CHAPTER

35

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina in preterm infants. Neonates born at less than 32 weeks of gestation are at risk of developing ROP. However, preterm infants born at 32 weeks or later can also develop severe ROP if they have had a turbulent clinical course or needed prolonged oxygen therapy. Nearly one-fourth of neonates undergoing screening may show some degree of ROP, which regresses on its own in the majority. In a few infants, ROP, if untreated it can progress to the stage of retinal detachment and blindness. Timely screening and treatment of ROP can prevent blindness and minimize visual handicaps.

What is the evidence?

Studies from India have reported ROP (any stage) in 20–52% of the screened neonates.[1–10] More recent studies have reported a lower incidence of ROP (20–32.3%) and severe ROP (17.7%).[1–3]

ROP CLASSIFICATION

International Classification of ROP (ICROP) 3rd edition is used for classifying ROP.[11] ICROP-3 describes vascularization of the retina and characterizes ROP by its position (zone), severity (stage), and extent (clock hours) (Fig. 35.1 and Table 35.1).

Aggressive ROP (A-ROP): This is a type of ROP with rapidly developing pathological neovascularization along with a severe plus disease. The typical feature of A-ROP is the risk of rapid progression to retinal detachment without sequential progression through the typical stages of ROP. A-ROP may also show abnormal retinal vessels posterior to the previous edge of vascularization. If not detected and managed, A-ROP can progress rapidly to retinal detachment. Although, typically described to develop in zone I or posterior zone II (hence, previously called aggressive-posterior ROP) and in extremely preterm neonates, this form of ROP has also

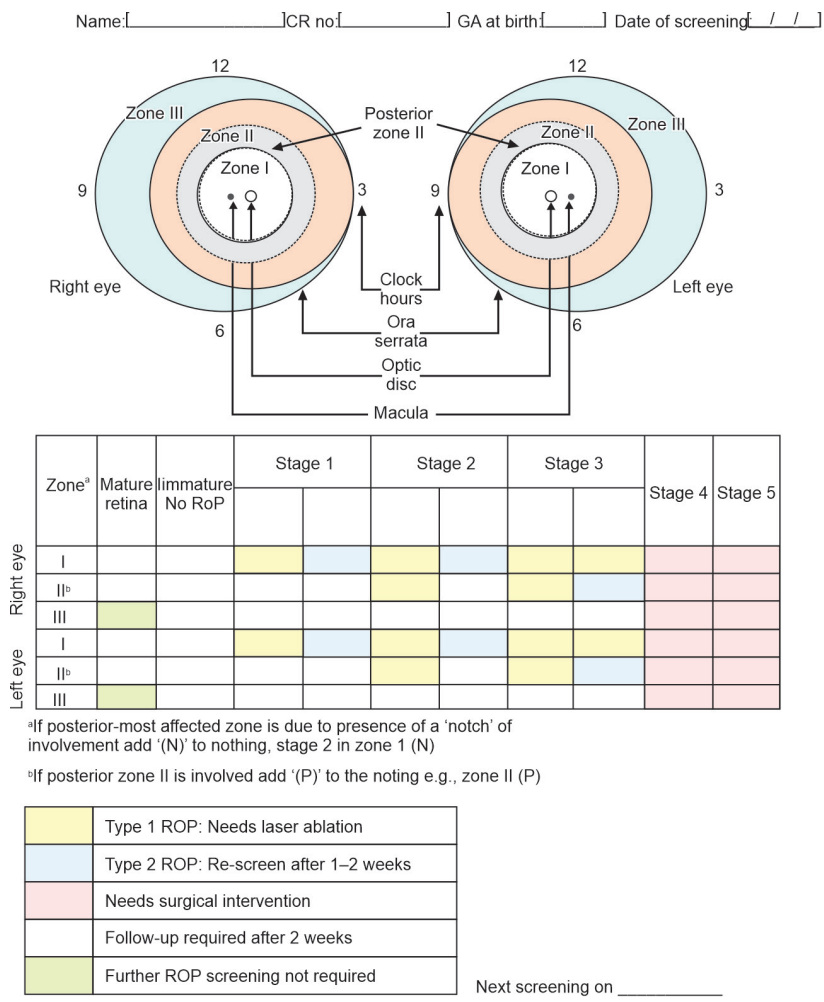

Fig. 35.1: Classification of retinopathy of prematurity

Table 35.1: International Classification of Retinopathy of Prematurity

Location	Zone I	Circle with an optic nerve at its center and a radius twice the distance from the optic nerve to the macula.
	Zone II	The concentric ring-like area from the edge of zone I to the nasal ora serrata and similar distance superiorly, inferiorly, and temporally. Within zone II, 'posterior' zone II is defined as an area of the size equal to the distance of two-disc diameters from the margin of zone I.

