

Retinopathy of Prematurity

Summary of Recommendations

- **Retinopathy of prematurity (ROP) is emerging as one of the leading causes of preventable childhood blindness in India.**
- **Screening for ROP should be performed in all preterm neonates who are born < 34 weeks gestation and/or < 1750 grams birth weight; as well as in babies 34-36^{6/7} weeks gestation or 1750-2000 grams birth weight if they have risk factors for ROP.**
- **The first retinal examination should be performed not later than 4 weeks of age or 30 days of life in infants born \geq 28 weeks of gestational age. Infants born < 28 weeks or < 1200 grams birth weight should be screened early, by 2-3 weeks of age, to enable early identification of AP-ROP.**
- **The retinal findings should be classified and documented based on the International Classification of Retinopathy of Prematurity guidelines (ICROP).**
- **Follow up examinations should be based on the retinal findings and should continue until complete vascularization or regressing ROP is documented or until treated based on the ETROP guidelines.**
- **Laser photocoagulation delivered by the indirect ophthalmoscopic device is the mainstay of ROP treatment.**
- **The responsibility of recognition of infants for screening lies with the pediatrician/neonatologist.**
- **Communication with the parents regarding timely screening for ROP, seriousness of the issue, possible findings and consequences is extremely important.**

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Introduction

The incidence of ROP in India is reported to vary between 38 – 51.9 % in low birth weight infants.¹⁻³ Out of the approximate 26 million annual live births in India, approximately 8.7% of newborns in India are < 2000 grams⁴ in weight. This would imply that almost 2 million newborns are at risk for developing ROP. The fundamental pathological process underlying ROP stems from incomplete vascularization at birth. Normal retinal vascularization progresses in-utero from the disc margin (16 weeks) and reaches the nasal ora serrata (by 36 weeks) and then temporally (by 39-41 weeks) to complete a mature vascular retina.⁵ Term infants have completely vascularized retina and hence are not at risk for developing ROP. Premature infants have avascular or incompletely vascularized retina at birth; ROP evolves over 4-5 weeks after birth. This relatively slow evolution gives a small window of opportunity to effectively conduct retinal examinations and timely interventions to improve visual outcome and avoid irreversible blindness due to retinal detachment from progressive untreated ROP. In this guideline an attempt has been made to address the following issues:

- Which neonates should be screened for ROP?
- When should such screening be initiated?
- How frequently should the infants be screened?
- When is the screening complete?
- Where and how should the examinations be done?
- When is treatment of ROP indicated?

Which infants should be screened for ROP?

Evidence: The American Academy of Pediatrics (AAP) guidelines^{6, 7} state that infants with a birth weight of less than 1500 g or gestational age of 30 weeks or less (as defined by the attending neonatologist) and selected infants with a birth weight between 1500 and 2000g or gestational age of more than 30 weeks with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk, should have retinal screening examinations. In India, the gestational age of infants is not always known or accurate; in addition, ROP has been reported in larger babies with a birth weight between 1500 and 2000 grams. There have been several anecdotal reports from ophthalmologists of babies between 1750 and 2000 grams being diagnosed with ROP. However, there is a paucity of population based data of ROP in these larger neonates.

There is a concern that screening all infants with a birth weight of < 2000 g will considerably increase the number of eligible infants; this is unlikely to be feasible in the current scenario of limited access to trained ophthalmologists. Hence, a birth weight of less than 1750 grams and/or gestational age of less than 34 weeks may be used as a cut-off for performing retinal screening examinations. Babies with a gestational age of 34 to 36^{6,7} weeks gestation or a birth weight between 1750 and 2000 grams should also be screened if risk factors for developing ROP are present.⁶⁻¹⁰ The traditional risk factors considered are mechanical ventilation, prolonged oxygen therapy and hemodynamic instability. It should be remembered that lack of taking these factors into serious consideration may inadvertently exclude the infants at risk for significant ROP and careful review for risk factors should be undertaken by the pediatrician.

Recommendation: Screening for ROP should be performed in all preterm neonates who are < 34 weeks gestation and / or < 1750 grams birth weight. Apart from these infants, those preterm infants between 34 to 36^{6,7} weeks gestational age or a birth weight between 1750 and 2000 grams with risk factors for ROP should also be screened. Risk factors for ROP in larger infants have not been clearly established. Multi-centre studies need to be undertaken to determine the incidence, risk factors and natural course of ROP in the larger preterm infants.

