Retinopathy of Prematurity Philippine Preventive Care Plan Strategy

A Joint Statement of the Philippine Society of Newborn Medicine (PSNbM) and the Philippine Academy of Ophthalmology - ROP Working Group (PAO-ROPWG)

Executive Summary

This joint statement is a recommendatory care plan for health care providers and institutions that cater to preterm infants. It aims to decrease the prevalence of Retinopathy of Prematurity (ROP) and ROP-related blindness, in connection with local perinatal practices and community resources. It seeks to impress upon stakeholders that ROP, with its sequelae, is a devastating but avoidable disease of premature babies in the Philippines.

These recommendations are based on recent international, local evidence and from agreement between the PSNbM and the PAO-ROPWG. They do not constitute clinical practice guidelines, which require a different process for development.

This statement and other clinical practice guidelines must be reviewed regularly as newer and better evidence become available and as the population, the environment and clinical practices evolve.

Key Recommendations

Population for ROP Screening

1. All newborns with gestational age of ≤32 weeks.[i]
2. All newborns with birth-weight of ≤1500g.[1]
3. Newborns with gestational ages of 32-36 weeks of gestation with the following risk factors:[1ii iii iv v vi vii]

S - **S**epsis (severe)*

T - PRBC **T**ransfusion within the first ten days of life due to anemia**

O - **O**xygen use especially without oxygen blender***

P – **P**rematurity with an unstable clinical course placing infants at high risk as assessed by their attending pediatrician or neonatologist.

****Other risk factors may be added as determined by future evidence/ studies.

Timing of ROP Screening

- For premature infants less than 28 weeks AOG, initial ROP screening is recommended at 31 weeks postnatal age or prior to discharge whichever comes earlier
- For premature infants 28 weeks and above, initial ROP screening is recommended at 20 days postnatal age or prior to discharge whichever comes earlier
- Follow up examinations will be as deemed necessary by the ophthalmologist depending on the findings on initial screening. For patients who will be discharged, outpatient follow up schedule must be properly coordinated.

Other recommendations

a. For resuscitation of the preterm, initial use of 30% oxygen then titrate accordingly based on the recommended pre-ductal oxygen saturation using the pulse oximetry. [6] [7] [viii]

1min: 60-65%
2min: 65-70%
3min: 70-75%
4min: 75-80%
5min: 80-85%
10min: 85-95%

b. Use of pulse oximetry during resuscitation and administration of oxygen.[6-8]

c. Judicious use of PRBC transfusion[5]

d. Use of human milk to decrease the incidence of any stage of ROP by as much as 75%.[ix]

Significance

ROP is recognized as an important cause of avoidable childhood blindness in the world. It is among the childhood eye diseases that need to be addressed according to the World Health Organization's (WHO) Vision 2020. In developing countries like the Philippines, sub-optimal resources and varying practices in neonatal intensive care settings tip the scale towards an increasing prevalence of ROP even in larger, more mature but sick babies. These babies are missed if ROP screening guidelines from developed countries like the United States (US) and United Kingdom (UK) are followed. It has been found that 13% of infants with severe ROP from moderately and poorly developed countries had birth weights (BW) and gestational ages (GA) exceeding those recommended for screening by the United Kingdom (UK) (BW < 1500 g and/or GA < 32 weeks).[3]

The Philippines ranks 113 in the 2018 UNDP HDI[x] classifying it as a poorly developed country. However, it is experiencing an increasing survival rate of preterms due to improving and evolving neonatal care and medical technology. Hospital-based data have shown ROP incidence to be 15% among preterms in Metro Manila.[xi]

Background

ROP is a retinal vasoproliferative disorder of premature babies. It is a major cause of childhood blindness, found in up to 60% of blind children in moderately developed countries. It is the leading cause of childhood blindness in the Philippines' Resources for the Blind, Inc., as well as in local schools for the blind.[xii] It is caused by a complex, dynamic interplay of multifactorial etiologies. Known risk factors are prematurity and low birth weight in conjunction with co-existing illnesses and consequent management. Much have been described in literature about the role of supplemental oxygen (02) and altered vascular endothelial growth factor (VEGF) regulation in the pathogenesis of ROP.[xiii xiv] Low IGF-I, which suppresses VEGF survival in retinal endothelial cells, also has a direct correlation with clinical ROP.[13] A recent study shows a possible correlation between poor postnatal weight gain and hydrocephalus with ROP in developed neonatal care systems.[xv]