(*Contd.*)

Table 35.1: International Classification of Retinopathy of Prematurity (*Contd.*)

	Zone III	Remaining crescent-shaped area of retina peripheral to zone II.
Severity	Stage 1	Presence of thin white demarcation line separating vascular from avascular retina
	Stage 2	Addition of height and width to the demarcation line of stage 1, so as the line becomes ridge
	Stage 3	Presence of extraretinal fibrovascular proliferation with abnormal vessels and fibrous tissue extending from ridge to vitreous
	Stage 4	Partial retinal detachment not involving macula (4A) and involving macula (4B)
	Stage 5	Complete retinal detachment: Stage 5A: Optic disc is visible by ophthalmoscopy (open-funnel detachment) Stage 5B: Optic disc is not visible because of retrolental fibrovascular tissue (maybe closed-funnel detachment) Stage 5C: Stage 5B plus anterior segment changes like, marked anterior chamber shallowing, iridocorneo-lenticular adhesions, corneal opacification (maybe closed-funnel detachment)
Plus disease		Presence of dilatation and tortuosity of retinal vessels at posterior pole of eye within zone I. Also associated with pupillary rigidity and vitreous haze.
Pre-plus disease		Presence of abnormal dilatation and tortuosity of retinal vessels insufficient for plus disease, but more than normal
Extent		Extent of ROP described in 30° clock hours (a total of twelve clock hours of 30° each)
Notch		An incursion by the ROP lesion of 1–2 clock hours into a more posterior zone. If a notch is observed on screening, the zone of the stage is defined by the posterior-most edge with a noting indicating the presence of the notch.

been reported in more anterior zones of the retina and in bigger neonates, especially in developing countries.[11]

Regression: Acute stage ROP can regress in two ways—natural spontaneous regression and treatment-induced regression. Regression of the ROP identified by thinning and whitening of

neovascular tissue can be detected within 1–3 days after anti-VEGF therapy and 7–14 days after laser photocoagulation. Regression can be accompanied by continuing normal vascularization of the remaining retina or arrested vascularization, the latter being called persistent avascular retina (PAR). PAR occurs with greater frequency and may involve a larger retinal area after anti-VEGF treatment. When documenting a retinal screening examination, PAR should be described by its location and extent.[11]

Reactivation: With laser ablation, the peripheral avascular retina, the source of VEGF in pathogenesis of ROP is obliterated and can no longer produce VEGF. However, when monotherapy with anti-VEGF agents is used, the peripheral avascular retina remains viable and can continue producing VEGF. As a result, the acute stage ROP can become reactivated after a phase of regression. Reactivation of ROP can be seen at any site including original site of ROP at the junction between vascular and avascular retina, at a new edge of intraretinal vascular growth, elsewhere in the vascularized retina, or at multiple sites. Reactivation is observed most between 37–60 weeks postmenstrual age. Incidence and time of reactivation is affected by choice of different anti-VEGF agents used and their doses.[11] Reactivation should be documented specifying presence and location of new ROP features with zone and stage using the modifier 'reactivated.'[11]

SCREENING

The aim of the screening program is to detect ROP early, follow it up closely during its evolution, and treat if it assumes potentially serious severity level.

Which Infants should be Screened?

Gestational age and/or birth weight are two important parameters taken into consideration while deciding which babies to screen for ROP.

The Rastriya Bal Suraksha Karyakaram (RBSK) recommends the following criteria for screening:

a. Born at less than 34 weeks of gestation, OR
b. If gestation at birth is not known conclusively, birth weight below 2000 g, OR
c. Born at 34–36 weeks of gestation AND having ANY of the following risk factors:need of respiratory support, oxygen therapy for more than 6 hours, sepsis, episodes of apnea and need

of blood transfusion, exchange transfusion or unstable clinical course as determined by pediatrician.In absence of reliable records, admission in neonatal intensive care unit (NICU) or special care newborn unit (SCNU) can be taken as a surrogate risk factor.

