# SLHD: Royal Prince Alfred Hospital Guideline

## Women and Babies: Retinopathy of Prematurity

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Women and Babies: Retinopathy of Prematurity

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SLHD - RPA Women and Babies: Retinopathy of Prematurity Guideline

1. Introduction
Screening for retinopathy of prematurity (ROP) is a standard procedure in Neonatal Intensive Care Unit. Neonates who are identified as high risk and with progressive ROP require laser therapy to prevent progression of eye disease and improve visual outcomes.

2. The Aims / Expected Outcome of this Guideline
- Minimising the risk of ROP.
- Identifying preterm infants with ROP.
- Classification of ROP based on standardised nomenclature.
- Identifying neonates who need ROP treatment early and providing treatment
- Improving visual outcomes for infants with ROP

3. Risk statement
- SLHD Enterprise Risk Management System (ERMS) Risk # 106 - Recognising and Responding to Clinical Deterioration in Acute Health Care
- Risk of not detecting retinopathy of prematurity early enough for effective intervention.

4. Policy Statement
The goal of this guideline is to identify all infants with ROP and provide timely treatment.

5. Scope
- Neonatal nursing and medical staff

6. Implementation
No special implementation required.

7. Key Performance Indicators and Service Measures
- Audit of ROP incidence and need for treatment through State (NSW NICUS) Database and Regional (ANZNN) Database.
- Monitoring of visual outcomes of infants who have had Laser therapy and/or Anti-VEGF therapy

8. Guidelines

8.1 Background
Retinopathy of prematurity (ROP) is a vascular disorder of the developing retina of low birth weight and preterm infants that can potentially lead to blindness in a small but significant percentage of those infants (1). An effective ROP screening program aims to identify the
infants who benefit from treatment and make appropriate recommendations on the timing of future screening and treatment interventions(2).

**Incidence and risk factors**
The incidence of ROP varies across Australia and New Zealand because of different screening criteria. Based on the current Australia and New Zealand Neonatal Network (ANZNN) inclusion criteria of gestational age less than 31 weeks and/or a birth weight less than 1250 grams, in 2013 the incidence of stage 3 or 4 eye disease was 6.4% and of these 42.3% received surgical treatment (3).

The incidence of all grades of ROP at RPA over 10 years (2007-2016) was 40.9%. The incidence of stage 3 or 4 eye disease was 7.5%, among whom 52.5% required laser treatment.

Risk factors reported in the development of ROP are:
- Prematurity
- Intrauterine growth restriction
- Hyperoxia
- Hyperglycaemia
- Low Insulin-like Growth Factor 1 (IGF-1)
- Neonatal infections
- Multiple births
- Male infants
- Genetic polymorphisms (4, 5)
- mechanical ventilation
- blood transfusion(6)

**Pathophysiology**
**Normal retinal development**
The development of the retina, which proceeds from the optic nerve head anteriorly, is incomplete in preterm infants, with the extent of immaturity depending on the degree of prematurity at birth (1). Retinal vascular network in the form of superficial and deep capillary plexuses begin to develop at 16 weeks of gestation from mesenchymal spindle cells and blood vessel precursors emerging from the optic nerve head (7). Retinal vessels reach the ora serrata nasally at approximately 32 weeks of gestation and temporally shortly after birth. During retinal vascular migration glial cells such as astrocytes form a template for endothelial cell migration and also serve as an important source of vascular endothelial growth factor (VEGF)(7). VEGF is mainly secreted in the maturing avascular retina in response to increased metabolic need and a local physiological hypoxia in developing retinal vessels, and acts as a mitogen for vascular endothelial cells needed for angiogenesis (8)

**Biphasic nature of ROP**
ROP is a biphasic disease; the first phase is a hyperoxic vessel obliteration and the second is a hypoxic neovascularization phase (9).

Neonatal hyperoxia, experienced by premature infants soon after birth and during the first few days of postnatal life, causes disruption of sections of the retinal vasculature, by apoptosis and excessive capillary regression, resulting in interruption of normal vascularization and later ischemia of the retina (phase I; hyperoxia-vasocoression) (7, 9). This first phase of ROP occurs from birth to approximately 30-31 weeks of gestation.
Administration of supplemental O2 in this phase may also cause hyperoxia, increasing the stage for vaso-obliteration of existing vessels. As the metabolic demand of the developing retina increases, the immature non-perfused area of the retina becomes more hypoxic and may stimulate an overproduction of VEGF pathologically, resulting in abnormal neovascularization of the retina (phase II; hypoxia-vasoproliferation). This phase begins around 31-32 weeks of gestational age.

Insulin like growth factor-1 (IGF-1) is also a key factor in normal vessel development. It regulates retinal neovascularization by controlling the activation of VEGF regardless of oxygenation (7). Loss of maternal long-chain polyunsaturated fatty acids seems to have a role in pathogenesis of retinopathy of prematurity (10). Progression of ROP to threshold ROP or the risk for proliferative ROP in very low birth weight infants may also be influenced by genetic polymorphisms in VEGF production (11, 12).