When should the first screening be done?

Evidence: The timing of first screening usually depends on the infant's postnatal age. The convention is not to delay the first screening later than 4 weeks of age or 30 days of life for infants born at or more than 28 weeks of gestation.^{6,9} Infants may be screened as early as 3 weeks of age. For infants born less than 28 weeks of gestation, the first screening should take place at 31 weeks of postmenstrual age (PMA) (gestational age at birth plus postnatal age in weeks) as per AAP guidelines. Some studies have shown serious ROP to be more related to PMA rather than to just postnatal age alone.⁶ It has also been well documented that very low birth weight babies may develop early and aggressive posterior ROP (AP-ROP).^{5,9} It is relatively common in Indian babies and may have a worse prognosis compared to classical ROP.^{11,12} This rapidly progressive type of ROP that can lead to retinal detachment without treatment, needs earlier screening.⁹ Infants <1200 grams or < 28 weeks gestational age may be strongly considered for screening at 2-3 weeks of life in view of the significant incidence of the AP-ROP in these infants.

Recommendation: The first screen should be performed not later than 4 weeks of age or 30 days of life in infants ≥ 28 weeks of gestational age. They may also be screened by the third week of life to enable diagnosis of AP-ROP. Infants <28 weeks or <1200 grams birth weight should be screened early at 2-3 weeks of age, to enable early identification of AP-ROP.

How frequently should the infants be screened?

Evidence & Recommendation: Follow up examination intervals are based on the retinal findings; these findings are classified according to the revised International classification of ROP (ICROP).¹³ The major changes from the previous ICROP classification are the description of aggressive posterior ROP (AP-ROP), the inclusion of pre-plus disease and a practical guide to measuring the extent of zone I. Based on the retinal findings, the follow up examination schedule (Table 1) is suggested.⁶

When should the screening be terminated?

Evidence & Recommendation: Retinal examinations may be terminated based on postmenstrual age or retinal findings. The following are the recommendations to guide when to stop further examinations:^{6,9}

- a) Full retinal vascularization; this usually occurs at about the 40th week of postmenstrual age and mostly completes by the 45th week⁵
- b) Regression of ROP noted

It is advisable to screen the baby every 1-2 weeks at least until the infant is 38-40 weeks of postmenstrual age.⁹

Where and how should the examinations be done?

Evidence & Recommendation: The ideal setting for screening is under a radiant warmer in the NICU, under the guidance of the neonatologist. Discharged and stable babies may be screened in the trained ophthalmologist's clinic or in the NICU itself. The treating team should not forget to communicate with the parents regarding the risk of ROP; the need for screening preterm babies must be addressed along with the initial admission counseling itself. The possible findings and consequences must be explained prior to the initial examination. Documentation of such a communication is highly desirable.

The baby should be swaddled and preferably fed one hour prior to examination. Incubator dependant babies can be screened (and even treated) within the incubator itself through the slanting wall without disturbing the equilibrium of the infant.¹⁴ Pupillary dilatation should be performed about an hour prior to screening. A combination of cyclopentolate 0.5% and phenylephrine (2.5%) drops is used two to three times about 10-15 minutes apart. Tropicamide 0.5-1% is an alternative to cyclopentolate. Atropine should not be used for dilatation. Excess eye drops should be wiped off to prevent systemic absorption through the cheek skin. Over dosage carries the risk of tachycardia and hyperthermia and must be avoided. A non-dilating pupil could indicate the presence of tunica vasculosa lentis and must be confirmed by the ophthalmologist before undue excess medication for dilatation is administered.

The examination is carried out under topical anesthesia without any sedation, using the indirect ophthalmoscope and a 20 D or 28 D condensing lens. Recordings of the findings should be done in the chart or card using standard notations. The date of subsequent follow-up should be clearly stated, and the neonatologist and parent counseled about the same. It must be remembered that retinal examinations are stressful and may be even painful to the infant. Swaddling the infant firmly in a thin blanket and administering 0.5-1 ml of 24% sucrose orally by syringe 1-2 minutes prior to the examination will help to provide comfort and relieve pain. Apnea and bradycardia may rarely develop during the examination in very premature babies. Resuscitation measures should be readily available.