In addition to prematurity, the aforementioned risk factors for developing ROP represent level of sickness. Sickness is therefore an important underlying factor that makes higher gestation preterm neonates at risk of developing ROP.[4]

AIIMS, New Delhi instituted its ROP screening program in early 1990s. We observed a change in the epidemiology of ROP by early 2000s. Though milder ROP could be seen in infants of 32 weeks or more of gestation, ROP requiring treatment occurred only in infants of less than 32 weeks gestation or sick infants of 32–35 weeks gestation. Overall, there was a significant reduction in ROP requiring treatment. Also, AROP has occurred very rarely in our NICU. Accordingly, we changed our screening criteria to reduce the unnecessary painful ROP screening and to optimize resource utilization. We believe that happened due to high quality of care provided at AIIMS NICU. Also, a screening program being in place helps in early ROP detection.

Our current criteria of ROP screening are as follows:

a. Born at less than 32 weeks of gestation, OR
b. If gestation at birth is not known conclusively, birth weight below 1500 g, OR
c. Born at 32–35 weeks of gestation AND having ANY of the following risk factors:need of respiratory support, oxygen therapy for more than 6 hours, sepsis, episodes of apnea and need of blood transfusion, exchange transfusion or unstable clinical course as determined by pediatrician.

When and How often to Screen

First screening examination should be carried out at 32 weeks of post menstrual age (PMA) or 4 weeks of postnatal age (PNA), whichever is later.[12]

In neonates less than 28 weeks of gestation or with birth weight less than 1200 g if gestation at birth is not confirmed conclusively, the first examination for ROP should be performed at 2–3 weeks postnatal age (PNA).

Practice tip

A good rule to remember is to perform first screening at 4 weeks of PNA.

What is the evidence?

Progression of ROP follows a distinct timeline as per PMA rather than postnatal age (PNA) of the infant. ROP may not be detected before 30 weeks of PMA or before 2–3 weeks of PNA.

The median age at detection of stage 1 ROP is 34 weeks. The vascularization is complete by 40–44 weeks of gestation. The critical phase during screening is 32–38 weeks when the infant is likely to reach a severe stage of disease that may require treatment for prevention of blindness.

Follow-up examinations are normally required every 1–2 weeks depending upon ROP staging and should be recommended by the examining ophthalmologist.

ROP screening can be terminated once there is complete vascularization of retina without any ROP, or if the ROP has shown regression. This normally happens at around 40–44 weeks of PMA. However, if anti-VEGF agents are used for treatment, screening examinations need to continue to detect reactivation after regression.

Where to Examine the Baby?

Neonates are best examined in the neonatal unit itself under supervision of attending pediatrician/neonatologist. It is not wise to transport small babies to ophthalmic outpatient or ward for examination.

How to Dilate the Pupils?

Pupils are dilated with a combination of phenylephrine 2.5% and tropicamide 0.5% eye drops. The combination can be instilled 2 times at 10 min intervals half hour before screening. Alternatively, one drop of tropicamide is instilled every 10 minutes up to 2 times starting half hour before the scheduled time for examination. This is followed by phenylephrine, just one drop instilled few minutes before examination. Phenylephrine is available in 10% concentration; it should be diluted 4 times before use in neonates. Repeated instillation of phenylephrine is avoided for the fear of hypertension.

Practice tip

If pupils are not dilating despite administration of adequate mydriatic drops, AROP should be suspected. These infants should be screened on priority and appropriate and timely action taken.

What does the Examination Entail?

Screening of ROP involves indirect ophthalmoscopy (IO) using 28/30 D lens by an experienced ophthalmologist. After instilling

a topical anesthetic drop like proparacaine, a wire speculum is inserted to keep the eyelids apart. First the anterior segment of the eye is examined to look for tunica vasculosa lentis, pupillary dilation, and lens/media clarity followed by the posterior pole to look for plus disease followed by sequential examination of all clock hours of the peripheral retina. A scleral depressor is often used to indent the eye externally to examine areas of interest, rotate and stabilize the eye. Use of scleral depressor increases the pain during screening examination and can be avoided if the examiner is skilled to complete the screening without it.

How to Record Findings during Screening?

