP appears to be a growing problem in the developing world, such as nations in Latin America and Eastern Europe.[7]

## International classification

The first international classification of acute stages of ROP was published in 1984.[8] This was expanded in 1987 to include classification of retinal detachment and ROP sequelae.[9]



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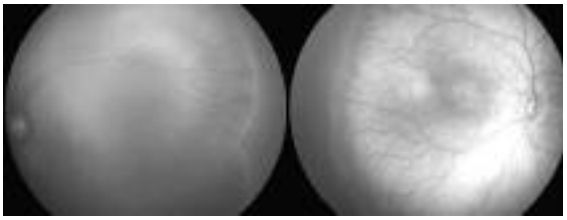
**Figure 1: Stage 1 in zone 2.** The left image is from a darkly pigmented fundus and the right from a Caucasian infant.



ROP can be graded by the following criteria:

- The "stage" of disease, which describes the severity of the disease, with "stage 1" being the least severe, and "stage 5" being the most severe.
- The "zone," which defines the extent of retinal vascularization.
- The extent of disease, which is expressed in terms of the clock hours of involvement.
- Plus disease, which describes a collection of clinical signs; the earliest indicator of plus disease is the level of venous dilation and arteriolar tortuosity around the optic disc.

The original classification of ROP has not changed, but descriptions of the severe form of disease, aggressive posterior ROP (AP-ROP), an intermediate level of posterior vascular abnormality called "pre-plus disease," and a simple clinical method of identifying zone 1 disease, were added in 2005.[10]

## Stages of ROP

**Stage 1:** A flat white demarcation line is established between the vascularized and avascular retina (Figure 1).

**Figure 2: Stage 2 in nasal retina.** The ridge (arrow) is clearly visible, as are 2 small intraretinal hemorrhages adjacent to the optic disc. Small hemorrhages may be observed around the posterior pole or adjacent to the ridge and can be caused by the relatively minimal trauma of globe rotation and scleral indentation during eye examinations in premature infants. "Popcorns" are clumps of new vessels posterior to the neovascular ridge that may be observed in Stage 2. Although popcorns may herald progression from Stage 2 to Stage 3 disease, their presence alone, posterior to the ridge, is not sufficient to classify Stage 3 disease.

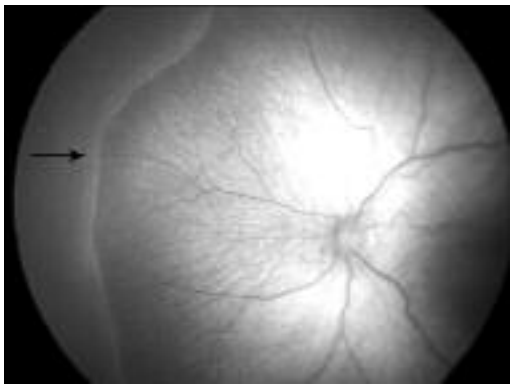
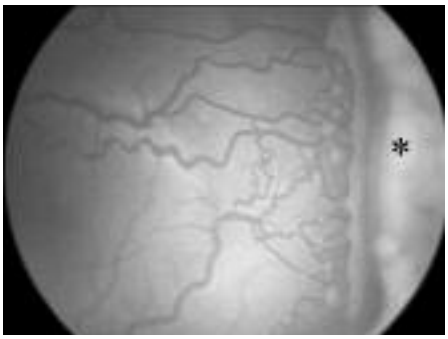


**Figure 3: Severe stage 3.** With higher magnification, preretinal hemorrhages are visible along the neovascular ridge. Popcorns are also visible. The application of almost confluent laser treatment to the avascular retina (asterisk) anterior to the ridge resulted in regression of disease.



**Stage 2:** The demarcation line increases in volume and may change colour, from white to pink. When observed in profile by external scleral indentation, the ridge may be observed to extend above the plane of the retina (Figure 2). Distinguishing between Stage 1 and Stage 2, especially on examination of 2-dimensional images of ROP, may be difficult.

**Stage 3:** Extra-retinal neovascularization is the hallmark of Stage 3 ROP. Fine new vessels emerge that are often above the plane of the retinal vessels and posterior to the ridge. These new vessels may initially be separate from the ridge, but later become continuous with it. As the disease progresses, new vessels may grow into the vitreous (Figure 3).

