Guideline for the prevention, screening and treatment of retinopathy of prematurity (ROP)

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Background. Retinopathy of prematurity (ROP), one of the most common causes of preventable blindness in preterm neonates, is emerging as a 'third epidemic' in middle-income countries including South Africa. This is due to the increasing survival of preterm neonates, insufficient monitoring of oxygen saturation (SaO_2) in most centres, and lack of an ROP screening guideline in most neonatal units.
Objective. To guide the standard of care for SaO_2 and ROP screening in preterm neonates weighing <1 500 g.
Validation. This guideline, endorsed by the United South African Neonatal Association (USANA), the Ophthalmological Society of South Africa (OSSA), and the South African Vitreoretinal Society, was developed by the ROP Working Group of South Africa, comprised of neonatologists, ophthalmologists and paediatricians.
Recommendations. All healthcare professionals involved in the care of preterm neonates should be aware of SaO_2 and ROP screening guidelines. Mothers should be counselled about the possible complications of prematurity.

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1. Introduction

As a middle-income country with a limited healthcare budget, South Africa (SA) faces many challenges. The country is making huge efforts to meet the Millennium Development Goals, specifically goals 4 and 5. Maternal and child health represents an important priority to improve morbidity and mortality rates.

Surviving premature infants have many unique healthcare needs, including screening for retinopathy of prematurity (ROP). The importance of this screening cannot be underestimated, as early detection and treatment reduces blindness and permanent disability.

SA has become part of the so-called 'third epidemic of ROP', with an increasing incidence as more premature infants survive due to improved neonatal care. As in other middle-income countries, infants with higher birth weights are at risk of ROP because treatment units may not have the skills or equipment to monitor oxygen appropriately. Resources may also be inadequate to identify at-risk infants.[1]

Each year >1 million babies are born in SA; 87% in the public healthcare sector, including almost half in district-level facilities, 10% in clinics or community health centres, and 38% in district hospitals. An equal number of neonates are delivered in facilities with specialist-run services; 32% in regional hospitals and 20% in tertiary and central hospitals.[2]

Data suggest that 12.8% of babies born in the public sector have a birth weight <2 500 g.[2] As the sector has limited facilities, few newborns have access to appropriate care. While public health and infrastructure interventions aim to improve facilities to ensure equitable access to care, such improvements take time. Even if these plans are realised, a mismatch in services for babies at risk of ROP will persist. Neonatal intensive care units (NICUs) are to be established in tertiary and regional hospitals, where ophthalmology expertise is often not available. Approximately 16 000 babies are at risk of ROP and require screening each year.[1] These disparate services necessitate innovative responses in the implementation of screening programmes to successfully minimise the consequences of ROP.

Studies in SA academic institutions have shown an acceptably low ROP incidence.[3] However, these centres have appropriate neonatal care facilities and adequate resources to screen high-risk infants.[4-6]

Larger, well-resourced centres may follow guidelines such as those of the American Academy of Pediatrics and the Royal College of Ophthalmologists. However, these guidelines may not be appropriate in under-resourced centres. Rather, guidelines proposed in other middle-income regions may be more fitting, e.g. those from South East Asia and Central/South America, where larger, more mature infants at risk have been identified.[7]

Barriers to screening must also be overcome,[8] including: the need to travel to a treatment/screening centre; the affordability and time-constraints of taking infants elsewhere for further screening; and loss to screening/follow-up programmes.

An absolute shortage of ophthalmologists in SA compounds the problem. The few appropriately trained state-employed ophthalmologists are based mainly in the larger urban centres.

In remote areas, new technologies such as digital photographic screening devices may offer remote screening via telemedicine. However, these electronic devices are expensive and require a trained technician to capture and transmit the images for evaluation.[9]

This 2012 consensus guideline, developed by paediatricians, neonatologists and ophthalmologists in SA public and private practice, has been endorsed by the United South African Neonatal Association (USANA), the Ophthalmological Society of South Africa (OSSA), and the South African Vitreoretinal Society. It is intended to guide the screening and appropriate neonatal care of infants at risk of ROP.

2. Oxygen saturation guideline after birth

Different centres in different countries report a varying incidence of severe ROP. The altered regulation of vascular endothelial growth factor from repeated episodes of hyperoxia and hypoxia is one important factor in ROP pathogenesis. Strict management of oxygen delivery and monitoring to minimise these episodes may be associated with decreased rates of ROP.

Oxygen is the most commonly used 'drug' in neonatal units. It is well documented that it is easy to damage the eyes of preterm infants by administering too much oxygen, especially in the first few weeks of life. Studies have shown a relationship between oxygen administration and the development of ROP.[10-12] In animal models, repeated cycles of hyperoxia and hypoxia were shown to produce more retinal neovascularisation than hypoxia or hyperoxia alone.[13] In the early 1990s, an increased incidence of severe ROP was shown in premature infants in the first several weeks of life with a transcutaneous oxygen tension ($tcPO_2$) ≥80 mmHg.[14]

In the first weeks of life, lower oxygen saturation (SaO_2) targets in preterm infants reduce ROP and pulmonary complications and may improve growth. Data from NICUs in Northern England[15] identified 4 oxygen policies in neonates according to SaO_2 limits that were set at: *(i)* 70 - 90%; *(ii)* 84 - 94%; *(iii)* 85 - 95%; and *(iv)* 88 - 98%. The occurrence of ROP requiring cryotherapy (threshold ROP (tROP)) was 4 times higher in the high SaO_2 group (88 - 98%) compared with the low SaO_2 group (70 - 90%). This was confirmed in a study which found that neonates nursed in SaO_2 >92% had more severe ROP than babies nursed in SaO_2 <93%.[16]

The Australian Benefits Of Oxygen Saturation Targeting (BOOST) trial compared an SaO_2 of 91 - 94% v. 95 - 98% in neonates.[17] While no difference was found in long-term development, there was an increase in the duration of oxygen therapy, an increase in the occurrence of home oxygen therapy, and more frequent chronic lung disease in the high SaO_2 group. High SaO_2 targets therefore have a detrimental effect on the lungs and the eye.