Although it was generally thought that transition between phase 1 and phase 2 depends on postmenstrual age (13), extremely preterm infants have been shown to transition more closely with postnatal age indicating that extreme prematurity confers an additional risk for developing retinopathy of prematurity (14).
Flowchart showing pathogenesis of ROP. Adapted from American academy of Ophthalmology (15)

- Prematurity
- Incomplete retinal vascularization
- Exposure to Increased Oxygen
- Vasoconstriction
- Vaso-obliteration and involution
- Peripheral retina ischemia stimulates production of VEGF
- Tortuosity of vessels
- Neovascularization
- Iris vessel dilatation
- Fibro-vascular proliferation and retinal detachment
Classification

The International Classification of Retinopathy of Prematurity (ICROP) first published in 1984 and revised in 2005 is used to classify ROP (16, 17). This classification system consists of four components:

1. **Location** refers to how far the developing retinal blood vessels have progressed. The retina is divided into 3 concentric circles or zones as shown in the figure below:

   ![Figure 1: adapted from Committee for the Classification of retinopathy of prematurity(18)](image)

   Each zone is centered on the optic disc. Zone I consists of a circle, the radius of which extends from the centre of the optic disc to twice the distance from the centre of the optic disc to centre of the macula. Zone II extends centrifugally from edge of zone I to the nasal ora serrata. Zone III is the residual crescent of the retina anterior to zone II.

2. **Extent** refers to the circumferential location of disease and is reported as clock hours in the appropriate zone.

3. **Staging of disease**

   Because more than 1 ROP stage may be present in the same eye, staging for the eye as a whole is determined by the most severe manifestation present. For the purposes of recording, each stage is defined and the extent of each stage by clock hours or sector is recorded.

   **A. Stage 1**

   Demarcation line – a flat whitish line of demarcation seen between vascularised and avascular retina (a normal retina has a tenuous, non-linear, feathery border).

   **B. Stage 2**

   Elevated ridge – demarcation is now a ridge rather than a line and has height and width and extends above the plane of the retina. Small isolated tufts of neovascular tissue (called popcorn) may be seen posterior to the ridge structure.

   **C. Stage 3**

   Neovascularization – From the surface of the ridge, abnormal blood vessels grow and extend into the vitreous (extra-retinal fibrovascular tissue) instead of following their normal growth pattern along the surface of the retina. This extraretinal proliferating tissue is continuous with the posterior aspect of the ridge, causing a ragged appearance.
D. Stage 4
Partial detachment of retina caused by traction from scar tissue. The extent of detachment depends on the number of clock hours of fibrovascular traction and their degree of contraction. Typically, retinal detachments begin at the point of fibrovascular attachment to the vascularised retina. Further divided into 2 parts:
- 4A Partial detachment sparing macula.
- 4B Partial detachment involving macula.

E. Stage 5
Total retinal detachment which are generally tractional and may occasionally be exudative. They are usually funnel shaped, and divided into anterior and posterior parts. When open both anteriorly and posteriorly, the detachment generally has a concave configuration and extends to the optic disc.

4. Plus and Rush Disease

**Plus disease** - Presence of dilatation and tortuositites of the posterior pole blood vessels involving at least two quadrants of the retina. Multicentre clinical trials have also used “a standard photograph” to define the minimum amount of vascular dilatation and tortuosity required to make a diagnosis of plus disease(19, 20).

![Standard photograph defining plus disease](image)

**Pre-’Plus’ Disease** - More arterial tortuosity and venous dilatation is seen than normal, but is not severe enough to be classified as ‘Plus’

**Rush” Disease (Aggressive Posterior ROP, AP-ROP):**
A rare and severe form of ROP with increased tortuosity and dilatation of vessels present in all 4 quadrants of zone 1 and sometimes zone 2 and is out of proportion to the peripheral retinopathy. May not sequentially advance through Stage 1 to 3 but often rapidly advances to stage 4 or 5. AP-ROP typically extends circumferentially and is often accompanied by a circumferential vessel.

**Prevention**
The most important strategy to prevent ROP has been to avoid wide variation in oxygenation and avoid hyperoxemic episodes (21, 22). Strict oxygen management policy with strict guidelines in practices of weaning oxygen and monitoring of oxygen saturation parameters in
the delivery room and through duration of nursery admission has been shown to reduce incidence of severe ROP and need for laser treatment (23, 24). It has been shown that targeting low range of oxygenation (85-89%) when compared to higher target range (91-95%) did not significantly decrease the composite outcome of severe retinopathy or death, but it resulted in an increase in mortality and a substantial decrease in severe retinopathy among survivors(24, 25). At RPA, we use higher oxygen targeting (90-95%) for preterm babies who are on oxygen because of the higher mortality risk associated with targeting lower oxygen saturations.

**Diagnosis**

1. **Screening**

**Who to screen?**

The aims of screening for ROP are to identify ROP which has the potential to reach stage 3, and severe (stage 3) ROP which may require treatment.