**Stage 4:** There is progression of disease with development of subtotal retinal detachment. This is classified as Stage 4a when the area of detachment does not involve the macula, and as stage 4b, when the macula is involved in the detachment. Figure 4a and 4b are the right and left eyes, respectively, in the same patient.

**Figure 4a: Laser scars are visible in the peripheral retina.** The retinal vessels are dragged temporally and the inferotemporal retina (bottom left section of the image) is elevated and, therefore, out of focus as compared with the rest of the retina. Although displaced temporally, the fovea is still attached. The area of detachment remained stable without surgical intervention.

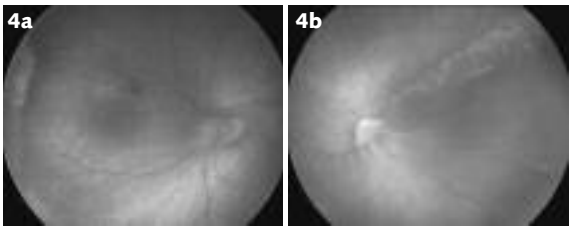
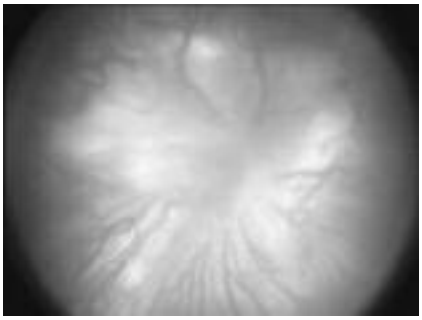



**Figure 4b: There is clear elevation of the temporal and inferior retina with marked dragging of all the retinal vessels temporally.** The macula is detached and the fovea cannot be identified. There is a band of exudates visible demarcating the edge of the retinal detachment superiorly.

**Figure 5: Stage 5 ROP.** There is anterior open funnel and total retinal detachment. Note marked dilation of retinal vessels and glassy appearance of the retina. The optic disc is no longer visible because it is enclosed in the retinal detachment.



**Stage 5:** This is the worst stage of ROP with total retinal detachment (Figure 5). This stage can be further subdivided, depending on the shape of the funnel and whether it is narrow or open, anteriorly and/or posteriorly. This stage of disease requires surgical treatment by vitrectomy, which is often not successful.

Figure 6 shows a diagram that can be used for easy representation of location and severity of ROP.

## ROP defined by zone of involvement

**Zone 1:** This is a circle centered on the optic disc, the radius of which is twice the distance between the optic disc and the fovea. ROP within zone 1 signifies the presence of a large area of avascular retina and is associated with a greater likelihood of progression of disease requiring treatment than when ROP develops in zone 2. Due to the immature appearance of the fovea in a premature neonate, it is often difficult to locate the fovea with certainty and thus, determine the extent of zone 1.

A simple clinical tool for assessing whether vascularization has progressed beyond zone 1 is to use the 25D (or 28D) fundus lens during indirect retinal examination (Figure 7). The nasal edge of the optic disc is placed on one side of the image seen within the lens and the temporal retina within the image is examined. If there is any avascular retina within the image seen through the lens, vascularization has not yet reached zone 2.

**Figure 6: A diagram for easy representation of location and severity of ROP**

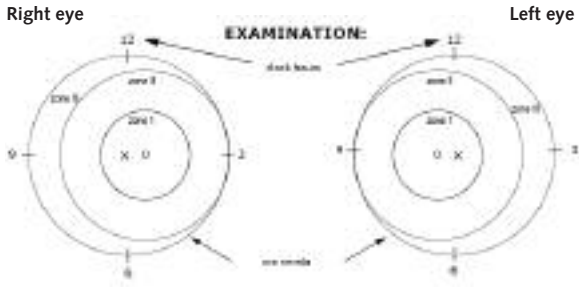
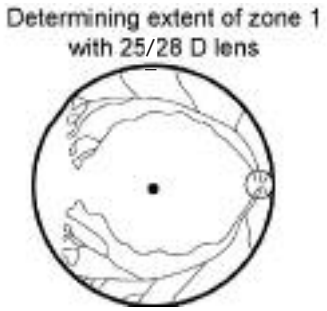



**Figure 7: Schematic representation showing the use of the 25/28D lens for determining whether retinal vascularization has progressed beyond zone 1.** The nasal edge of the optic disc is placed on one side of the image. The black hexagon in the centre represents the approximate location of the fovea.




