Updates on Retinopathy of Prematurity:

Lessons learned from the 2015 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO)

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Retinopathy of prematurity (ROP) is a vaso-proliferative disorder affecting the retina of premature babies. It is a potentially blinding disease and is now one of the most common causes of life-long vision impairment and blindness in children in middle-income countries like the Philippines.

ROP Screening

The Incidence of ROP in the U.S. The incidence and early course of ROP reported by 3 prospective multi-center studies (CRYO-ROP,[1] ETROP,[2] e-ROP[3]) described the changes in demographic characteristics of ROP from 1986 to 2013. Over the past 27 years, lower birth weight (<750 g), and more premature (<27 weeks gestational age) infants were increasingly more common in the U.S. The improving neonatal care resulted in the increasing survival of the youngest and sickest babies. In the U.S., a decrease in ROP incidence among larger and more mature infants has been observed over time.

Screening Criteria and Initiation of Screening. Because of the above data, the American Academy of Pediatrics (AAP) and American Academy of Ophthalmology (AAO) currently recommend ROP screening[4] for "infants with a birth weight (BW) of ≤1500 g or gestational age (GA) of 30 weeks or less and selected infants with a BW between 1500 and 2000 g or GA of >30 weeks with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk for ROP". However, as reported by Gilbert,[5] developing and middle-income countries are seeing a different demographic of infants compared to the U.S. The growing number of children with ROP in these countries has been labeled as the "Third Epidemic of ROP".[6]

A tertiary ophthalmology center in Mexico showed that 14 out of 34 eyes of preterm babies who required ROP treatment weighed greater than the 1500 g-birth weight cut-off.[7] Also, 56 out of 104 patients requiring treatment were also above the 30 weeks GA cut off and did not have any risk factors. Therefore, if the current U.S. criteria were followed, these babies would not have been screened for ROP. Similarly in our country, where the current national ROP screening guideline is based on the AAP-AAO, older and heavier babies are increasingly diagnosed with ROP – and may be missed. A report by the Philippine ROP Working Group demonstrated that 16.2% of children with ROP would be missed if the current criteria were used.[8] The proposal to modify the screening criteria to less than 35 weeks GA and less than or equal to 2000 g BW still awaits approval, pending the results from a larger prospective multicenter study.[9] It is recommended by the PAO-ROP Working Group that the first examination be performed at 2 weeks post-natal age or at 32 weeks post-conceptional age, whichever comes earlier.[9]

Screening and Follow Up. Classification and staging of ROP is based on the ICROP study (Table 1) with the recommended follow-up examinations (Table 2).[10] It is recommended that a pediatric ophthalmologist, retina specialist, or any general ophthalmologist with sufficient knowledge and experience to identify accurately the location and sequential retinal changes in ROP, perform ROP screening in preterm infants.[9]

Screening Strategy. Globally, screening for ROP faces several challenges. There is shortage of ophthalmologists competent in ROP screening and treatment. Because of regional variability, ROP screening strategies that address the specific needs, demographics, and economics are lacking. Key considerations[11] when choosing a screening strategy include: (1) the risk of ROP within the NICU; (2) the ability to ensure post discharge or transfer follow up; and (3) local resource availability (ophthalmologist and reliable reading center).

A novel tele-education system by Chan et al[12] was developed to provide ophthalmologists-in-

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Table 1. Classification of ROP.[10]

Stage	
Immature retina	no retinopathy of prematurity
Stage 1	demarcation line
Stage 2	ridge
Stage 3	extraretinal fibrovascular proliferation
Stage 4a	partial retinal detachment (extrafoveal)
Stage 4b	partial retinal detachment (foveal)
Stage 5	total retinal detachment
Zone	
Zone I	the innermost zone consists of a circle, the radius of which extends from the center of the optic disc to twice the distance from the center of the optic disc to the center of the macula.
Zone II	extends centrifugally from the edge of zone I to the nasal ora serrata (at the 3-o'clock position in the right eye and the 9-o'clock position in the left eye)
Zone III	Zone III is the residual crescent of retina anterior to zone II
Plus Disease	
No Plus	no arterial tortuosity and venous dilation
Pre-Plus	vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilatation than normal
Plus	sufficient vascular dilatation and tortuosity present in at least 2 quadrants of the eye.