The unexpected finding of excess deaths from pulmonary causes among infants in the high SaO_2 group – albeit not statistically significant – accords with the findings of the only other trial in which preterm infants were randomly assigned to different target SaO_2 ranges – namely the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial.[18] The trial showed an increased rate of adverse pulmonary sequelae (although not an increased rate of death due to pulmonary causes) among preterm infants with pre-tROP when a higher SaO_2 range (96 - 99%) was targeted.

Chow *et al.*[19] emphasised the importance of avoiding peaks in SaO_2 and the constant training of staff to keep the saturation within strictly defined limits. Oxygen toxicity, particularly in preterm infants, can inhibit lung healing and contribute to ongoing lung injury.[20]

A meta-analysis of the association between SaO_2 measured by pulse oximetry and risk of severe ROP indicated a statistically significant risk reduction of 52% with low SaO_2 (70 - 96%) in the first postnatal weeks and 46% with high SaO_2 (>94 - 99%) at a postmenstrual age (PMA) of ≥32 weeks.[21] The analysis revealed that high SaO_2 has different effects at postnatal points that correspond roughly to the first and second phases of ROP.

High partial oxygen pressure (PaO_2) occurs very rarely in neonates breathing supplemental oxygen when pulse SaO_2 values are 85 - 93%. This pulse SaO_2 range also is infrequently associated with low PaO_2 values. Pulse SaO_2 values of >93% are frequently associated with PaO_2 values >80 mmHg, which may be of risk for some newborns receiving supplemental oxygen.[22]

The optimal SaO_2 is not known in infants of extremely low birth weight, but data indicate that it should be kept at ≤93%. In the SUPPORT trial, a target SaO_2 range of 85 - 89%, compared with 91 - 95%, did not affect the combined outcome of severe ROP or death. However, it increased mortality while substantially decreasing severe ROP among survivors. Caution should be exercised in targeting levels of SaO_2 in the low range for preterm infants, as it may lead to increased mortality.[23] Many centres therefore aim for saturations of 88 - 92%. Fluctuations with peaks in SaO_2 should be avoided.

Table 1 lists clinical trials which compared outcome parameters in infants according to higher and lower SaO_2 groups.

Table 2 summarises the characteristics of studies that assessed the association between high SaO_2 and severe ROP risk among preterm infants in the first several weeks of life. Meta-analysis of the pooled estimates showed a significantly decreased risk of ROP with lower SaO_2 (relative risk (RR) 0.48; 95% confidence interval (CI) 0.31 - 0.75).

Table 3 summarises the characteristics of studies that evaluated the association between SaO_2 and severe ROP risk after a PMA ≥32 weeks in preterm infants. Meta-analysis of the pooled estimates showed a statistically significant RR of 0.54 (95% CI 0.35 - 0.82).

In a meta-analysis of high or low oxygen saturation and severe ROP, Chen *et al.*[21] concluded that low SaO_2 (70 - 96%) in the first several postnatal weeks was associated with a reduced risk of severe ROP (RR 0.48; 95% CI 0.31 - 0.75) and high SaO_2 (94 - 99%) after a PMA of 32 weeks was associated with a decreased risk for progression to severe ROP (RR 0.54; 95% CI 0.35 - 0.82).[21]

Currently, the ongoing Neonatal Oxygen Prospective Meta-analysis (NeOProM) study is questioning whether targeting a lower oxygen range in extremely premature neonates increases or decreases the composite outcome of death or major disability in survivors by ≥4%.The results of the study will be available in 2014.

All neonates receiving supplemental oxygen (ventilator, continuous positive airways pressure (CPAP), nasal prongs or head box oxygen) should be monitored with a pulse oximeter and SaO_2 should be recorded. Oxygen should be humidified. An oxygen saturation guideline (Appendix I) should be displayed in the neonatal ICU.

Table 1. Prospective clinical trials comparing outcome parameters in infants dichotomised into high and low SaO_2 groups*

Study	Subject population	SaO_2 groups	Survival	CLD	ROP 3 - 4	ROP therapy
Tin *et al.*[15]	<27 weeks	Low (70 - 90%)	53%	18%		6%
		High (88 - 98%)	52%	46% (p<0.0001)		27%
Sun[31]	≤1 500 g	Low (≤92%)	83%	27%	10%	4%
		High (>95%)	76%	53% (p<0.0001)	29% (p<0.0001)	12% (p<0.001)
Anderson *et al.*[16]	≤1 500 g	Low (≤92%)			5.7%	1.4%
	>2 weeks	High (>92%)			2.5% (p<0.001)	3.3% (p<0.0001)
Chow *et al.*[19]	500 - 1 500 g	Low (85 - 93%)	88%		2.5%	0 - 1.3%
		High (90 - 98%)	81%		12.5% (p<0.01)	4.4% (p<0.001)
Askie *et al.*[17†]	<30 weeks	Standard (91 - 94%)	97%	46%	16%	11%
	≤32 weeks	High (95 - 98%)	95%	64% (p<0.001)	12%	6%

*Adapted from Tin *et al.*[32]

†Randomisation after 32 weeks. Survival after randomisation. CLD = chronic lung disease

Table 2. High v. low oxygen SaO_2 and severe ROP in the first few weeks of life: A meta-analysis[21]

Author	Cohort	Recruitment period	GA (week)	Birth weight (g)	*N*	Oxygen timing and duration	Target SaO_2 (%)	Severe ROP (%)
Wright *et al.*[24]	Prospective	1998 - 2002	<30	500 - 1 500	350	Immediate post-gestation life	Low (83 - 93) v. high (89 - 95)	1.3 v. 7.3
Wallace *et al.*[25]	Retrospective	2002 - 2005	≤30	<1 250	105	First 6 weeks	Low (90 - 96) v. high (98 - 100)	14.0 v. 18.0
Van der Veen *et al.*[26]	Retrospective	2000 - 2003	≤28	<1 250	323	First 4 weeks	Low (85 - 93) v. high (87 - 97)	5.6 v. 17.5
Tin *et al.*[15]	Prospective	1990 - 1994	<28	810 - 1 074	295	First 8 weeks	Low (70 - 94) v. high (85 - 98)	8.8 v. 19.7
Deulofeut *et al.*[27]	Prospective	2000 - 2004	26 - 27 (mean)	<1 250	373	Started at birth	Low (85 - 93) v. high (92 - 100)	4.0 v. 7.0

tROP = threshold ROP; SaO_2 = saturation oxygen.