**RPA ROP screening flowchart**

- **ROP screening**
  - All infants born at <30 weeks gestation and/or
  - All infants born with a birth weight of <1250grams
  - Clinician discretion in infants at high risk of ROP

- **Time of ROP screen in eligible infants**
  - At 32 weeks postmenstrual age for infants less than 28 weeks gestational age
  - At 4-6 weeks postnatal age for infants 28 weeks gestation and above.

- **Follow up of infants with ROP**
  - 1-2 weeks- High risk of progression
  - 2-3 weeks- Low risk of progression
  - Stop screening- Vascularised retina

**Evidence-base for ROP screening**

The 2008 UK guideline development group reviewed 23 articles involving 10,481 screened babies of whom 643 (6.1%) developed sight threatening ROP (26). Among those with sight threatening ROP, 29 (4.6%) had a gestational age (GA) of 30-31 weeks and 8 (1.2%) had a GA ≥32 weeks while 15 (2.6%) babies had a birth weight between 1251 and 1500g and 8
babies (1.4%) had a birth weight >1500g. Only one baby requiring treatment would have been missed if either the GA criterion was <31 weeks or the birth weight criterion <1250g (26).

In a retrospective cohort study of 994 infants of infants greater than 30 weeks gestation and with a birth weight greater than 1250 g, the prevalence of any ROP was low (2.0%); however there were no cases of stage 3 or higher ROP in this group (27). A retrospective cohort study of 1007 neonates where infants <32 weeks gestational age and <1500g birth weight were screened for ROP identified 13 babies (1.3%) who were >31 weeks gestation or birth weight >1250g, of whom 2 had stage 3 ROP(28). Three studies specifically examined the incidence of ROP in infants ≥30 weeks’ GA and/or having a birth weight ≥1250 g; of 1749 infants screened, only four (0.2%), all born before the year 2000, developed severe ROP (27, 29, 30).

A review of ANZNN data from New Zealand showed only 2 infants would have been missed if screening criteria were confined to <30 weeks or <1250g but had been examined on clinician discretion (2) (Figure 3).

![Figure 3- Stage 3 or 4 ROP by birth weight and gestational age](image)

New Zealand recommends screening infants >1250g birth weight and >30 weeks gestation based on clinician discretion or having any of but not limited to: *In utero* hydrops, grade 3 or 4 intraventricular haemorrhage, post haemorrhagic hydrocephalus, severe sepsis, treatment with nitric oxide for pulmonary hypertension, affected twin-twin transfusion infants or prolonged periods of high inspired oxygen (2).

**When to screen?**

The scheduling of ROP screening examinations should ensure that eyes likely to need treatment are identified in a timely manner. The initiation of acute-phase ROP screening should be based on infant’s postmenstrual age (1). Data from two large clinical trials – the Multicenter Trial of Cryotherapy for ROP and the Effects of Light Reduction on ROP – have been used to suggest an evidence-based schedule for the first eye examination to detect pre-threshold ROP with 99% confidence (31).

However as the evidence base for infants born at <25 weeks gestation is low, AAP recommends that these infants should be considered for earlier screening at 6 weeks.
chronological age in the presence of co-morbidities such as necrotising enterocolitis, sepsis or need for assisted ventilation or inotropes (1). A prospective study of ROP screen in infants born less than 27 weeks gestation showed that the first examination could safely be postponed until PMA of 31 weeks because the onset of ROP stage 3 did not occur before then and criteria for treatment were not reached before PMA of 32 weeks (14).

How often to screen?
Regardless of ROP, all preterm infants need increased surveillance of visual function during childhood. Follow-up screening examinations should be recommended by the examining ophthalmologist. The follow up recommendations at RPA generally follow the schedule from AAP.

Table - Follow up ROP examination schedule

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Indications</th>
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<tbody>
<tr>
<td>1 week or less</td>
<td>• Immature vascularization, zone I – no ROP</td>
</tr>
<tr>
<td></td>
<td>• Immature retina extends into posterior zone II, near boundary of zone I</td>
</tr>
<tr>
<td></td>
<td>• Stage 1 or 2 ROP, no plus disease, zone I</td>
</tr>
<tr>
<td></td>
<td>• Stage 3 ROP, no plus disease, zone II</td>
</tr>
<tr>
<td></td>
<td>• Presence or suspected presence of aggressive posterior ROP</td>
</tr>
<tr>
<td></td>
<td>• Inability to determine zone due to hazy view</td>
</tr>
<tr>
<td>1 to 2 weeks</td>
<td>• Immature vascularization, posterior zone II</td>
</tr>
<tr>
<td></td>
<td>• Stage 2 ROP, no plus disease, zone II</td>
</tr>
<tr>
<td>2 weeks</td>
<td>• Stage 1 ROP, no plus disease, zone II</td>
</tr>
<tr>
<td></td>
<td>• Immature vascularization, zone II – no ROP</td>
</tr>
<tr>
<td></td>
<td>• Unequivocally regressing ROP, zone II</td>
</tr>
<tr>
<td>2 to 3 weeks</td>
<td>• Stage 1 or 2 ROP, no plus disease, zone III</td>
</tr>
<tr>
<td></td>
<td>• Regressing ROP, zone III</td>
</tr>
<tr>
<td>Stop screening</td>
<td>• Vascularization in zone III without previous zone I or II ROP</td>
</tr>
<tr>
<td></td>
<td>• Full retinal vascularization in close proximity to the ora serrata for 360°</td>
</tr>
<tr>
<td></td>
<td>• Postmenstrual age of 50 weeks and no prethreshold or worse ROP</td>
</tr>
<tr>
<td></td>
<td>• Regression of ROP (no abnormal vascular tissue capable of reactivation and progression present in zone II or III)</td>
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2. Screening technique