Premature infants still have incomplete vascularization of the retina. Coming from the intrauterine environment where arterial oxygen pressure of the fetus is 22-24 mm Hg, premature birth of these infants results in relative hyperoxia which may down regulate VEGF production. Administration of supplemental oxygen to the preterm infant may lead to sustained hyperoxia, promoting obliteration of existing vessels and arrest of vascularization.[16]

As the metabolic demands of the developing eye increase, the non-perfused areas of the retina become hypoxic and VEGF may be produced pathologically. High levels of VEGF trigger retinal neovascularization, which in severe cases may cause retinal fibrosis and retinal detachment. Repeated cycles of hyperoxia-hypoxia may favor the progression of ROP.[xvi]

The usual recognizable progression of the disease is noted at around 3-6 weeks postnatal age or 31-33 weeks post-conceptional age. Hence, initial screening is suggested at around 4 weeks postnatal age or between 31-33 weeks.[xvii] Varying local clinical practices may result in some premature infants being discharged from the hospital without having been screened for ROP. Therefore, parents' awareness of the need for ROP screening, follow-up and the availability of qualified screeners on out-patient basis or at transfer institutions are critical considerations for adequate care.

The first epidemic of ROP occurred in the 1940's to 1950's from excessive use of supplemental oxygen in neonates. This was subsequently controlled with judicious use of oxygen in clinical practice.[3]

The second ROP epidemic was noted in the 1970's to 1980's, particularly in developed countries like the US and UK with improving neonatal intensive care and increasing survival of premature infants. ROP screening guidelines in these developed countries were set for preterms less than 30/32 weeks gestational age (GA) and/or birth weight less than 1500 grams and selected infants over 1500 grams/32 weeks GA with unstable clinical course. Improved medical care and evolving technology coupled with these guidelines for early detection and treatment saw the decline of incidence and severity of ROP and ROP-related visual impairment in these areas.

Nevertheless, ROP still remains prevalent in those less than 27/ 28 weeks GA and in sick immature babies even in developed countries.

Presently, we are experiencing the 3rd epidemic of ROP in moderately developed countries (HDI ranking 31-100), where its prevalence is increasing even among bigger or more mature babies. Several reasons have been postulated to cause the epidemic in these areas. First, birth rates and prematurity rates are higher. Second, sub-optimal neonatal care due to lack of resources leads to higher rates of severe ROP both in extremely premature and in larger, more mature infants. Third, lack of awareness, skilled personnel and financial constraints have caused inconsistent availability of screening and treatment programs in neonatal units in many cities.[3] Fourth, there is a disregard for the 3rd criterion of referring babies who may be more mature, and heavier but with (neonatologist-determined) risk factors. The study by Gilbert et al found that 13% of the included 1091 infants from less developed countries exceeded the UK screening guidelines for gestational age or birth weight and developed severe ROP. 3.6% even exceeded the more inclusive criteria of less than 34 weeks and/or less than 1750 grams. The study cited complex interactions between case mix, neonatal care, survival rates as well as variation in screening practices and follow-up rates of discharged patients as possible reasons for these findings.[3]

Traditionally, US screening guidelines have been followed in the Philippines. However, recent international developments of bigger and older babies getting ROP have brought about the conclusion that "screening guidelines developed in highly developed countries may not suit all situations"[3]. Gilbert et al recommended that moderately developed and poorly developed countries should come up with "region-specific criteria that need to be evaluated and revised if necessary," due to the "variations in levels of neonatal care, policies, practices, levels of training and expertise of service providers".[3]

Thus, in 2013, after a parallel local experience of ROP in unscreened larger and/or older premature infants was documented[11], the PAO through its ROPWG, recommended the Revised Philippine Guidelines for Screening and Referral of Retinopathy of Prematurity,[xviii] to address this "3rd ROP epidemic". It was proposed that babies less than 35 weeks GA or less than 2000 grams should be screened at two weeks postnatal age or 32 weeks post-conceptual age, whichever comes first. The third criterion of whoever the pediatrician or neonatologist identifies as high risk was kept. From the PAO standpoint, with a goal of "zero babies blind from ROP," centers of neonatal intensive care were enjoined to adopt this protocol to better evaluate the best practices for our setting. A more inclusive screening criteria will ensure that the ROP screening program will include most if not all infants who are at risk.