3. Screening protocol

ROP is a disorder of the developing retina of preterm infants that potentially leads to blindness in a small but significant percentage. ROP cannot occur in term neonates, as the retina is fully developed. The disease is a preventable cause of blindness if supplemental oxygen therapy is used appropriately, and a screening programme is in place for preterm neonates who have received such therapy. An effective goal of a screening programme is to identify the preterm infants at risk of ROP and who require treatment (from the much larger number of at-risk infants), while minimising the number of stressful examinations required for these sick infants. Any screening programme designed to implement an evolving standard of care has inherent defects such as over-referral or under-referral, and by its nature, cannot duplicate the precision and rigor of a scientifically based clinical trial.

The recommendations for screening are modified from the guidelines of the American Academy of Pediatrics and those of the United Kingdom. In SA, most pregnant mothers do not know their gestation, and gestational age assessment is not accurate. It is therefore recommended that weight rather than gestational age is used for screening high-risk preterm neonates. There are few studies regarding the incidence of ROP in sub-Saharan Africa. An early study of children in schools for the blind in SA revealed that 10.6% of blindness was due to ROP; only 1.25% of this was in black children.[33] Kirsten *et al.*[6] reported a 30% frequency of ROP (7% with stage 3 or worse) in a multiracial study population. Delport *et al.*[5] reported an ROP frequency of 24.5% in a hospital treating predominantly black patients (Kalafong), with 6.4% developing stage 3 ROP and 4.2% requiring treatment (including 1 neonate with a birth weight >1 250 g).

The incidence of childhood blindness due to ROP in certain Latin American and Eastern European countries has been reported to be as high as 38.6% and 25.9%, respectively.[33] The incidence of ROP in a Vietnamese study[34] was 45.8% in neonates weighing <2 000 g and 81.2% in babies weighing <1 250 g. In total, 25% of the babies weighing <1 250 g developed tROP.

A large prospective study of ROP at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto – a tertiary referral centre for indigent South Africans[4] – reported a 2.5% overall occurrence rate of stage 3 ROP. Those with tROP requiring treatment represented 1.6% of the total cohort. No tROP was observed in neonates weighing >1 250 g at birth, but many patients with ROP were lost to follow-up before witnessing progression or regression of tROP. The SA studies have been among small cohorts in tertiary centres. Multicentre studies must be performed to establish the actual incidence of ROP. Most level 2 hospitals admit preterm neonates who are given supplemental oxygen. These facilities do not perform ROP screening due to a lack of resources and shortage of ophthalmologists. A screening guideline must be implemented in level 2 centres, to identify and appropriately refer at-risk neonates.

3.1 Screening guideline

3.1.1 Who to screen

- All neonates born prior to 32 weeks' gestation
- All preterm neonates weighing <1 500 g.
- Preterm infants weighing 1 500 - 2 000 g may also be at risk of ROP if they have risk factors such as: a family history of ROP, cardiac arrest, multiple (>2) blood transfusions, exchange transfusion or severe HIE. If their oxygen monitoring has been suboptimal, then screening can be considered if resources allow, but ensuring appropriate oxygen monitoring is more cost-effective.

3.1.2 When to screen

- Screening should be performed at 4 - 6 weeks chronological age or 31 - 33 weeks post-conceptional age (whichever comes later). If gestational age is unknown, then chronological age should be used.
- Threshold is usually reached by 37 weeks – it is therefore important to assess the baby before 37 weeks post-conceptional age.
- After the initial screening, follow-up for ROP will be determined by the ophthalmologist.

3.1.3 Where to screen

- Outpatient screening should be performed in a facility capable of caring for a child who develops apnoea during the examination and where ophthalmological services are available. Where there is limited access to ophthalmologists, other screening modalities (such as photographic screening – see below) may be considered.
- A guide for screening for ROP (Appendix II) should be displayed in the neonatal ICU.

3.1.4 Preparation of the infant for screening

- Benoxinate (local anaesthetic): apply 1 drop to each eye at the outset
- Cyclomydril (2 mg cyclopentolate hydrochloride, 10 mg phenylephrine hydrochloride) (to dilate the pupils): apply 1 drop to each eye every 15 - 20 min, commencing approximately 45 minutes prior to the eye examination, until the pupil is dilated (an average of 3 drops)
- Chlorampenicol (topical antibiotic): apply 1 drop at the end of the examination
- Refer to Appendices III, IV and V.

4. Guideline for ophthalmologists performing ROP screening

Patients should be referred to the ophthalmologist by the neonatologist according to the referral protocol above. Should an ophthalmologist not be available, photographic screening may be an option (see below).

4.1 Where to screen

To avoid physiological stress on the infant, examination should ideally be performed by the ophthalmologist in the neonatal unit with appropriate monitoring, as guided by the treating neonatal healthcare professionals. Should this not be possible, personnel and equipment needed for neonatal resuscitation should be easily accessible to the ophthalmologist at the time of examination.

4.2 How to screen

- The discomfort and systemic effect of the examination should be minimised by pre-treatment of the eyes with a topical anaesthetic agent such as proparacaine or benoxinate.
- The use of pacifiers or oral sucrose may be considered.
- Pupils should be dilated with Cyclomydril drops, applied every 15 - 20 minutes (1 drop to each eye, commencing 45 - 60 minutes prior to the eye examination – refer to Appendices III, IV and V).
- Examination must be performed by a qualified examiner using binocular indirect ophthalmoscopy (Appendix VI).
- Detailed notes should be kept (e.g. see Appendix VII).
- In the absence of qualified examiners, photographic screening should be done.