Ophthalmological notes should be made after each ROP examination, detailing zone, stage and extent in terms of clock hours of any ROP and the presence of any pre-plus or plus disease. These notes should include a recommendation for the timing of the next examination (if any) and be kept with the baby's medical record.

What Precautions are Taken during Examination?

ROP screening examination can have short-term effects on blood pressure, heart rate and respiratory function in the premature baby.[14] The examination should be kept as brief as possible and precaution is taken to ensure that emergency situations can be dealt with promptly and effectively. ROP screening is a painful procedure if not done properly. It should be minimized by administrating a combination of topical anesthetic eye drops (0.5% proparacaine) 30 seconds prior to examination. Some prefer oral 24% sucrose or 25% dextrose in the dose of 0.5 ml/kg for sucking on gauze just before the insertion of eye speculum. Baby should not be fed one hour before examination to avoid vomiting and aspiration. Hand hygiene should be practiced to maintain asepsis.

What is the evidence?

A systematic review and meta-analysis comprising four studies has reported that oral sucrose reduces pain during eye examination.[13,14] Of two studies reporting the role of topical proparacaine drops has observed significant pain reduction.[15]

Use of Wide-field Digital Camera for Screening: Wide-field digital cameras capable of retinal imaging have been evaluated as an alternative to IO for screening in preterm infants. Retinal images taken by camera can be stored, transmitted to expert, reviewed, analyzed and sequentially compared over time and are useful for

tele-screening purposes in community programs. However, due to high cost and variable sensitivity, wide-field digital cameras have not been used widely as replacement for IO.[16] Various lower cost alternatives have now become available. However, efficacy of these cameras is dependent not only on technical capabilities but also on the expertise and supervision of healthcare worker obtaining the retinal image, mechanism in place for timely review of images and ability to provide treatment when severe ROP is detected. A program with all these components needs to be validated before new generation wide-angle cameras are put into use.

What is the evidence?

Studies comparing wide-field retinal imaging with indirect ophthalmoscopy (IO) have reported variable sensitivity but good specificity.[16]

TREATMENT

The treatment involves ablation of peripheral normal avascular retina and thereby abolishing hypoxic drive of retina (mediated by over-expression of vascular endothelial growth factor; VEGF).This results in regression of established ROP.

Indication for Peripheral Retinal Ablation: Treatment of ROP is based on differentiation of following two types of ROP:

Type 1 ROP (needs treatment):

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

(A-ROP in any zone is also an indication of treatment)

Type 2 ROP (needs close follow up):

- Zone I, stage 1 or 2 ROP without plus disease
- Zone II, stage 3 ROP without plus disease

Peripheral retinal ablation should be conducted for all cases with type 1 ROP and continued serial examinations are advised for type 2 ROP.

What is the evidence?

Classification of ROP into type 1 and 2 is based on results of Early Treatment for Retinopathy of Prematurity Randomized Trial (ETROP).[17] Before ETROP study laser ablation was performed in neonates with threshold ROP, a classification based on location and stage of ROP.

ETROP study demonstrated improved visual outcome if laser ablation is performed in eyes with 'high-risk' pre-threshold ROP.Type 1 ROP includes threshold ROP and subset of pre-threshold ROP likely to benefit from early treatment.

Treatment modalities: ROP may be treated by laser treatment of avascular retina, intravitreal Anti-VEGF drugs or vitreoretinal surgery in advanced cases.

A. Laser Treatment

Peripheral retinal ablation is conducted by diode/double-frequency YAG laser.Ideally, laser therapy should be carried out in the NICU under the supervision of the neonatology team.

What is the evidence?

In a Cochrane systematic review peripheral retinal ablation as compared to no treatment was associated with improved structural and functional outcome in treated eyes.[18] Due to ablation of peripheral avascular retina, visual fields were reduced in treated eyes.

Preanesthetic preparation: Oral feeds should be discontinued 3 hours prior to the procedure. Baby should be started on intravenous fluids and put on cardio-respiratory monitor. Dilatation of pupil is to be ensured (as described earlier).

Anesthesia/sedation: Topical anesthesia alone provides insufficient analgesia for ROP treatment and should not be solely relied upon. Ideally, neonates should be treated under general anesthesia or analgesia plus sedation in an operation theatre.However, in absence of such options in resource limited settings, use of intravenous fentanyl (bolus of 2 µg/kg followed by infusion of 2 µg/kg/hour titrated to a maximum of 5 µg/kg/hour to reduce pain) can be considered for providing analgesia during the procedure. Use of fentanyl is associated with important but transient side effects and therefore requires continued observation of the infant for at least 24 hours after the procedure.[19]

What is the evidence?