The PSNbM, under the umbrella of the Philippine Pediatric Society (PPS), whose members are front-liners in the care of "unstable neonates" had some concerns on increasing the age and weight criteria for screening. First, most of these larger or more mature (32 – 35 weeks GA) babies in the NICU or newborn service have minimal prematurity issues like respiratory distress and apnea. They are at low risk for developing ROP-related blindness. Second, financial issues and logistic burden, such as sufficient eligible screeners and ROP specialists for follow up and intervention beg the question on the practicality of widening the age and weight range to include more preterm infants for screening. Mandatory implementation of broader screening criteria may not be possible in all areas nationwide. Third, the benefit-risk ratio of routinely screening larger

babies (greater than 32 weeks or 1500 grams) needs to be further explored in conjunction with available local/ unit practices, resources and outcome data. In recent years there have been changes in prognosis of infants with ROP attributed to better understanding of its risk factors and pathogenesis which led to improvements in neonatal care. More conservative use of supplemental oxygen, meticulous monitoring of blood oxygen levels, aggressive management of instability of the infant are probably the most important factors responsible for the lower risk in more mature infants.

Conclusion

Multi-sector coordination of different stakeholders from private and government medical institutions (DOH, Philhealth, PPS, PSNbM, PAO, etc) is needed to address this "avoidable" disease that translates to economic loss and is an important health indicator of the country. Decision-making and responsibility lie importantly on health care providers and well-informed parents.

Oxygen supplementation while using 02 saturation monitors and changes in fi02 and 02 saturation guidelines should be fully understood and strictly implemented in daily practice. Oxygen is a drug. It has the potential for adverse side effects in preterm infants if not properly administered. Avoiding hypoxia is important, but prolonged hyperoxia can lead to oxidative stress and injury, particularly in the eye.

A comprehensive, collaborative, coordinated, and cost-effective strategy must be developed to address the problem of ROP in the country, taking into consideration the outcome and resource status of different areas and with deliberation among the different stakeholders. Understanding the many facets of ROP is vital in solving the problem of ROP-associated blindness. Early screening, detection and prompt intervention are important in the management of ROP and ROP-associated blindness.

Centers providing advanced neonatal care for preterm babies should adopt a standard ROP screening program. When lower weight and younger age are used as screening criteria (older ROP screening guidelines), increased vigilance of referring preterm babies that fall under the third criterion (having risk factors as determined by the pediatrician and neonatologists) is paramount. Implementation may be simplified by using the larger and older cut-off values in the 2013 revised PAO guidelines but it carries the risk of increasing the number of unnecessary procedures, and increasing burden on the health system. Each center may have differing parameters, resources, and conditions and thus choose to adopt the guidelines that are more applicable to their setting. The bottom-line recommendation should be based on providing whatever is best for the preterm children under our care.

Due to the wide inter-center and regional variability of service availability, comprehensive screening programs must be established in all units that admit high risk infants using local protocols developed from national guidelines. Ophthalmologists, pediatricians and nurses must work together to fully implement these programs. It is the responsibility of the attending care provider (pediatrician/neonatologist) and the institution in collaboration with the ophthalmology

service to assure appropriate screening and follow-up care. Necessary interventions and available resources should be in place at the NICU, at transfer units and after discharge. Patients should not be discharged or transferred until this plan of care is in place and is documented with informed parents.

Multi-sector Recommendations for Care

The problem of ROP must be approached from different levels and aspects of preterm care:

1. Decreasing premature births and antenatal steroid use from the OB-Gyn standpoint is important.

2. Hospitals providing newborn care must be equipped with basic neonatal devices to properly deliver 02 supplementation (pediatric flowmeter, 02 blender, NCPAP, oximeter) as part of the requirements for DOH certification.

3. Hospitals providing newborn care must be staffed with medical providers certified in NRPH+ training as part of the requirements for DOH certification.

4. Mandatory maternal/neonatal transfer to a facility capable of the appropriate level of care is followed when medically and logistically feasible

5. Post-delivery/NICU Care must follow NRPH+ guidelines. The use of 02 Blenders has to be emphasized. Use CPAP before ventilator support.