Table 3. High v. low SaO_2 and severe ROP at PMA ≥32 weeks: A meta-analysis[21]

Author	Study type	Recruitment period	GA (week)	Birth weight (g)	*N*	Oxygen timing or duration (week)	Target SaO_2 (%)	Severe ROP (%)
McGregor *et al.*[28]	Prospective cohort	1996 - 1999	26.2±1.8 (mean)	Unknown	365	36.7±2.5 (mean PMA)	High (>94) v. low (≤94)	25 v. 46
STOP-ROP group[18]	RCT	1994 - 1999	25.4±1.5 (mean)	726±160	649	35.4±2 (mean PMA)	High (96 - 99) v. low (89 - 94)	41 v. 48
Gaynon *et al.*[29]	Retrospective cohort	1985 - 1993	26 - 27 (mean)	814 - 986	153	36 - 38 (+9 - ~10) (mean PMA)	High (99) v. low (92 - 96)	7 v. 37
Askie *et al.*[17]	RCT	1996 - 2000	<30	917	358	32 (+1) - ~10 (PMA)	High (95 - 98) v. low (91 - 94)	12 v. 16
Seiberth *et al.*[30]	Cohort	1994 - 1996	24 - 32	Unknown	117	33 - 42 (PMA; ROP stage 3)	High (≥98) v. low historic	1.8 v. 4.2

SaO_2 = saturation oxygen; tROP = threshold ROP; RCT = randomised controlled trial; PMA = postmenstrual age; STOP-ROP = Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity study.

Table 4. Pulse oximeter saturation guideline for preterm neonates receiving supplemental oxygen[17]

Infants	PaO_2 (kPa)	mmHg	Saturation range	Alarm limits
<36 weeks (<2 400 g)	6.5 - 9.0	50 - 70	88 - 92%	86 - 94%
CLD **and** 36 weeks PMA	8.0 - 10.0	60 - 75	90 - 95%	88 - 96%

PaO_2 = partial oxygen pressure, CLD = chronic lung disease

4.3 How to follow-up and manage

Follow-up examinations should be recommended by the examining ophthalmologist on the basis of retinal findings classified according to international classification[35] (Appendix VIII). The following schedule is suggested:

- 1 week or less follow-up
  - Stage 1 or 2 ROP in zone I
  - Stage 3 ROP in zone II
- 1 - 2 weeks follow-up
  - Immature vascularisation in zone I (no ROP)
  - Stage 2 ROP in zone II
  - Regressing ROP in zone I
- 2 weeks follow-up
  - Stage 1 ROP in zone II
  - Regressing ROP in zone II
- 2 - 3 weeks follow-up
  - Immature vascularisation in zone II (no ROP)
  - Stage 1 or 2 ROP in zone III
  - Regressing ROP in zone III.

The presence of plus disease (defined as dilation and tortuosity of the posterior retinal blood vessels) in zones I or II suggests that peripheral ablation, rather than observation, is appropriate.[36]

Practitioners involved in the ophthalmological care of preterm infants should be aware that the retinal findings that require strong consideration of ablative treatment were revised according to the Early Treatment for Retinopathy of Prematurity (ETROP) randomised trial.[37] The identification of tROP, as defined in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CryoROP), may no longer be the preferred time of intervention. Treatment may also be initiated for the following retinal findings:

- Zone I ROP: any stage with plus disease
- Zone I ROP: stage 3, no plus disease
- Zone II ROP: stage 2 or 3 with plus disease.

Special care must be taken in determining the zone of disease. The number of clock hours of disease may no longer be the determining factor in recommending ablative treatment. Treatment should generally be accomplished, when possible, within 72 hours of determination of treatable disease to minimise the risk of retinal detachment.

4.4 When to stop screening

The conclusion of acute retinal screening examinations should be based on age and retinal ophthalmoscopical findings.[36] Findings that suggest that examinations can be curtailed include:

- Zone III retinal vascularisation attained without previous zone I or II ROP (if the examiner doubts the zone or if the postmenstrual age is <35 weeks, confirmatory examinations may be warranted)
- Full retinal vascularisation
- Postmenstrual age of 45 weeks and no pre-threshold disease (stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present
- Regression of ROP[38] (care should be taken to ensure that no abnormal vascular tissue is present that is capable of reactivation and progression).

5. General information

It is very important that healthcare staff members communicate with guardians. Guardians should be made aware of ROP examinations and be informed if their child has ROP, with subsequent updates on ROP progression. The possible consequences of serious ROP should be discussed at the time that a significant risk of poor visual outcome develops. Documenting such conversations with parents in the nurse or doctor notes is highly recommended.

If hospital discharge or transfer to another neonatal unit or hospital is contemplated before retinal maturation into zone III has occurred, or if the infant has been treated by ablation for ROP and is not yet fully healed, then the availability of an appropriate follow-up ophthalmological examination must be ensured. Specific arrangements for that examination must be made before discharge or transfer. The transferring primary doctor, after communication with the examining ophthalmologist, should be responsible for communicating which eye examinations are needed and their required timing to the infant's new primary doctor. The latter should ascertain the ocular examination status of the infant from the record and via communication with the transferring doctor. Necessary examinations by an ophthalmologist experienced in examining preterm infants for ROP can thereby be arranged promptly at the receiving facility, or as an outpatient if discharge is contemplated before the need for continued examination has ceased.

If guardians are delegated responsibility for arranging follow-up ophthalmological care after discharge, then they should understand: the potential for severe visual loss, including blindness; that there is a critical time window to be met for treatment success; and that timely follow-up examination is essential to successful treatment. This information should preferably be communicated verbally and in writing (Appendix IX). If such arrangements for communication and follow-up after transfer or discharge cannot be made, then the infant should not be transferred or discharged until an appropriate follow-up examination can be arranged by the discharging unit.