When is treatment of ROP indicated?

Evidence: Prior to December 2003, the CRYO-ROP¹⁵ treatment guidelines were followed. Only a more advanced proliferative stage termed as 'threshold disease' was treated. This was defined as "at least 5 contiguous or 8 cumulative clock hours of stage 3 ROP in zone I or II in the presence of plus disease." The Early Treatment for Retinopathy of Prematurity study (ETROP)¹⁶ study showed that early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree. Ablative therapy is indicated for high risk ROP or type 1 ROP, defined as any of the following: a) Zone I, stage 1 to 3 ROP with plus disease, b) Zone I, stage 3 ROP without plus disease and c) Zone II, stage 2 or 3 ROP with plus disease.

Recommendation: The guidelines from the above study are the currently recommended indications for ablative treatment and are summarized in table 2. AP-ROP also needs early and aggressive laser treatment, often in multiple sessions to prevent retinal detachment^{11, 17}

How should ROP be treated ?

Evidence & Recommendation: The aim of the treatment is to ablate the entire avascular retina up to the ora serrata in a near confluent burn pattern getting as close to the edge of the ridge as possible.^{18, 19} Treatment should be carried out in the NICU or in a setting where monitoring and resuscitation facilities

and trained personnel are readily available. Laser photocoagulation delivered by the indirect ophthalmoscopic device is the mainstay of ROP treatment. Laser has supplanted cryotherapy due to better structural and functional outcomes. It is a safer and a more controlled procedure. Laser therapy can be done under topical anesthesia (0.5% proparacaine HCl, 4% xylocaine), general anesthesia or sedation. Laser treatment, using the ETROP guidelines, has a greater than 90% successful outcome.

Post-treatment recommendation: The child can be fed after about 30 minutes following completion of the procedure. Vital signs must be monitored. It is preferable that the child be under the supervision of the neonatologist or an anesthesiologist for at least 2-3 hours following the procedure. Post-treatment hypothermia and hypoglycemia are common and must be prevented. Mild conjunctival chemosis and hyperemia following the procedure may last for a few days and the parents must be counseled regarding this.

Follow-up visits recommendation: This may be typically scheduled after week 1, 2, 4 and 12 following treatment based on the findings recorded by the treating ophthalmologist. Long-term follow up for development of visual problems is also essential.²⁰

How should retinal detachment be treated?

Stage 4 or 5 ROP requires vitreo-retinal surgical intervention; retinal detachment carries a high risk of irreversible blindness. Lens sparing vitrectomy is the procedure of choice in stage 4A and subtypes of 4B.^{21, 22} Timely lens sparing surgery may in fact result in reasonable to fairly good visual outcomes. A lensectomy–vitrectomy may be performed in stage 5. The prognosis is guarded and results continue to be poor.²³ Visual rehabilitation must be offered to all visually challenged ROP babies.

How should the long term follow up of these infants be planned?

Evidence: Infants with ROP, regardless of whether they have required treatment, are at risk for developing visual disorders such as strabismus, amblyopia, myopia and cataract;^{6, 20} Retinal detachment may also occur during adulthood in infants with ROP. Moreover, prematurity may itself predispose to refractive errors, strabismus and lenticular opacities. Appropriate follow-up for these potential problems after discharge from the NICU is essential.^{6, 9}

Recommendation: Following development of ROP, babies need to be under more intensive follow up for the first 6 months followed by a less intensive follow up schedule until young adulthood period to identify long term complications promptly.

What is the future of ROP screening and what is the role of Photo-documentation and Tele-ophthalmology in ROP screening?

The use of retinal wide field digital imaging (WFDI) using a portable pediatric fundus camera such as the RETCAM II, III and RETCAM shuttle (Clarity MSI, CA, USA) has become a useful adjunct to the documentation of ROP and as a screening and teaching tool.²⁴ The PHOTO-ROP study reports have shown that WFDI compares well with indirect ophthalmoscopy with a high diagnostic sensitivity.^{17, 25} In India, an on-going Tele-ROP trial using non-physician imagers cum graders is being validated against ophthalmologists; preliminary results are encouraging.²⁶ In our country where trained ophthalmologists for ROP management are so few in number when the need is much more, the role of tele-ophthalmology

in screening infants in peripherally situated semi-urban and rural centers by ROP experts in the tertiary care centers seems promising. This may enable timely referral of the affected infants to appropriate centers for further evaluation and treatment.