- **Indirect Ophthalmoscopy**

Retinal screening examinations by using binocular indirect ophthalmoscopy should be performed by an experienced ophthalmologist. Eye drops to dilate the pupils and provide local anaesthesia should be given before each eye examination. Amethocaine (Tetracaine) 0.5%, Tropicamide 0.5% and Phenylephrine 2.5% one drop of each medication is instilled into each eye one hour prior to procedure. Examination should take place in the usual
environment of the infant (e.g. humidicrib) with minimal handling and disturbance of the infant and maintenance of current monitoring and therapy (e.g. oxygen).

Although non-invasive, a scleral indentor needs to be used for ophthalmoscopy which can cause systemic complications such as fluctuations in heart rate and oxygen saturation. A Cochrane systematic review of local anaesthetic eye drops for prevention of pain in preterm infants undergoing screening showed administration of topical anesthetic drops 30 seconds prior to the ophthalmological evaluation was associated with a reduction in pain scores especially at the time of speculum insertion (32). Screening remains a painful procedure despite topical anaesthetic drops and should be used in conjunction with oral sucrose and other non-pharmacological measures like swaddling (33).

- **Digital retinal imaging**

  Digital photographic retinal images that are captured and interpreted remotely is also being used in some units that do not have ready access to paediatric ophthalmologists (34). RetCam™ is one such bed-side imaging system that takes digital photographs of baby’s retina by utilizing a microscope with a high-quality camera attached to it. RetCam’s unique integrated system combines wide-angle viewing of the retina with 130° field of view, full resolution image selection from real-time digital video with a comprehensive relational database(35).

  Retinal images can be performed by trained nurse/technicians and the images electronically transferred, so that they can be reported remotely by the ophthalmologist from his office at suitable time. Ability to store images as soft copies help in tracking the progression of ROP more objectively and also provides as additional documentation for medico legal purposes (34). A prospective comparative study between digital retinal imaging and conventional indirect ophthalmoscope in 86 infants showed digital retinal imaging is associated with a significantly lower stress-related response than conventional indirect ophthalmoscopy (36). Digital retinal imaging may also be a useful tool for teaching NICU staff and parents about the examination results (1). A systematic review of digital retinal photography versus binocular ophthalmoscope examination identified three prospective (n=120) and three retrospective (n=579) which showed sensitivity of 45.5-100% with the majority being more than 90%; specificity 61.7-99.8% with the majority being more than 90%, positive predictive value 61.5-96.6% and negative predictive value of 76.9-100% for diagnosing clinically significant ROP(37). Quinn et al demonstrated a sensitivity of 90%, specificity of 87%, negative predictive value of 97.3% and positive predictive value of 62.5% comparing digital retinoscopy with binocular ophthalmoscopic examination in 5520 examinations from 1257 infants (38).

  The main limiting factor that is preventing the widespread use of this technology is the high initial capital cost of acquiring a retinal camera (each device costs approximately more than A$100 000) (34). However Jackson et al showed that costs per Quality adjusted light year (QALY) were $3193 with telemedicine/digital imaging and $5617 with binocular ophthalmoscopy (BIO) in a cost/utility analysis (39). The other limitations which have been described are difficulty in imaging the extreme periphery of the retina, lack of stereoscopic view compared to indirect ophthalmoscopy (40). AAP currently recommends that digital retinal imaging should be an adjunct and not a replacement to binocular ophthalmoscopy (41).

  Any case identified by RetCam™ as suspicious for ROP requiring treatment needs to be confirmed by the gold standard bedside BIO examination performed by the ophthalmologist. It is also recommended that indirect ophthalmoscopy be performed at least once by a qualified ophthalmologist before treatment or termination of screening of ROP for infants at risk for ROP (1). If a digital retinal imaging program is to be established a suitable training
and accreditation program and protocol for tracking infants undergoing digital retinal imaging determining long term visual outcomes needs to be in place(41).

3. Documentation
Using the International Classification of ROP (16, 17), the following signs should be recorded (for details see Appendix C):
- severity by stage
- location by zone
- extent
- 'plus' disease
- other clinical signs such as: changes in the cornea, anterior chamber, iris, Pupil, lens and vitreous, signs of regressed ROP.