In an open label randomized control trial (NOPAIN-ROP) with two intervention arms, regimens of intravenous fentanyl and intravenous ketamine provided adequate analgesia in only a minority of infants (16.3% and 4.5%). Even the revised higher dose regimens of fentanyl and ketamine did not improve these proportions (23.1% and 7.1%). Though, in general, the drugs were well tolerated but a minority did experience significant side effects that required prolonged monitoring (>24 hours).[19]

Procedure: Both the eyes can be treated in the same sitting unless contraindicated by instability of the baby. If baby is not able to

tolerate the procedure, consider abandoning the procedure for the time being.Vital signs and oxygen saturation should be monitored very closely.

Monitoring after laser therapy: After laser therapy first examination should take place 5–7 days after treatment and should be continued at least weekly for signs of decreasing activity and regression. Treatment of any skip areas should be performed if there has been a failure of the ROP to regress.

Postoperative care:

- The baby should be closely monitored.If condition permits, oral feeds can be started shortly after the procedure.
- Premature babies, especially those with BPD may have increase or re-appearance of apneic episodes or an increase in oxygen requirement.Therefore, they should be carefully monitored for 48–72 hours after the procedure.
- Antibiotic drops (such as chloramphenicol) should be instilled 6–8 hourly for 2–3 days.

B. Intravitreal Anti-VEGF Drugs

Anti-VEGF drugslike bevacizumab or ranibizumab when injected directly into the vitreous chamber, cause regression of abnormal vessels without destroying the peripheral retina. As VEGF is an important mediator of lung growth and brain development, and there is significant systemic absorption of anti VEGF medication after intravitreal injection, there are concerns regarding toxicity of such therapy.

Intravitreal anti-VEGF drugs may be used for treatment of type 1 ROP involving zone I and zone II posterior ROP. Proper aseptic injection techniques are important to prevent iatrogenic complications like cataract and endophthalmitis. Currently there is insufficient evidence for use of anti-VEGF drugs other than bevacizumab and ranibizumab.

What is the evidence?

A systematic review suggests that there is no significant difference in incidence of complete or partial retinal detachment (RR: 1.04; 95%CI: 0.21–5.13) between bevacizumab and laser therapy.There was increased risk of recurrence of ROP with bevacizumab therapy (RR: 5.36, 95% CI: 1.22–23.50). On subgroup analysis, the risk of recurrence of ROP needing retreatment was increased in patients with zone 2 ROP while decreased in zone 1 ROP.[20]

(*Contd.*)

(*Contd.*)

In a three-arm, parallel group, superiority trial (RAINBOW study), bilateral intravitreal dose of ranibizumab 0·2 mg, ranibizumab 0·1 mg, and laser therapy were compared. The primary outcome of treatment success (defined by survival without active ROP, unfavorable structural outcome, or need for treatment switch up to 24 weeks after starting investigational treatment) occurred in 80%, 75% and 66% infants, respectively.Data on long-term effect including neurodevelopmental outcome is lacking.[21]

Long-term follow-up retinal examinations including the retinal periphery are needed till at least 60–65 weeks postmenstrual age (PMA) after the use of anti-VEGF drugs as there is a definite risk of reactivation needing a second injection or laser ablation. Other complications include retinal detachment, persistent avascular retina, macular anomalies, retinal vascular changes, vitreous hemorrhage and glaucoma. Due to lack of evidence about long-term effects including neurological outcomes, parents must be informed about the benefit and risks, and a written informed consent must be obtained for use of anti-VEGF drugs, including off-label use.

C. Vitreoretinal Surgery

Vitreoretinal surgery is done for advanced cases of ROP with retinal detachment in Stage 4–5. The outcomes of early surgery in stage 4 ROP are good, but prognosis in end stage 5 ROP is poor.

PREVENTION

Antenatal

Antenatal steroids: Use of antenatal steroids is a well-known approach to prevent respiratory distress and intraventricular hemorrhage, two important risk factors of ROP. Though antenatal steroids have not reduced occurrence of ROP, perhaps because it saves smaller babies who are at higher risk of developing ROP, but, as it reduces sickness level in preterm infants, it is likely to reduce severe ROP.