**Zone 2:** This is an area of retina outside of zone 1, centered on the optic disc. The radius of zone 2 is equal to the distance between the optic disc and the nasal ora serrata.

**Zone 3:** This is the remaining area of the retina outside zone 2; it is in the shape of a crescent with its greatest area on the temporal side of retina.

## Plus disease

Plus disease is a combination of clinical signs that represents active acute ROP. The hallmark of plus disease, the appearance of engorgement of retinal venules and retinal arteriolar tortuosity in the area adjacent to the optic disc, involves at least 2 of the 4 quadrants of the posterior pole vessels (Figures 8a and b). Plus disease does not refer to the vascular changes seen in the peripheral retina. As the disease worsens, the iris vessels become dilated and there is the development of pupil rigidity with failure of pupillary dilation. Later, the vitreous can become hazy, preventing an adequate view of the retina.

## Pre-plus disease

The diagnosis of plus disease is based on standard photographs. If fewer than 2 quadrants of the posterior pole vessels are involved, or the degree of vascular dilation and tortuosity is greater than normal but does not meet the 'standard' photograph of plus disease, the term "pre-plus" is assigned (Figure 9). Standard photographs of pre-plus disease that can be used for reference are now available.[10]

## Aggressive posterior ROP (AP-ROP)

The term "AP-ROP" describes a form of severe ROP that affects very low BW infants. ROP develops in zone 1 or posterior zone 2 (ROP within 1 disc diameter of limit of zone 1). It typically progresses rapidly, tends not to go through stages 1 to 3 (as in the classic progression of ROP), and can quickly present with plus disease in all 4 quadrants. The severity of plus disease usually appears to be out-of-proportion to the deceptively featureless retinopathy. Less experienced examiners may easily miss the diagnosis in its early stages,

**Figure 8a: Plus disease.** Dilation of retinal veins and tortuosity of arterioles is evident in all 4 quadrants close to the optic disc.

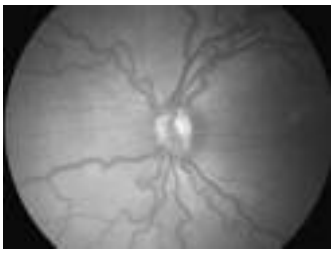
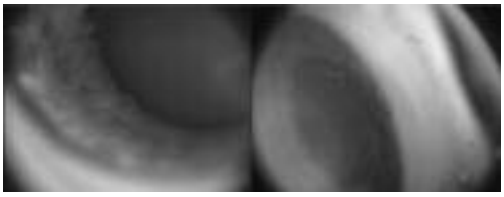


**Figure 8b: Anterior segment sign of plus disease.** There is engorgement of the iris vessels and persistent vasculosa lentis.



resulting in a significant delay in referral for treatment.

## Early treatment for ROP – An update on treatment guidelines

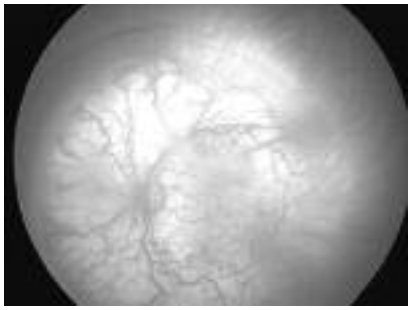
Following the publication of the results of the Early Treatment for Retinopathy Of Prematurity (ETROP) study in December 2003, the indications for treatment of ROP have been modified. The study revealed that earlier treatment of high-risk pre-threshold eyes resulted in a reduction in unfavourable visual acuity and structural outcomes.[11] In a randomized trial, eyes treated at conventional "threshold" were compared with eyes treated when type 1 pre-threshold disease was diagnosed.