6. Prevention and reduced infection with EINC/KMC practices and judicious antibiotic use must be followed.

7. Caffeine citrate must be made available to control and manage hyperoxia/hypoxic spells

8. Appropriate pulse oximetry devices for reliable reading with blood gas correlation must be available if needed

9. Adoption of unit/regional "target 02" saturation (90-95%) with "alarm limits" (89-96%) coupled with strict FI02 supplementation policy must be included in a strict implementation program. Oxygen saturation levels must be strictly monitored.

10. ROP screening is recommended for the following populations at risk:
    - All newborns with gestational age of $\leq$32 weeks.[1]
    - All newborns with birth-weight of $\leq$1500g.[1]
    - Newborns with gestational ages of 32-36 weeks of gestation with the following risk factors:[1-7]

      S - **S**epsis (severe)*

      T - PRBC **T**ransfusion within the first ten days of life due to anemia**

      O - **O**xygen use especially without oxygen blender***

P – **P**rematurity with an unstable clinical course that places infants at high risk as assessed by their attending pediatrician or neonatologist.

*Sepsis is defined as severe infection with hypotension requiring inotropic support. Pro-Inflammatory cytokines produced by the microorganisms and/or their products might exert a direct effect on neovascularization via inflammation-regulated VEGF availability.[4-5]

**Transfusion of packed red blood cell within the first 10 days of life is associated with about four-fold increased risk of severe retinopathy of prematurity. Each transfusion increases the risk of ROP by 9%.[5]

4, 6, 7, 8 xix xx

***Oxygen supplement, that is administered via cannula, CPAP or mechanical ventilation without meticulous monitoring with pulse oximeter or blood gas levels increases ROP risk. Phase 1 involves the cessation of normal retinal vascularization in the setting of hyperoxia. Phase 2 results in abnormal neovascularization of the retinal vessels. The major factor is exposure to changing oxygen levels then to high and low levels of retinal growth factors like vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF).

****Other risk factors may be added as determined by future evidence/ studies.

11. Timing of Initial ROP Screening [1-2, 17]
    - For premature infants less than 28 weeks AOG, ROP screening is recommended at 31 weeks postnatal age or prior to discharge whichever comes earlier
    - For premature infants 28 weeks and above, ROP screening is recommended at 20 days postnatal age or prior to discharge whichever comes earlier
    - Follow up examinations will be as deemed necessary by the ophthalmologist depending on the findings on initial screening. For patients who will be discharged, outpatient follow up schedule must be properly coordinated.

12. Other recommendations:

a. For resuscitation of the preterm, initial use of 30% oxygen then titrate accordingly based on the recommended pre-ductal oxygen saturation using the pulse oximetry. [6-8]

1min: 60-65%
2min: 65-70%
3min: 70-75%
4min: 75-80%
5min: 80-85%
10min: 85-95%

b. Use of pulse oximetry during resuscitation and administration of oxygen.[6-8]

c. Judicious use of PRBC transfusion[5]

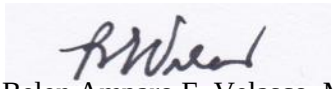
d. Use of human milk to decrease the incidence of any stage of ROP by as much as 75%[9]

13. A regular review of guidelines must be performed every 3 to 5 years as the population of infants at risk changes over time. Standardized, prospective studies to determine the most appropriate screening criteria and guidelines need to be implemented to gather evidence for these guidelines.

14. Supplemental infrastructures such as public awareness campaigns, legislation and strengthening of Philhealth reimbursement schemes must be implemented.