6. Telemedicine screening and monitoring of ROP

A lack of skilled personnel to perform screening often restricts both the screening and management of ROP. Proposed revisions in the management of high-risk pregnancies, the improvement in neonatal survival and the development of new neonatal units may dramatically increase the number of premature infants requiring screening. The ability to offer a comprehensive screening service at all hospitals in which neonates at risk are managed may be limited by a lack of suitably trained paediatric ophthalmologists.

The advantages of telemedicine screening in ROP[39-43] include the ability to train neonatal nursing staff, medical officers and optometrists to capture and transmit screening photographs to a suitably trained ophthalmologist for assessment.

Use of the digital wide-field retinal imaging Retcam II is well described for ROP screening. The Retcam has the advantage over other digital retinal imaging systems in being a hand-held contact-based camera that is suitable for use in neonatal units or operating theatres and does not require patient co-operation or a seated position. Studies have confirmed the sensitivity and specificity of the Retcam, and its use is a safe, effective alternative for providing

screening where appropriate ophthalmologists are not available. The Retcam is also widely used to document disease management and response to treatment.

7. Conclusion

ROP is a preventable disease. Optimal management of oxygen therapy is the most important preventive measure. Every unit which cares for preterm neonates should have protocols and guidelines on oxygen therapy and SaO_2 targets in neonates. Timeous referral to the ophthalmologist for ROP screening is important to enable early diagnosis and treatment of ROP in preterm infants weighing <1 500 g and in larger unstable preterm infants where oxygen monitoring and management has been suboptimal.

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References

1. Varughese S, Gilbert C, Pieper C, Cook C. Retinopathy of prematurity in South Africa: An assessment of needs, resources and requirements for screening programmes. Br J Ophthalmology 2008;92:879-882. [http://dx.doi.org/10.1136/bjo.2008.137588]
2. District Health Information System. DHIS data 2010/2011. Oslo, Norway: DHIS, 2011. http://www.dhis2.org (accessed 31 January 2012).
3. Straker CA, van der Elst CW. The incidence of retinopathy of prematurity at Groote Schuur Hospital, Cape Town. S Afr Med J 1991;80:287-288.
4. Mayet I, Cockinos C. Retinopathy of prematurity in South Africans at a tertiary hospital: A prospective study. Eye 2006;20:29-31. [http://dx.doi.org/10.1038/sj.eye.6701779]
5. Delport SD, Swanepoel JC, Odendaal PJL, et al. Incidence of retinopathy of prematurity in very low birth weight infants born at Kalafong Hospital, Pretoria. S Afr Med J 2002;92:986-990.
6. Kirsten GF, Van Zyl JI, Le Grange M, et al. The outcome at 12 months of very-low-birth-weight infants ventilated at Tygerberg Hospital. S Afr Med J 1995;85:649-654.
7. Gilbert C, Fielder A, Gordillo L, et al. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate and high levels of development: Implications of screening programs. Pediatrics 2005;115:e518-e525. [http://dx.doi.org/10.1542/peds.2004-1180]
8. Attar MA, Gates MR, Iatrow AM, et al. Barriers to screening infants for retinopathy of prematurity after discharge or transfer from a neonatal intensive care unit. J Perinatology 2005;25:36-40. [http://dx.doi.org/10.1038/sj.jp.7211203]
9. Castillo-Riquelme MC, Lord J, Moseley MJ, et al. Cost-effectiveness of digital photographic screening for retinopathy of prematurity in the United Kingdom. International Journal of Technology Assessment in Health Care 2004;20(2):201-213.
10. Bedrossian RH, Carmichael P, Ritter A. Retinopathy of prematurity (retrolental fibroplasia) and oxygen: part 1. Clinical study: part II. Further observations on the disease. Am J Ophthalmol 1954;37:78-86.
11. Kinsey VE. Retrolental fibroplasia: Cooperative study of retrolental fibroplasia and the use of oxygen. Arch Ophthalmology 1956;56:481-543. [http://dx.doi.org/10.1001/archopht.1956.00930040489001]
12. Flynn JT, Bancalari E, Bawol R, et al. Retinopathy of prematurity. A randomized, prospective trial of transcutaneous oxygen monitoring. Ophthalmology 1987;94:630-638.
13. Penn JS, Henry MM, Wall PT, Tolman BL. The range of PaO_2 variation determines the severity of oxygen-induced retinopathy in newborn rats. Invest Ophthalmol Vis Sci 1995;36:2063-2070.
14. Flynn JT, Bancalari E, Snyder ES, et al. Cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med 1992;326(16):1050-1054. [http://dx.doi.org/10.1056/NEJM199204163261603]
15. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed 2001;84:F106-F110. [http://dx.doi.org/10.1136/fn.84.2.F106]
16. Anderson CG, Benitz WE, Madan A. Retinopathy of prematurity and pulse oximetry: A national survey of recent practices. J Perinatol 2004;24:164-168. [http://dx.doi.org/10.1038/sj.jp.7211067]
17. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003;349:959-967. [http://dx.doi.org/10.1056/NEJMoa023080]
18. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics 2000;105:295-310.
19. Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics 2003;111:339-345. [http://dx.doi.org/10.1542/peds.111.2.339]
20. Weinberger B, Laskin DL, Heck DE, Laskin JD. Oxygen toxicity in premature infants. Toxicology and Applied Pharmacology 2002;181:60-67. [http://dx.doi.org/10.1006/taap.2002.9387]
21. Chen ML, Guo L, Smith LEH, et al. High or low oxygen saturation and severe retinopathy of prematurity: A meta-analysis. Pediatrics 2010;125(6):e1483-e1492. [http://dx.doi.org/10.1542/peds.2009-2218]
22. Castillo A, Sola A, Baquero H, et al. Pulse oxygen saturation levels and arterial oxygen tension values in newborns receiving oxygen therapy in the neonatal intensive care unit: Is 85% to 93% an acceptable range? Pediatrics 2008;121(5):882-889. [http://dx.doi.org/10.1542/peds.2007-0117]
23. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med 2010;362:1959-1969.
24. Wright KW, Sami D, Thompson L, Ramanathan R, Joseph R, Farzavandi S. A physiologic reduced oxygen protocol decreases the incidence of threshold retinopathy of prematurity. Trans Am Ophthalmol Soc 2006;104:78-84.
25. Wallace DK, Veness-Meehan KA, Miller WC. Incidence of severe retinopathy of prematurity before and after a modest reduction in target oxygen saturation levels. J AAPOS 2007;11(2):170-174.
26. Vanderveen DK, Mansfield TA, Eichenwald EC. Lower oxygen saturation alarm limits decrease the severity of retinopathy of prematurity. J AAPOS 2006;10(5):445-448.
27. Deulofeut R, Critz A, Adams-Chapman I, Sola A. Avoiding hyperoxia in infants ≤1250 g is associated with improved short- and long-term outcomes. J Perinatol 2006;26(11):700-705.
28. McGregor ML, Bremer DL, Cole C, et al. Retinopathy of prematurity outcome in infants with prethreshold retinopathy of prematurity and oxygen saturation >94% in room air: The High Oxygen Percentage in Retinopathy of Prematurity study. Pediatrics 2002;110(3):540-544.
29. Gaynon MW, Stevenson DK, Sunshine P, Fleisher BE, Landers MB. Supplemental oxygen may decrease progression of prethreshold disease to threshold retinopathy of prematurity. J Perinatol 1997;17(6):434-438.
30. Seiberth V, Linderkamp O, Akkoyun-Vardarli I, Jendritza W, Voegele C. Oxygen therapy in acute retinopathy of prematurity stage 3. Invest Ophthalmol Vis Sci 1998;39:S820.
31. Sun SC. Relation of target SpO_2 levels and clinical outcome in ELBW infants on supplemental oxygen. Pediatr Res 2002;51:350.
32. Tin W. Optimal oxygen saturation for preterm babies. Biology of the Neonate 2004;85:319-325. [http://dx.doi.org/10.1159/000078173]
33. Gilbert C, Rahi J, Eckstein M, et al. Retinopathy of prematurity in middle income countries. Lancet 1997;350:12-14. [http://dx.doi.org/10.1016/S0140-6736(97)01107-0]
34. Phan MH, Nguyen PN, Reynolds JD. Incidence and severity of retinopathy of prematurity in Vietnam, a developing middle income country. J Pediatr Ophthalmic Strabismus 2003;40(4):208-212.
35. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005;127(7):991-999.
36. Reynolds JD, Dobson V, Quinn GE, et al. Incidence and severity of retinopathy of prematurity in Vietnam, a developing middle income country Arch Ophthalmol 2002;120:1470-1476.
37. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol 2003;121:1684-1696.
38. Repka MX, Palmer EA, Tung B. Involution of retinopathy of prematurity. Arch Ophthlamol 2000;118:645-649. [http://dx.doi.org/10.1001/archopht.118.5.645]
39. Wu C, Petersen RA, van der Veen DK. Retcam imaging for retinopathy of prematurity. J AAPOS 2006;10(2):107-111. [http://dx.doi.org/10.1016/j.jaapos.2005.11.019]
40. Kemper AR, Wallace DK, Quinn GE. Systematic review of digital imaging screening strategies for retinopathy of prematurity. Pediatrics 2008;122(4):825-830. [http://dx.doi.org/10.1542/peds.2007-3667]
41. Lorenz B, Spasovska K, Elflein H, Schneider N. Wide-field digital imaging based telemedicine for screening for retinopathy of prematurity. Six year results of a multicentre field study. Graefe's Archive for Clinical and Experimental Ophthalmology 2009;247(9):1251-1262. [http://dx.doi.org/10.1007/s00417-009-1077-7]
42. Salcone EM, Johnston S, Van der Veen D. Review of the use of digital imaging in retinopathy of prematurity screening. Seminars in Ophthalmology 2010;25(5-6):214-217. [http://dx.doi.org/10.3109/08820538.2010.523671]
43. Richter GM, Williams SL, Starren J, Flynn JT, Chiang MF. Telemedicine for retinopathy of prematurity diagnosis: evaluation and challenges. Survey Ophthalmology 2009;54(6):671-685.