Arrangements for review should be indicated in the hospital records.

Counselling the parents

For parents of all babies at risk
Written information about the need to screen for ROP should be provided as part of the general information provided by the neonatal unit for parents of premature infants. It is important to emphasise that mild ROP is very common and spontaneously resolves without adverse sequelae in the vast majority.

For parents of infants with, or close to, severe ROP
As soon as it is apparent that an infant has ROP which is close to and likely to advance to type 1 ROP, it is preferable that the ophthalmologist personally discusses the issues with the parents. It is recommended that a member of the neonatal unit staff who knows the family, such as the consultant paediatrician or a senior neonatal nurse, is present so that post-interview queries can be dealt with. Severe ROP often occurs just when parents are beginning to relax for the first time after stressful weeks of uncertainty.

Parents should be kept fully and frequently informed. The complexity of accurately monitoring visual functions and the difficulty of predicting the future must not be underestimated. Nevertheless measuring visual functions at each stage of the review process does enable the clinician to advice parents on progress.

For parents of infants with advanced ROP
The need to keep in close contact with the family cannot be overemphasised. Generally, parents can accept with time that not all disorders can be successfully treated, but they cannot accept lack of interest or care.

The brochure given to parents at RPA can be found on the RPA Newborn Care web-site under guidelines

Interventions

1. When to intervene?
Where the maximum stage reached is 1 or 2, all cases of acute ROP undergo spontaneous resolution and do not result in visually disabling sequelae. Nevertheless, this group still requires follow-up for less severe visual problems.

In the Multicentre trial of Cryotherapy for ROP (CRYO-ROP) study, infants were treated with cryotherapy at Threshold disease (5 contiguous, or 8 cumulated clock hours of stage 3 ROP
in zone 1 or zone 2 with plus disease), a point in disease progression at which retinal neovascularization was equally likely to progress to retinal detachment (42). The Early Treatment for ROP (ETROP) trial subsequently established the efficacy and benefit of earlier treatment for pre-threshold ROP with laser therapy(43). Earlier CRYO-ROP treatment criteria have been now replaced by ETROP designations Type 1 ROP requiring treatment and type 2 ROP which needs follow up (44). There was a reduction of unfavourable visual acuity outcomes from 19.5% to 14.5% (p=.01) and in unfavourable structural outcomes from 15.6% to 9.1% (p<.001) with early treatment in ETROP study.

Hence treatment of ROP should be undertaken if any of the following features are present (44):
• Zone 1 any ROP with plus
• Zone 1 stage 3 without plus
• Zone 2, stage 2 or 3 with plus

The aim of treatment is to remove the stimulus for vessel growth, i.e. ablate the peripheral avascular retina. Transpupillary diode laser photocoagulation of the avascular retina is the preferred treatment for ROP and has replaced cryotherapy (43). Treatment should be undertaken as soon as possible, ideally within 2-3 days of the identification of threshold disease. Follow-up is recommended in 3 to 7 days after treatment to ensure that there is no need for additional treatment in areas where ablative treatment was not complete (1).

2. Laser therapy
Diode laser retinal ablation is the preferred treatment option at RPA. The aim of the treatment is to prevent further abnormal vessel proliferation in the retina, prevent detachment and promote normal vessel development. The Developmental Follow Up coordinator will liaise with the ophthalmologist and parents, organize equipment, order medical records and assist the registered nurse caring for the infant throughout the procedure.

A Cochrane systematic review of peripheral retinal ablation in 319 infants showed that it reduces the risk of early unfavorable retinal structure from 47.9% to 28.1% (absolute risk reduction 19.8% [95% CI 27.9 - 11.8%]), unfavorable retinal structure in early childhood from 44.3% to 26.3% (absolute risk reduction 18% [95% CI 27.0 - 9.1%]) and unfavorable visual acuity in early childhood from 63% to 50.6% (absolute risk reduction 12.2% [95% CI 21.2 - 3.1]) (45). A subsequent meta-analysis by Laser ROP group in 293 eyes showed that the combined estimate of the risk for an unfavourable outcome with laser therapy was 8.4% while with cryotherapy it was 19.2% and concluded that laser therapy was as effective as cryotherapy for treating most cases of threshold ROP(46-48). Diode laser photocoagulation has been to shown to have better visual outcomes and fewer adverse events (49, 50).