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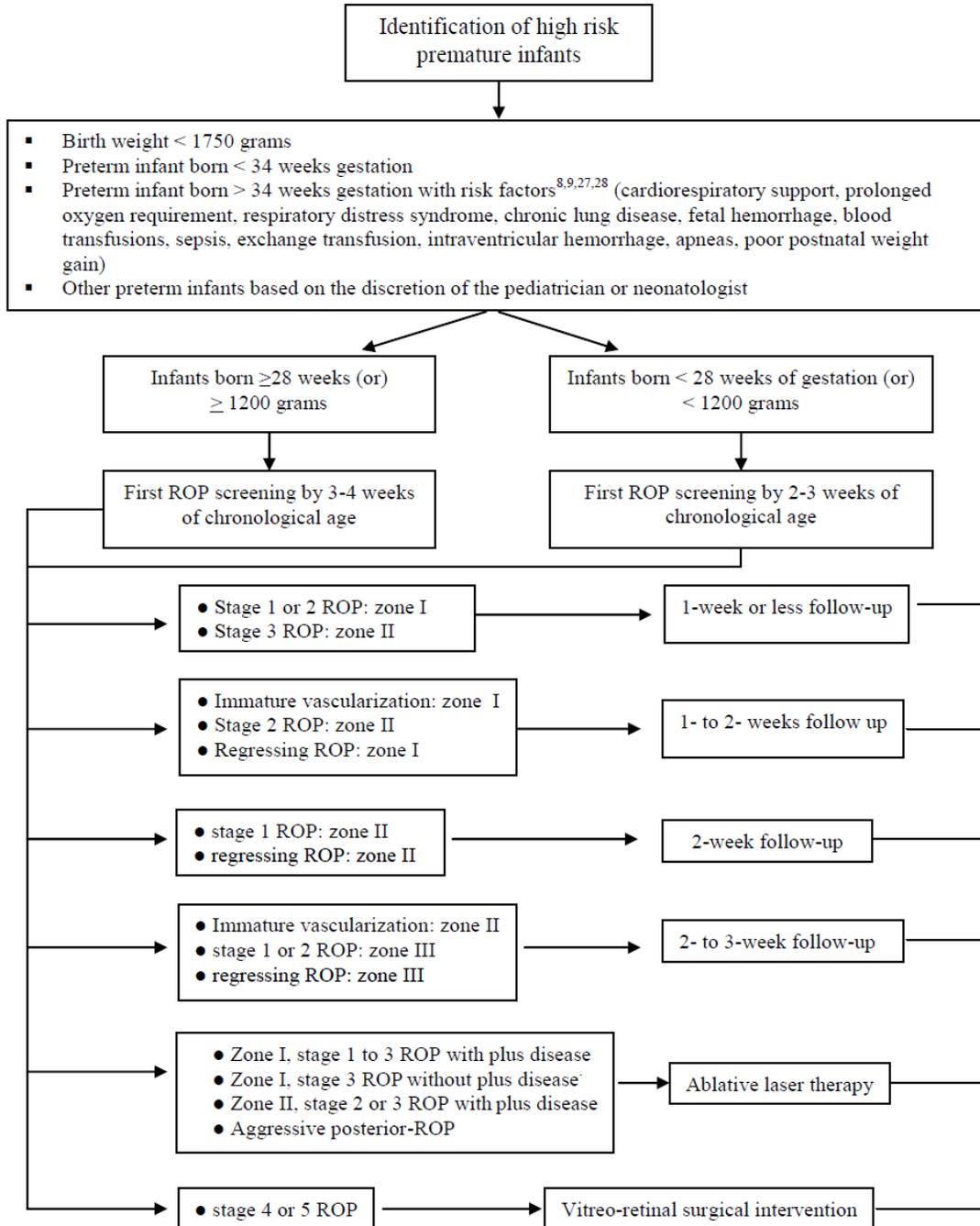
Table 1. Follow up examination schedule based on retinal findings