Type 1 pre-threshold was defined as zone I, any stage of ROP with plus disease; zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease

At 9 months, visual acuity was assessed using Teller Acuity Cards. Unfavourable visual acuity outcomes – as defined by CRYO-ROP – were reduced from 19.5% in conventional 'threshold' eyes to 14.5% in earlier-treated eyes ($p=0.01$). Similarly, unfavourable structural outcomes were reduced from 15.6% in conventional 'threshold' eyes to 9.1% in the earlier-treated eyes ($p<0.001$). As a result, treatment for ROP should be undertaken for eyes reaching 'threshold,' but also strongly considered for 'pre-threshold' type 1 eyes in the light of this new evidence.

In addition, eyes identified with pre-threshold type 2 ROP (defined as: zone I, stage 1 or 2 without plus disease, or zone II, stage 3 without plus disease) should be observed carefully to allow timely recognition of progression to type 1 or

**Figure 9: Aggressive posterior-ROP (AP-ROP).** Note the absence of a clear demarcation line or ridge in the temporal retina. In the periphery choroidal, vasculature can be seen through the immature avascular retina. Extra-retinal neovascularization is visible nasally and extends into the vitreous, obscuring the view of the underlying retinal vessels. There is severe plus disease.



'threshold' ROP, which would then require treatment. Suggested management for ROP, based on ETROP, is shown in Table 1. Currently there are no clear recommendations for the treatment of ROP in zone III; however, as with all guidelines that are applied to patients, individual variations and clinical circumstances must be taken into consideration to help arrive at the most appropriate management plan.

Once ROP is deemed to be severe enough to require peripheral retinal ablation, it is recommended that treatment be carried out within 72 hours. This advice is meant to provide guidance on the *maximum* amount of time that could be allowed to elapse before treatment is carried out. There are no advantages in delaying treatment and, in the presence of severe ROP such as AP-ROP, all efforts should be made to apply treatment to the avascular retina as soon as possible. The most widely used method for peripheral retinal ablation is indirect laser photocoagulation (which has largely replaced cryotherapy), since laser treatment appears to be associated with fewer ocular complications.

**Table 1: Suggested management for ROP, based on ETROP**

| | | | |
|---|---|---|---|
| Zone I | Plus disease | Any stage | Treatment |
| Zone I | No plus disease | Stage 3 | Treatment |
| Zone I | No plus disease | Stage 1 or 2 | Type 2 pre-threshold, Close observation |
| Zone II | Plus disease | Stage 2 or 3 | Consider treatment |
| Zone II | Plus disease | Stage 1 | Observation |
| Zone II | No Plus disease | Stage 3 | Type 2 pre-threshold, Close observation |
| Zone II | No plus disease | Stage 1 or 2 | Observation |

## Update on recommended screening guidelines for detection of acute ROP

The goal of establishing a cost-effective screening program is to allow detection of severe ROP, enabling treatment in a timely manner for infants at significant risk of blindness, while reducing the unnecessary stress of an ophthalmic examination in neonates at negligible risk of developing severe ROP. The American Academy of Pediatrics, in association with The American Academy of Ophthalmology and The American Association for Pediatric Ophthalmology and Strabismus, have recently published an update on the recommended screening guidelines for infants at risk of ROP.

Current recommendations are to screen all premature infants whose BW is <1500 grams or were born at ≤32 weeks GA. Premature infants with higher GA and birth weights may also be referred for ophthalmology assessment if their attending physician believes that they are at significant risk. The use of a topical anesthetic drop (eg, proparacaine) and supportive oral sucrose is recommended. An infant lid speculum and scleral depresser are used whenever possible during the indirect ophthalmoscopy.

Timing of the first retinal examination should be at 31 weeks post-menstrual age (PMA) for babies born with a GA of 22 to 27 weeks. Beyond 27 weeks GA, the initial eye examination should be done at 4 weeks after birth. Recommendations for subsequent examinations are determined by the status of the retina at first exam and are shown in Table 2.

Screening examinations for ROP requiring scleral indentation can be stopped when there is evidence of:

- full retinal vascularization
- retinal vascularization into zone III without previous zone I or zone II ROP
- PMA of 45 weeks and no pre-threshold disease or worse ROP is present
- regression of ROP, ensuring there is no abnormal vascularization that may progress.