CONSENT
Parents should be informed of the procedure and the need for intubation, and informed consent must be obtained by medical officer prior to laser surgery. This is a difficult time for parents, who may be recovering from the stress of their baby’s acute illness. The news that their baby has a potentially blinding condition which requires urgent treatment must be handled with the utmost consideration. This is helped by the provision of written information explaining screening and severe ROP.
EQUIPMENT
Indirect Ophthalmoscope and power source, 20D and 28D lens, indentor, eye speculum, laser protection glasses and teaching mirror from Developmental Follow Up Coordinator (ext. 56141: page 80655).
Diode Laser can be requested the day before from RPA Eye Theatre NUM - Anne Barnes 50107. If this is not available ring Dr. James Smith to arrange the use of Save Sight’s Diode Laser.
Open care system.
SpaO2 and cardio-respiratory monitors.
Normal Saline ampoules to lubricate eyes. Cotton buds and gauze swabs.
Once infant is ventilated and sedated, tape may be needed to close eyes shut prior to procedure in order to prevent corneal drying.
Emergency resuscitation and intubation equipment.

Pre-medication and sedation
• Usual medications for induction/intubation according to intubation protocol. Sedation is to be used throughout the laser procedure for analgesia and sedation as per the sedation policy. This is usually followed immediately following completion of laser procedure.
• A survey of ophthalmologists in UK showed that 50% of ophthalmologists used general anesthesia and 37% used IV sedation combined with topical anesthesia(51). A multicentre observational trial Japan showed better sedation and analgesia with inhalation anesthesia using air, oxygen and sevoflurane mixture (52). Analgesics such as morphine do not completely obtund autonomic response to noxious stimuli while sedatives such as midazolam do not provide analgesia and a mixture of sedative and analgesic drugs would be a suitable option for laser therapy outside of the operating theatre(53).

EYE DROPS
• Amethocaine 0.5%, Tropicamide 0.5% and Phenylephrine 2.5% one drop of each medication into each eye one hour prior to procedure. Repeat Tropicamide 0.5% and Phenylephrine 2.5% drops in half an hour if pupils not dilated. If required 0.5% cyclopentolate may also be given 30 minutes prior to laser on the recommendation from the ophthalmologist.
• Caution should be used in repeat doses of eye drops, especially cyclopentolate in view of reported systemic side effects including oxygen desaturation, apnea, bradycardia, transient hypertension, paralytic ileus and seizures (54-60).

FEEDS
• Withhold feeds for at least 4-6 hours prior to intubation. An IV cannula needs to be inserted for sedation and fluids. IG tube should be left in situ during the procedure. Recomence feeds as tolerated after procedure.

PROCEDURE

Before
• Collect all equipment and move the baby to a level three cot (baby needs to have head at end of open care system for the procedure) some hours before the procedure. Connect the baby to monitors and ensure a clear recording is available. Place a temperature probe on the baby. Record baseline observations including blood gas and blood sugar level.
• Check emergency equipment and ventilator.
• Aspirate residual gastric contents.
• Insert IV cannula (small amount of sucrose not contra indicated), order intubation medication, sedation and fluids.
• Neonatal fellow/staff specialist will intubate baby following the induction for intubation policy – these infants are not be intubated by the registrar or transitional nurse practitioners
• Ensure the baby is stable and adequately sedated prior to commencing procedure. Babies are not routinely given muscle relaxants for laser treatment.
• One dose of atropine (dose 10mcg/kg IVI) may be given prior to the procedure to reduce the incidence of bradycardia from vagal stimulation due to indenting of the eyes.
• Limit movement of the baby on the open crib by wrapping securely (i.e. ‘seat belt’ and mittens).
• Ensure neonatal fellow/staff specialist is available in the unit throughout the procedure.

During
• Two registered nurses should be present during the procedure. Primary RN limits movement of the infant as necessary, maintains the baby's airway, oxygen, and routine care of the ventilated baby. The second nurse (usually Follow Up coordinator) should observe for changes in vital signs and call a pause in the procedure if significant apnea or bradycardia occurs.
• Keep the eyes lubricated with saline drops during the procedure.
• Document number of laser episodes in each eye in the progress notes.

After
• Inform parents when procedure completed and ensure their questions/concerns are discussed.
• If parents are waiting, they should be seen by the ophthalmologist otherwise contact via phone should be made as pre-arranged
• Recomence feeds when baby is stable.
• Eye drops are prescribed 8hrly post-laser as follows:
  Tropicamide 0.5%
  Prednisolone 0.5%
  Chloramphenicol 0.5%
• Paracetamol prn may be ordered if baby shows signs of discomfort post-surgery.

Monitoring during treatment
Experienced staff must be in attendance throughout and cardiorespiratory monitoring which must be continued until the baby has fully recovered. Staff should be aware of the systemic (bradycardia, cyanosis) and local (oedema, haemorrhage, burns) complications of therapy that might arise in the subsequent hours and days, and monitor for them.

COMPLICATIONS
• Swelling around the eye is uncommon following laser therapy, though some may occur.
• Apnea and bradycardia are more common in smaller babies and ventilation or CPAP is usually needed overnight.
• Increases in oxygen and respiratory support may be required.
3. Anti-vascular endothelial growth factor (VEGF) therapy

Two anti-VEGF drugs, pegaptanib sodium and ranibizumab have been approved by the United States Food and Drug administration for use in adult neovascular and age related macular degeneration, however Bevacizumab (Avastin) has been used off-label for treatment of these adult conditions as well as ROP.