| <i>Zone of retinal findings</i> | <i>Stage of retinal findings</i> | <i>Follow up interval</i> |
|---------------------------------|----------------------------------|---------------------------|
| Zone 1 | Immature vascularization | 1-2 weeks |
| | Stage 1 or 2 | 1 week or less |
| | Regressing ROP | 1-2 weeks |
| Zone 2 | Immature vascularization | 2-3 weeks |
| | Stage 1 | 2 weeks |
| | Stage 2 | 1-2 weeks |
| | Stage 3 | 1 week or less |
| | Regressing ROP | 1-2 weeks |
| Zone 3 | Stage 1 or 2 | 2-3 weeks |
| | Regressing ROP | 2-3 weeks |

Table 2: Treatment guidelines for ROP adapted from the current ETROP guidelines.¹⁶

| | | | |
|--------|---------|---------|--------|
| ZONE 1 | NO PLUS | Stage 1 | Follow |
| | | Stage 2 | Follow |
| | | Stage 3 | Treat |
| | PLUS | Stage 1 | Treat |
| | | Stage 2 | Treat |
| | | Stage 3 | Treat |
| ZONE 2 | NO PLUS | Stage 1 | Follow |
| | | Stage 2 | Follow |
| | | Stage 3 | Follow |
| | PLUS | Stage 1 | Follow |
| | | Stage 2 | Treat |
| | | Stage 3 | Treat |

Fig 1: Algorithm for management of Retinopathy of prematurity



Annexure

Staging of ROP

ROP is described based on the 1) location of retinal involvement by zone 2) extent of retinal involvement by clock hour, and 3) stage of the disease at the junction of the avascular and vascular retina.

Location of the disease

Zones are centered around the optic disc and not the macula.

Zone I (innermost) is a circle, the radius of which extends from the center of the optic disc to twice the distance from the center of the optic disc to the center of the macula.

Zone II extends centrifugally from the edge of zone 1 to the nasal ora serrata.

Zone III is the residual crescent of retina temporal to zone 2.

Extent of the disease

The extent of the retinal involvement is recorded as hours of the clock or as 30 degrees sectors.

Stage of the disease

The clinical appearance of the stages of ROP is related to the appearance of the retinal vessels at the avascular-vascular junction. More than one stage may be present in the same eye; staging then is determined by the most severe manifestation present.

Immature or incompletely vascularized retina: this is seen prior to the development of ROP and is characterized by dichotomously branching retinal vessels of normal caliber.

Stage 1: A flat demarcating line is seen delimiting vascularized retina from the anterior avascular retina. Abnormal branching or arcading of vessels is seen leading up to the demarcation line.

Stage 2: The demarcation line develops into a 'ridge'. This ridge is raised and has 'volume'.

Stage 3: Extra-retinal neovascularization into the vitreous is seen with the development of abnormal shunt vessels at the ridge.

Stage 4: ROP associated with retinal detachments are classified into stage 4A (partial retinal detachment, not involving the macula) and stage 4B (involving the macula).

Stage 5: Total retinal detachment is usually tractional and funnel shaped and presents as a leucocoria or white pupillary reflex.

Plus disease: refers to venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least two quadrants of the eye. Engorgement of iris vessels, pupillary rigidity and vitreous haze may also be seen. A plus symbol is added to the ROP stage number to designate the presence of plus disease.

Pre-plus is the term used to denote vascular abnormalities of the posterior retina that are insufficient for the diagnosis of plus disease, but that cannot be considered normal.

Aggressive-posterior ROP (AP-ROP) (previously called type II ROP and ‘rush disease’): is a rapidly progressing, severe form of ROP which if untreated progresses to stage 5 ROP. The features include posterior location (zone I and sometimes posterior zone II), prominence of plus disease, ill-defined nature of the retinopathy, flat network of neovascularization and hemorrhages. The earliest phase of this disease shows abnormal closed-loop vessels (and not the normal dichotomous branching pattern) with mild tortuosity that can develop into the full-blown picture in less than a week. The disease does not proceed from the classical stages of 1 through 3. Diagnosis can be made on a single visit and does not require evaluation over time.