Table 2. Recommended follow up.[4]

1 week or less	Immature retina, zone I Immature retina at zone II posterior, near boundary of zone I Stage 1 or 2 ROP, zone I Stage 3 ROP, zone II Presence or suspected APROP
1-2 weeks	Immature retina, posterior zone II Stage 2 ROP, zone II Unequivocally regressing ROP, zone I
2 weeks	Stage 1 ROP, zone II
	Immature retina, zone II
	Unequivocally regressing ROP, zone II
2-3 weeks	Stage 1 or 2 ROP, zone III Regressing ROP, zone III

training and practicing ophthalmologists a resource to learn how to diagnose and manage ROP. The ROP tele-education system has been shown to be effective in improving the diagnostic accuracy of ROP by the 31 ophthalmologists-in-training that participated in the program in the United States and Canada. The said tele-education system has also increased the diagnostic performances of trainees from Brazil, Mexico, and the Philippines.[13]

The availability of handheld fundus imaging has allowed remote screening and diagnosis of preterm infants with ROP (tele-ophthalmology). The Stanford University Network for Diagnosis of ROP (SUNDROP)[14] and Karnataka Internet Assisted Diagnosis of ROP (KIDROP)[15] studies have proven the effectiveness of remote screening strategy in the real world scenario. The Ophthalmic Technology Assessment report[16] of the AAO also recognized that remote digital fundus imaging has high accuracy for detection of clinically significant ROP. A number of studies[17-19] have shown that non-physician readers with no previous knowledge of ROP can also be successfully trained. A mathematical model has indicated that telemedicine in ROP screening is cost-effective.[20] Based on the KIDROP data, telemedicine was determined to be the most cost-effective solution when compared to the following: a) ROP specialist examines and treats at a single private center, b) ROP specialist screens and treats at different centers within the city limits, and c) ROP specialist performs screening and treatment in a general/teaching hospital. Overall, the Economic Model of ROP (EcROP)[21] demonstrated that effective screening and treatment of infants with ROP provides more cost-saving (US= $949,261; Mexico= $ 413,869) and is more cost-effective than not having a screening program in place. ROP screening and treatment ranks as one of the highest cost-benefit profiles of any treatment in medicine, and the extrapolated data highly impact the socio-economic aspect.

ROP Ancillary Diagnostics

Fluorescein Angiogram (FA) in ROP. The advent of the wide-field neonatal and pediatric retinal imaging with FA led the way to demonstrate subtle vascular pathologies in ROP.[22] Vinekar[23] reported the use FA in post-laser infants with persistent active disease to reveal avascular areas still requiring treatment. Flat areas of neovascularization is more easily detected with FA, as are non-perfusion, vascular abnormalities and leakages in areas of vascularized retina.[24] With FA, there is an improved sensitivity for certain subtypes of ROP zone, stage, and category, as well as increase in inter-grader agreement for treatment-requiring ROP.[25,26] Serial FA is also useful in the evaluation of the peripheral retina because of the possibility of prolonged peripheral ischemia,

delayed normal retinal vascularization,[27] abnormal vascular patterns,[28] and late reactivation[29,30] that have been reported to occur in ROP patients treated with anti-VEGF agents.