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Appendix I. Oxygen saturation guideline*

Pulse oximeter saturation guideline for preterm neonates receiving supplemental oxygen

(i) Babies receiving or likely to require supplemental oxygen should be monitored by continuous pulse oximetry.

(ii) All neonates receiving supplemental oxygen (ventilator, CPAP, nasal prongs or head box oxygen) should be monitored with a pulse oximeter and saturation should be recorded. Oxygen should be humidified.

Infants	PaO_2 (kPa)	Saturation range	Alarm limits
Preterm <36 weeks	6.5 - 9.0	88 - 92%	86 - 94%
CLD and 36 weeks PMA	8.0 - 10.0	90 - 95%	88 - 96%

PaO_2 = partial oxygen pressure; PMA = postmenstrual age.

(iii) Nasal prong oxygen therapy:flow should be 0.5 - 1 l/min. A blender should be used to administer oxygen.

(iv) Head box oxygen:flow should be 2 - 3 l/kg/min. Head box oxygen is not recommended, but if utilised, arterial saturation of oxygen should be monitored with pulse oximetry (SpO_2).

(v) Pulse oximetry upper alarm should never be set at 100% if infants are receiving supplemental oxygen.

(vi) Avoid SpO_2 changes >93 - 95% in very low birth weight infants (VLBW) (<1 500 g).

*Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003;349:959-967.

Appendix II. Screening for ROP*

**Compiled by: R Singh, L Visser*

Who to screen

(i) All neonates born <32 weeks gestation

(ii) All preterm neonates weighing <1 500 g.

Note: Preterm infants weighing 1 500 - 2 000 g may also be at risk of ROP if they have risk factors such as: a family history of ROP, cardiac arrest, multiple (>2) blood transfusions, exchange transfusion or severe HIE. If oxygen monitoring has been suboptimal in this group of infants, then screening can be considered.