**Bevacizumab Eliminates the Angiogenic Threat of ROP** (BEAT ROP), a prospective randomized control trial of bevacizumab monotherapy versus laser showed significant benefit of intravitreal bevacizumab (IVB) monotherapy for stage 3+, zone I disease; Retinopathy of prematurity recurred in 4 infants in the bevacizumab group (6 of 140 eyes [4%]) and 19 infants in the laser-therapy group (32 of 146 eyes [22%], P=0.002) (61). A Cochrane systematic review of Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity in 239 infants showed that Intravitreal bevacizumab reduces the risk of refractive errors during childhood when used as monotherapy while intravitreal pegaptanib reduces the risk of retinal detachment when used in conjunction with laser therapy in infants with type 1 ROP, although the quality of evidence was defined as Low (62).

The long-term ocular and systemic side effects of intravitreal anti-VEGF therapy remain unknown(63, 64) so, in accordance with the Australia and New Zealand ROP Group Consensus on Avastin in ROP, Intravitreal bevacizumab should be considered when one of the following indications is met (2):

- ROP failed to respond to adequate laser treatment
- Laser treatment was not possible because of poor view of retina, or the baby was too unwell to tolerate laser
- Aggressive Posterior-ROP
- Type 1 ROP in zone 1

At RPA Hospital, Avastin is commenced as per the advice of the paediatric Ophthalmologist.

The recurrence of ROP in BEAT-ROP study tended to occur considerably later than that after conventional laser peripheral retinal ablative treatment (16 ± 4.6 weeks vs. 6.2 ± 5.7 weeks). Hence if intravitreal bevacizumab therapy was used, weekly ophthalmic follow-up until 54 weeks post menstrual age (PMA), or longer, is required to ascertain that ROP regression has taken place and there is no recurrence of active ROP.

Although there are distinct ocular advantages to anti-VEGF pharmacotherapy for some cases (such as eyes with zone I disease or aggressive posterior ROP), the disadvantages are that the ROP recurrence rate is higher, and vigilant and extended follow-up is needed because retinal vascularization is usually incomplete (65). The effects of anti-VEGF treatment on the developing organ systems of premature infants are unknown, and there are limited long-term data on potential systemic and neurodevelopmental effects after anti-VEGF use for ROP treatment (65).

**Candidate interventions for prevention and treatment of ROP**

Since persistently low serum IGF-1 in preterm infants are associated with ROP and other morbidities, it is proposed that supplementation of IGF-1 would improve postnatal growth and reduce ROP. An IGF-1 replacement trial (NCT01096784) is underway with reduction in
the severity of retinopathy of prematurity as the primary endpoint and brain growth and other complications of premature birth as secondary endpoints (4).

There are also studies using β-blocker propranolol (NCT01238471 and NCT01079715) and carbohydrate inositol (NCT00349726, NCT01030575). D-pencillamine and avoidance of light have been reviewed for potential role in prevention of ROP in Cochrane systematic reviews and current data is inadequate to support these methods. The potential role of Vitamin E supplementation in ROP has also not shown conclusive treatment effect (66).

**Consequences of disease and treatment**

Most ROP regresses spontaneously by a process of involution or evolution from a vasoproliferative phase to fibrotic phase (16). In some infants this proliferative retinopathy progresses to inflammatory, haemorrhagic, and ultimately fibrotic retinal scarring and detachment, which may lead to blindness (13). Involutional sequelae include a broad range of peripheral and posterior vascular and retinal changes. Commonly seen features of involution include abnormal branching of vessels with formation of arcades, prominent areas of retinal vascularity and retinal pigmentary changes.

Infants treated with transpupillary laser for severe retinopathy of prematurity have an increased risk of myopia, anisometropia and strabismus (67).

**Follow-up**

Premature babies who qualified for ROP screening, irrespective of having ROP are at higher risk of developing other ocular morbidities such as strabismus and amblyopia. All infants with ROP of any stage require a follow-up examination the first 6 months of life (1) and then at intervals as dictated by the findings. Infants with stage 3 ROP and those who have received therapy require particularly close surveillance in the preschool years as the incidence of strabismus and other problems is particularly high in this group.

Parents of infants with severe visual impairment need support and advice about treatment options. Referral to specific support groups for the visually impaired, such as State/Territory societies or institutes for the blind, should be offered.