**Table 2: Timing of subsequent retinal examinations in neonates depends on retina status during the first examination**

**1 week follow-up**
- stage 1 or 2 : zone I
- stage 3 : zone II

**1-2 weeks follow-up**
- immature vascularization: zone I – no ROP
- stage 2 : zone II
- regressing ROP: zone I

**2 weeks follow-up**
- stage 1: zone II
- regressing ROP: zone II

**2-3 weeks follow-up**
- immature vascularization: zone II – no ROP
- stage 1 or 2: zone III
- regressing ROP: zone III

## Wide-angle digital imaging

The development of the RetCam II has provided the ability to image an infant's retina using a specially designed, hand-held camera. This enables physicians caring for premature infants to directly document their observations, which can then be shared with nurses, residents, and parents. There are several potential benefits associated with use of the RetCam:

- It allows visualization of a large area of the fundus in one image, thus providing a qualitatively different appreciation of the disease from that seen using indirect ophthalmoscopy, which allows the examiner to view only a smaller area of the retina at any one time.
- The availability of digital images allows comparison between visits and a more accurate assessment of progression
- It is an excellent tool for communicating with other ophthalmologists experienced in ROP to request a second opinion.
- It can be used as a teaching aid, which can reduce the number of repeated examinations of at-risk premature infants
- It has the potential to deliver care via telehealth by making use of remote expert readers. This could eliminate the need to transfer infants to specialized centres with expertise in ROP, thus reducing the potential morbidity associated with transporting at-risk premature infants.

Recent studies that compared digital imaging with indirect ophthalmoscopy for the purposes of ROP screening have shown promising results[12,13] and may help in alleviating the problem of the increasing shortage of ophthalmologists who are experienced in ROP. By allowing the centralization of reading of images taken from infants at several nurseries by a group of regional expert readers, only those infants in whom digital imaging cannot be obtained or who develop severe disease need be transferred for indirect ophthalmoscopy and possible treatment.

## Ophthalmic follow-up after resolution of acute ROP

The risk of poor visual outcome in infants who develop ROP requiring treatment is significant. Refractive errors, myopia, and strabismus[14,15] have been reported at a higher frequency in infants who develop ROP when compared with term neonates. Careful ophthalmic follow-up by an ophthalmologist to detect associated morbidities is recommended. Premature infants with mild ROP that has resolved without treatment (Stage 1 or 2 ROP) or who did not develop ROP are

normally followed up by comprehensive ophthalmologists. As a general guideline adopted from the ETROP study, one should consider prescribing refractive correction in presence of:

- myopia > -4 Dioptres (D)
- myperopia > +5D
- astigmatism >2.5 D
- anisometropia of >1.5 D spherical equivalent of astigmatism, if there is evidence of amblyopia

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*Clinical images in this document have been included by kind permission from Lippincott Williams & Watkins to use figures from The Hospital for Sick Children Atlas of Pediatric Ophthalmology and Strabismus, editors Levin AV and Wilson T; In Press.*

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## Upcoming International Meeting

14-16 September 2006
**World Retinopathy of Prematurity (ROP) Meeting: East Meets West**
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## University of Toronto Department of Ophthalmology and Vision Sciences

### Upcoming events

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|---|---|
| **Oct. 14, 2006** | International Ocular Neuroprotection Meeting<br>The Sutton Place Hotel, Toronto, ON<br>Contact: CME Office 416-978-2719 |
| **Nov. 11-14, 2006** | American Academy of Ophthalmology, Las Vegas, Nevada |
| **Dec. 8-9, 2006** | Walter Wright Day, The Old Mill<br>Toronto, ON<br>Update in Medicine and Ophthalmology<br>Contact: CME Office 416-978-2719 |
| **Feb. 3, 2007** | Toronto Cataract Course<br>Contact: CME Office 416-978-2719 |

**Note: Next year's (September 2006 to May 2007) VPP rounds will be held at Sunnybrook Hospital, 2075 Bayview Avenue, Toronto 5:30 PM - 7:30 PM**

*Disclosure Statement: Dr. Najm-Tehrani has stated that she has no disclosures to announce in association with this publication.*

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