When to screen

- At 4 - 6 weeks chronological age or 31 - 33 weeks post-conceptional age (whichever comes later).
- If gestational age is accurate then neonates <28 weeks post-conceptional age should be screened at 6 weeks after birth and neonates >28 weeks post-conceptional age at birth should be screened 4 weeks after birth.

Where to screen

Outpatient screening should be performed in a facility capable of caring for a child who develops apnoea during examination. It should be performed wherever there are ophthalmological services in a cubicle in the nursery. Where there is limited access to ophthalmologists, other screening modalities may be considered (e.g. Retcam). If there is no screening facility in a hospital, then arrangements must be made for the neonate to be seen by an ophthalmologist at the nearest hospital, and the mother should be informed about the risks of ROP.

Follow-up

A follow-up guideline for ROP should be determined by an ophthalmologist after the initial screening.

Appendix III. Preparation of infants for ROP screening

All requirements must be met in the morning prior to ROP assessment (preparation should not start when the ophthalmologist arrives). Requirements:

(i) All patients should be identified and dilatation should be started 45 minutes - 1 hour before the start of the clinic:

- Benoxinate eye drops: apply 1 drop to each eye at the outset only
- Chloramphenicol eye drops: apply 1 drop to each eye at the beginning and end of examination only
- Cyclomydril eye drops: apply 1 drop to each eye every 15 - 20 minutes.

(ii) Working cardiac trolley, a basinet, a soft blanket for swaddling and a table to write on

(iii) A dedicated staff nurse to be allocated to help during the procedure

(iv) A separate sterile pack with 10 ml of water for injection per infant

(v) Diluted Hibitane for sterilisation of speculum

(vi) All request forms should be completed by the referring doctor

(vii) Every neonate booked for the clinic should have an ROP form completed in duplicate

(viii) A diary should be kept with all appointments.

Appendix IV. Prescription for eye drops for ROP screening

Name of patient: _____

Birth weight: _____

Hospital number: _____

Age:

Benoxinate drops: apply to each eye at the outset.

Cyclomydril drops: apply 1 drop to each eye every 15 - 20 minutess (repeat 3 - 4 times)

Chloramphenicol drops: apply at the end of the examination.

Doctor name and signature _____

Appendix V. Procedure for mydriasis (dilatation of the pupil)

- Infants undergoing retinal examinations should have their pupils dilated with a cycloplegic mydriatic agent prior to examination to ensure optimal evaluation of the retina.
- The following procedures should be followed to limit systemic absorption and related symptoms:

Procedure for administration of Cyclomydril eye drops prior to neonatal retinal examinations in infants (adapted from Tygerberg Hospital)

Step	Action
1	Commence with administration of Cyclomydril eye drops 45 mins prior to eye examination
2	Administer 1 drop of Cyclomydril eye drops into each eye every 20 minutes for a **maximum of 3 dosages**
3	Wipe excess eye drops away and apply gentle pressure over the nasolacrimal duct for 1 minute following instillation of eye drops, to prevent systemic absorption and possible side-effects
4	Monitor infant for signs of tachycardia, restlessness, apnoea, desaturation and bradycardia for a minimum of 12 hours after commencement of Cyclomydril administration and report to paediatrician immediately
5	Dim lights and keep the infant's eyes covered with an eye cloth for a minimum of 12 hours after commencement of Cyclomydril administration in order to minimise pain experienced due to pupil dilation

Side-effects of Cyclomydril

If any of these rare side-effects of Cyclomydril eye drops occur (including signs of systemic absorption), then admit the patient to the nursery and observe:

- apnoea
- desaturation
- bradycardia/tachycardia
- fever
- vasodilatation
- restlessness
- delayed gastric emptying
- urinary retention
- light sensitivity.

Appendix VI. Equipment required for ROP screening

(i) Indirect ophthalmoscope
(ii) A 20, 28 or 30 dioptre lens
(iii) Scleral depressor
(iv) Infant wire speculum with 4 mm blades
(v) Soft blanket for gentle swaddling of the infant
(vi) An alternative method of screening is the use of a Retcam, where a wide-angle retinal camera is used by a hospital technician and the images are sent to the ophthalmologist to interpret the findings at a tertiary level.

Appendix VII. ROP screening form

Date booked for examination: _____ Hospital booked at: _____

Name: _____ Hospital number: _____

Date of birth: _____

HIV-exposed/-unexposed/unknown: _____ Sex: _____

Birth weight (g): _____ Multiple birth (1,2,3): _____

Gestational age at birth: _____ Growth at birth – AGA/SGA/LGA: _____

Duration of oxygen IPPV: _____ CPAP: _____ Nasal O_2: _____

Indication for ROP screening in this patient: please tick appropriate box:

☐ weight <1 500g

☐ gestational age <32 weeks at birth

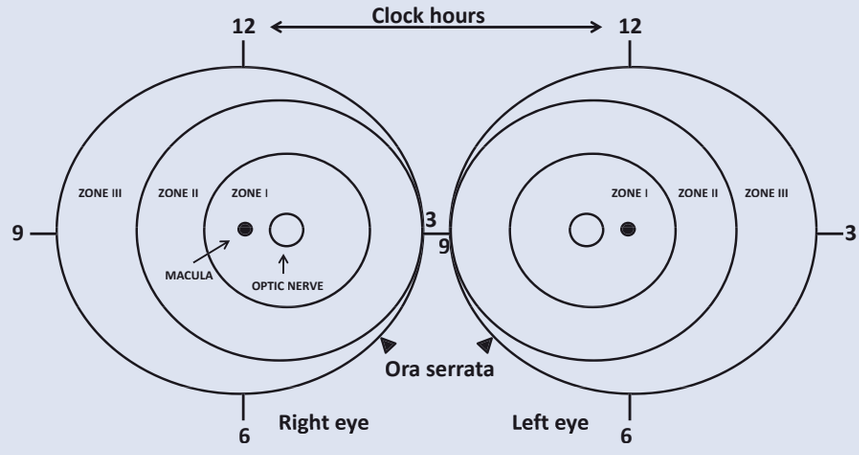
☐ weight 1 500 - 2 000 g with unstable clinical course