Postnatal: Most important risk factor for ROP is prematurity. It is difficult to prevent prematurity but there are other modifiable risk factors which require high quality neonatal care.

Delivery Room Interventions

- **Delayed cord clamping:** Reduces need of blood transfusion and hence reduces a potential risk factor for ROP.

- **Temperature regulation:** Maintaining normothermia reduces the risk of severe ROP.
- **Gentle respiratory management:** Avoiding injury to lungs and maintaining preductal saturation in target range for preterm infants reduces the risk of ROP.

Interventions in neonatal unit: Summarized as POINTS[22] of care:
Pain control
Oxygen management
Infection control
Nutrition
Temperature control
Supportive care

Pain control: Unnecessary painful procedures should be avoided as pain makes babies unstable and can increase oxygen requirement as well as increase the respiratory distress. Use of swaddling and oral sucrose solution or breastmilk during painful procedures helps to reduce pain.

Judicious oxygen therapy: Oxygen is a drug, and it should be used judiciously. Each neonatal unit should have a written policy regarding when and how to use oxygen and target saturations.

If a preterm neonate <32 weeks' gestation needs resuscitation at birth, inhaled oxygen concentration (FiO_2) should be titrated to prevent hyperoxia and achieve gradual increase in oxygen saturation (70% at 3 minutes and 80% at 5 minutes after birth).[23] During acute care of a sick preterm neonate, ROP is more likely to develop if partial pressure of oxygen in arterial blood is more than 80 mm Hg.

Oxygen levels in blood should be continuously monitored using pulse oximetry keeping a saturation target of 91–95%. It is important that a work culture is inculcated wherein physicians and nurses respond to monitor alarms.

What is the evidence?
A large scale RCT (SUPPORT trial) indicated that maintaining low saturations (85% to 89%) compared to high saturations (91–95%) death preterm infants <28 week did not reduce composite outcome of in or severe ROP but it resulted in lower severe ROP and higher death rates.[24]

Therefore it is recommended that saturations in preterm neonates be maintained between 91 and 95%. Saturations should be monitored in preterm infants receiving oxygen therapy to prevent hyperoxia or hypoxia.

Infection control: Infection control bundles like hand washing, steps of hand hygiene, maintaining sterility during invasive procedures, measures to maintain skin integrity and antibiotic stewardship are often beneficial.

Nutrition: Good nutrition including early and exclusive breastmilk feeding to premature infants has proven short term as well as long term benefits, including lowering the rates of ROP. Poor postnatal weight gain is an important risk factor for significant ROP.

Other: Judicious use of blood transfusions: Transfusion of packed RBCs is another risk factor of ROP. Adult RBCs are rich in 2,3 DPG and adult Hb binds less firmly to oxygen, thus releasing more oxygen to the retinal tissue. Refer to the Chapter 51: Blood Component Therapy.

Other interventions: Supplementation of high doses of Vitamin E or reduced ambient light exposure is not associated with reduced incidence of ROP. In neonates with initial stages of ROP, administration of supplementation oxygen to achieve oxygen saturation in supraphysiological range and to reduce retinal hypoxia is not associated with halt in progression of ROP.

Quality Improvement

Protocolized Approach

- All units caring for babies at risk of ROP should have a written protocol for screening and treatment of ROP. The neonatologists have the responsibility of followingup the babies discharged from the unit till ROP screening is complete.
- If babies are transferred either before ROP screening is initiated or when it has been started but not completed, it is the responsibility of the consultant neonatologist to ensure that the neonatal team in the receiving unit is aware of the need to start or continue ROP screening.
- Whenever possible, ROP screening should be completed prior to discharge.There should be a record of all babies who require review and the arrangements for their follow-up.
- For babies discharged home before screening is complete, the first follow-up out-patient appointment must be made before hospital discharge and the importance of attendance explained to the parents.

Auditing

Following outcomes should be regularly audited in units with ROP screening and treatment program.

- Completeness of screening program: Percentage of eligible babies who receive at least one ROP eye examination.
- Timing of first screen: Percentage of eligible babies receiving first ROP screening exam by 4 weeks of postnatal age.
- Timing of treatment: Percentage of babies needing ROP treatment who are treated within 48 hours of the decision to treat being made.

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