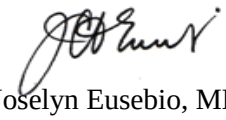
Document prepared by:

Victor Q. Zapanta, MD (PSNbM)
Andrea Kristina Monzon – Pajarillo, MD and Alvina Pauline Santiago, MD (PAO-ROPWG)



Belen Amparo E. Velasco, MD
President
Philippine Society of Newborn Medicine

Pearl Tamesis – Villalon, MD
Chair
PAO – ROP Working Group



Joselyn Eusebio, MD
President
Philippine Pediatric Society

Margarita Lat – Luna, MD
President
Philippine Academy of Ophthalmology

References:

[i] Paulino JAT, et al. Comparison of the Detection Rates for Retinopathy of Prematurity (ROP) of the 2013 Philippine Academy of Ophthalmology (PAO) Revised Philippine Guidelines and the 2005 Philippine Academy of Ophthalmology (PAO)-Philippine Pediatric Society (PPS) Guidelines for ROP Screening in the Philippine General Hospital. A 5-year Review. Presented at the PAO Fellows' Research Competition, PAO Annual Meeting 2019

[ii] Fierson WM. Screening Examination of Premature Infants for Retinopathy of Prematurity. **Pediatrics** December 2018, 142 (6)

[iii] Gilbert C, et al. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: Implications on screening programs. 2005 Pediatrics 15 (5): e518-e525.

[iv] Lee J and Dammann O. Perinatal infection, Inflammation and Retinopathy of Prematurity.

[v] Lust C, Vesoulis C, Jackups R, Liao S, Rao R, and Mathur AM. Early red cell transfusion is associated with severe retinopathy of prematurity. **Perinatol**. 2019 March ; 39(3): 393–400. doi:10.1038/s41372-018-0274-9.

[vi] Philippine Society of Newborn Medicine **Manual of Neonatal Resuscitation** (NRPh+, 2018). Philippine Society of Newborn Medicine, Quezon City, Philippines.

[vii] WHO Library Cataloguing-in-Publication Data. WHO recommendations to improve preterm birth outcomes. Contents: Appendix: WHO recommendations on interventions to improve preterm birth outcomes: evidence base. 1. Premature Birth prevention and control. 2. Infant, Premature 3. Infant Mortality - prevention and control. 4. Prenatal Care. 5. Infant Care. 6. Guideline. I. World Health Organisation . ISBN 978924150898 8 (NLM Classification : WQ 330)

[viii] Sweet DG, Carnielle V, Greisen G, Hallman M, Ozek E, Te Pas, Plavka R, Roger CC, et al. European Consensus guidelines on the management of RDS in preterm infants. **Neonatology** 2019: 115(4): 432-50

[ix] Muneer A, Bari A, Naveed S and Ali AS. Is human milk feeding protective for Retinopathy of Prematurity? **Pak J Med Sci** November - December 2018 Vol. 34 No. 6, pp1534-1538.
xwww.hdr.undp.org. Global human development indicators 2018

[xi] Corpus K., et al. Proposed new retinopathy of prematurity screening criteria: evidence for including older and heavier Filipino premature babies. 2013 Philipp J Ophthalmol; 38: 1-8

[xii] Del Mundo, PS and Chua CM. Causes of blindness and severe visual impairment among children enrolled in an early intervention and preschool program of a school for the blind in the Philippines. Philipp J Ophthalmol 2015; 40(1):41-46

[xiii] Hellstrom A, et al. Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells: Direct correlation with clinical retinopathy of prematurity. PNAS 2001; 98 (10): 5804-5808.

[xiv] Hellstrom A., et al. Retinopathy of prematurity. Lancet. 2013 Oct 26; 382 (9902): 1445-1457

[xv] Binenbaum G, et al. Validation of the postnatal growth and retinopathy of prematurity screening criteria. JAMA Ophthalmol. published online November 14, 2019. doi:10.1001/jamaophthalmol.2019.4517

[xvi] Chow LC, et al. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003 Feb; 111(2): 339-45

[xvii] Royal College of Ophthalmologists and Royal College of Paediatrics and Child Health. Guideline for the screening and treatment of retinopathy of prematurity. UK Retinopathy of Prematurity Guideline 2008

[xviii] Philippine Academy of Ophthalmology (PAO) et al. Proposed Philippine guidelines for screening and referral of retinopathy of prematurity (ROP). Philipp J Ophthalmol 2013; 38:64-71

[xix] Palmer EA, Flynn JT, Hardy RJ, et al; The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity. **Ophthalmology**. 1991;98(11):1628–1640.

[xx] Price KE, Martinez-Castellanos MA, Chan RVP. Screening criteria for Retinopathy of Prematurity in Mexico, a Middle-income Country **Investigative Ophthalmology & Visual Science** June 2015, Vol.56, 956.