Examination

Date: _____ Examiner initials: _____ Current age: _____

Anterior segment: _____

Fundus



Stage: _____ Stage: _____

Plan: _____

_____

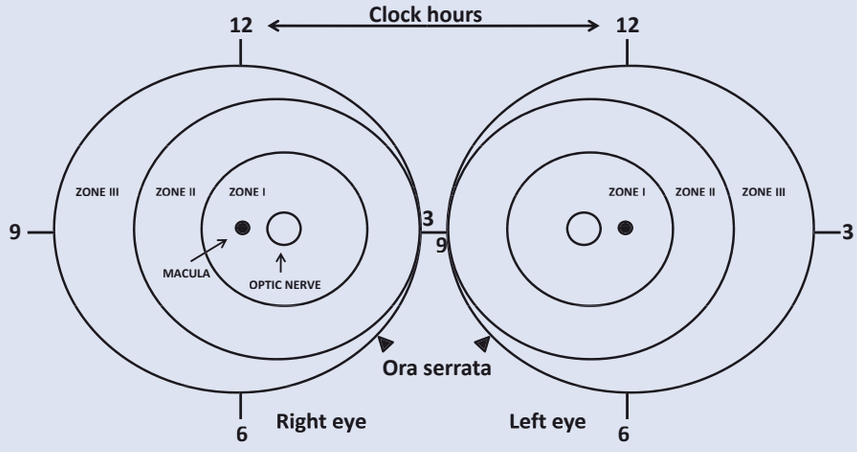
_____

_____

Appendix VII: ROP screening form (continued)

Follow-up visit

Date of examination: _____ Age: _____



Stage: _____ Stage: _____

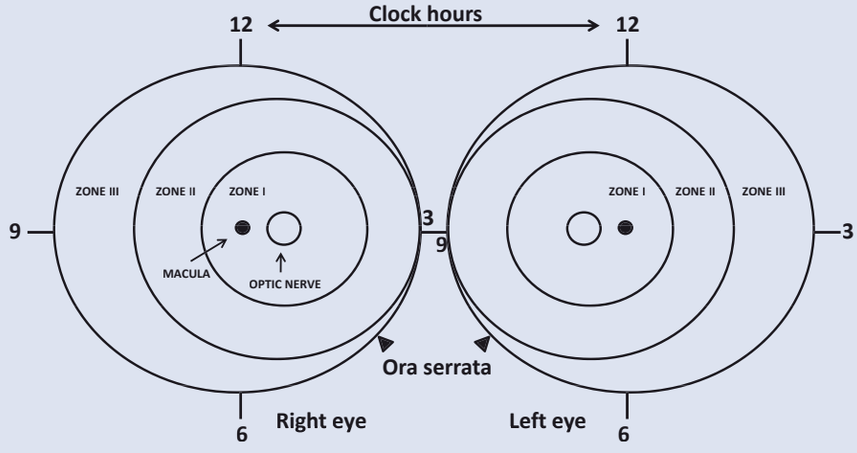
Plan: _____

_____

_____

Follow-up visit

Date of examination: _____ Age: _____



Stage: _____ Stage: _____

Plan: _____

_____

_____

Appendix VIII. International classification of ROP

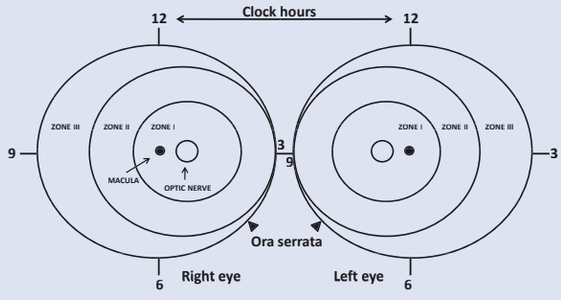
Stages (1 - 5)

1	Flat white demarcation line separates the vascular from the avascular retina
2	Ridge of fibrous tissue protrudes between the vascular and avascular retina
3	Blood vessels and fibrous tissue grow along the ridge and extend into the vitreous
4	Partial retinal detachment (4A – macula not involved; 4B – macula involved) is seen
5	Total retinal detachment has developed

Zones (I – III) and extent (clock hours)

I	The most central zone, centred on the optic nerve with a radius equal to twice the distance from the disc to the fovea
II	Extends concentrically from the edge of zone I to the nasal ora
III	The remaining temporal crescent

In addition, extent is denoted in the number of clock hours affected (1 - 12)



Plus disease

Blood vessels in the posterior pole appear tortuous and dilated. In addition, there may be vitreous haze, engorgement of iris vessels and poor dilatation of the pupil. The presence of plus indicates more severe ROP and rapid progression may follow.

Rush disease/AP-ROP (aggressive posterior ROP)

ROP in zone I with plus

Appendix IX. Neonatal nursery checklist for preterm neonates

- ☐ Diagnosis
- ☐ Associated complications
- ☐ Therapy indicated
- ☐ Complications of therapy
- ☐ Risk of intraventricular haemorrhage (IVH)
- ☐ Risk of necrotising enterocolitis (NEC)
- ☐ Risk of ROP
- ☐ Risk of developmental delay
- ☐ ROP booking (if applicable)
  - Date: _____
  - Venue: _____
- ☐ Risk of hearing loss
- ☐ Audiology booking (if applicable)
  - Date: _____
  - Venue: _____
- ☐ If dysmorphic, has mother been counselled
- ☐ Discharge medication
- ☐ Date of follow-up
  - Date: _____
  - Venue: _____
- ☐ Discharge summary given to mother
- ☐ Road to Health Card summary
- ☐ Six-week follow-up at local clinic for immunisation
- ☐ If retroviral disease (RVD)-exposed: 6-week polymerase chain reaction (PCR) and Bactrim prophylaxis and nevirapine (NVP) (if breastfeeding)

Doctor name and signature _____

Mother signature _____