**Key points:**

<table>
<thead>
<tr>
<th>Classification of ROP should use the ICROP nomenclature</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
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<td>Classification of ROP should use the ICROP nomenclature</td>
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<td>D</td>
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<tr>
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<td>I56-57</td>
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## 9. Definitions

| Pre threshold ROP(42) | Zone I, any stage ROP less than threshold  
|                       | Zone II, stage 2 ROP with plus disease  
|                       | Zone II, stage 3 ROP without plus disease  
|                       | Zone II, stage 3 ROP with plus disease but fewer than 5 contiguous or 8 cumulative clock hours  
| Threshold ROP(42)     | Five or more contiguous or eight cumulative 30° sectors [clock hours] of stage 3 ROP in zone 1 or 2 in the presence of "plus" disease  
| Pre Plus disease(18) | Vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosities and more dilatation than normal  
| Plus disease(18)      | Dilatation and tortuosities of posterior retinal blood vessels in at least 2 quadrants (6 or more clock hours)  
| Type 1ROP(46)         | Zone I, any stage ROP with plus disease  
|                       | Zone I, stage 3 ROP with or without plus disease  
|                       | Zone II, stage 2 or 3 ROP with plus disease  
| Type 2 ROP(46)        | Zone I, stage 1 or 2 ROP without plus disease  
|                       | Zone II, stage 3 ROP without plus disease  
| Aggressive posterior ROP(18) | Rapid, progressive severe form of ROP with presence of plus disease in a posterior location and ill-defined nature of retinopathy (aka Rush disease)  

10. **Consultation**

RPA Newborn Care guideline development committee which includes all senior medical and nursing staff. This guideline was also reviewed by the two paediatric ophthalmologists that perform the screening, Drs James and Jeremy Smith.

11. **References**


35. RetCam™ shuttle ophthalmic imaging system: Clarity Medical Systems Inc.; [Available from: www.claritymsi.com.]


68. Trese MT. Laser Photocoagulation and Retinopathy of Prematurity-VEGF has received increasing attention, but laser is still the standard. Retinal Physician. 2013;10(October 2013):51-3.

11.1 National Safety and Quality Health Service (NSQHS) Standards, Version 2

Standard 1, Clinical Governance Standard

Standard 8, Recognising and Responding to Acute Deterioration Standard
Appendix 1

Royal Prince Alfred Hospital And Save Sight Institute

<table>
<thead>
<tr>
<th>Date</th>
<th>Birth weight</th>
<th>Gestational Age</th>
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Tetracaine (= Amethocaine) 0.5% one drop in each eye
Tropicamide 0.5% one drop in each eye
Phenylephrine 2.5% one drop in each eye

Eye Maturity: Regression of Pupillary membrane

27, 28 □ 29, 30 □ 31, 32 □ 33, 34 □ 35, 36 □

Hyaloid artery regressed: Yes / No (Normally by 32 weeks)

Zones - centred on optic disc:
1. circle radius 2x disc-foveal distance (about 30°)
2. extends from edge of zone 1 to ora serrata on nasal side and encircles equator
3. includes all retina, temporally superiorly, inferiorly, which is anterior to zone 2

* Nasal retina vascularised by 32 weeks and temporal just after term

** Threshold ROP:
Stage 3+ Plus Involving 5 contiguous or 8 non contiguous clock hours

Right Stages of ROP
- No ROP
- 1: demarcation line
- 2: ridge
- 3: 2 + extra retinal proliferation
- 4: 3 + retinal detachment
- regressed ROP

Left Watch
- Stage 1, 2 without+
- Stage 3 without+

Treatment Criteria
- Stage 1, 2, 3 with +
- Stage 3 without+

Right Plus Disease
- A: dilatation/tortuosity of retinal vessels
- B: iris vessel dilatation
- C: pupil rigidity
- D: vitreous haze
- E: haemorrhages
- F: no plus disease

Left Cicatrical Changes
- Peripheral Vascular
- Retinal
- Posterior Vascular
- Retinal
- Cup/Disc Ratio:
- Right: 
- Left:

Comments

Follow up required in: ____________________________

Signed: ____________________________

Name (please print): ____________________________

Date: ____________________________
Appendix 2

**ROP Stage 1**: flat white demarcation line separates the avascular and vascular retina (15)

![Image of ROP Stage 1]

**ROP Stage 2**: A ridge develops between vascular & avascular retina, and occupies some volume (15)

![Image of ROP Stage 2]

**ROP Stage 3**: The ridge is associated with neovascularization entering the vitreous (15)

![Image of ROP Stage 3]

**ROP Stage 4a**: Partial retinal detachment sparing the macula(15)
ROP Stage 4b: Partial retinal detachment involving the macula(15)

ROP Stage 5: Complete retinal detachment(15)

Pre-plus disease: Arterial tortuosity and venous dilatation more than normal but not severe enough to be classified as "Plus disease"(15)
**Plus disease:** Presence of dilatation and tortuosity of the posterior pole blood vessel involving at least two quadrants of the retina\(^{(15)}\)

**Aggressive posterior ROP:** Increased tortuosity and dilatation of vessels present in all 4 quadrants of zone 1 and sometimes zone 2\(^{(15)}\)

**Laser Photocoagulation for ROP:** Following treatment, fundus image shows a fairly confluent laser application and resolution of ROP\(^{(68)}\)
Avastin therapy for ROP:

(A) Pre-treatment Photograph Showing Posterior Zone 2 Disease Associated with plus Disease.
(B) Four Days after Injection.
(C) Three Weeks after Injection.
(D) Repeat treatment after 4 months