Hand-Held Spectral Domain-Optical Coherence Tomography (SD-OCT). SD-OCT macular findings help provide insight on the macular changes in patients with ROP. Long-term morphological and functional results were correlated with foveal morphology seen in SD-OCT among children at risk for ROP.[31] Results revealed that 62% had absent or reduced foveal pit in children with severe ROP compared to 17% in preterm infants with no ROP. Findings in SD-OCT imaging have also been correlated with retinal and neurovascular development in premature babies with and without ROP.[32] Macular edema of ROP, retinal nerve fiber layer thinning, and delayed photoreceptor maturation were noted to be associated with functional and anatomic brain abnormalities, as well as poorer visual outcomes in these infants.[33,34,35,36] These reports implied that retinal development on OCT reflects a continuum of delayed, diseased, and abnormal neurovascular development of the brain and retina. Future studies are still needed to determine the precise indications and clinical utility of FA and SD-OCT in ROP. Binocular dilated indirect ophthalmoscopy remains to be the gold standard for ROP screening.[4]

ROP Treatment

When to Treat. The CRYO-ROP and the ETROP study provided the definitions and guidelines regarding the treatment of babies with acute ROP. The CRYO-ROP defined treatment for threshold ROP (five contiguous or 8 total clock-hours of stage 3, zone I or II, with plus disease) and ETROP study recommended treatment for type 1 ROP (zone I, any stage with plus; zone I, stage 3 without plus; and stage 2-3, zone II with plus).[1,2] Nevertheless, there have been anecdotal reports of certain cases of ROP milder than type 1 and threshold ROP (type 2 ROP) that also responded to early treatment. A multicenter prospective study[37] reviewed the treatment for eyes with disease milder than type 1 ROP. Out of 1444 eyes, 13 eyes were treated due to the following indications: fellow eye treated for type 1 ROP (15%), tangential traction with temporal vessel straightening (62%), severe stage 3 with concerns for progression to stage 4A (23%), persistent active ROP at late PMA (23%), vitreous hemorrhage (23%), and persistent retinal ischemia at an older age (8%). This study implied that the traditional classification system may not always capture the nuances of the qualitative nature of the disease and that the importance of individual clinical judgment in the treatment of these preterm babies cannot be overemphasized.

Treatment Practice Patterns. Retinal ablation of the peripheral avascular retina using laser photocoagulation has been the gold standard of treatment for type 1 ROP. However, treatment patterns seemed to change over the past decade. In a study of Tawse et al evaluating the treatment preferences of 302 ophthalmologists in the US,[38] 54% performed intravitreal anti-VEGF in type 1 ROP compared to 43% who preferred traditional laser. Preference for anti-VEGF over laser for initial treatment in zone I high-risk ROP with stage 3 and plus disease was also reported by the BEAT-ROP study which described that majority (78%) of the respondents preferred intravitreal bevacizumab (IVB) while 22% used intravitral ranibizumab (IVR) in all treatment scenarios presented.

Laser Photocoagulation. Vinekar[23] reported long-term outcomes of laser-treated ROP in the KIDROP program and described that green laser was comparable to the results of diode laser.[39] Other laser techniques, such as primary or secondary laser posterior to the ridge[40] and two-staged laser ablation of flat neovascularization in zone 1 APROP,[41] were also described. The 3 clinical scenarios wherein laser treatment were performed included smouldering ROP (24%), type 1 ROP (66%), and APROP or aggressive posterior ROP (10%). Smouldering ROP was defined as stage 2 ROP that persisted beyond 48 weeks post-menstrual age or more. Out of the 969 laser-treated eyes, there were no differences in vision among the 3 groups treated with over 2 years of follow up.

Intravitreal Bevacizumab. The results of the BEAT-ROP study[41] have shown significant benefit of intravitreal bevacizumab over laser for type 1 ROP (zone I, stage 3 with plus ROP). A retrospective review[42] reported the involution pattern of type 1 ROP following intravitreal bevacizumab treatment. Plus disease resolved as early as 8 days while stage 3 resolved in 4 weeks. Stage 1 or 2 ROP recurred after initial regression but did not require treatment nor resulted in unfavorable structural outcome. In a report of Mintz-Hittner,[43] there was no recurrence in 477 out of 513 eyes treated with bevacizumab monotherapy. In the 36 eyes with recurrence, the indication for treatment was APROP and stage

3 with plus. The risk factors for ROP recurrence were APROP and low BW, and recurrence occurred between 46-56 weeks adjusted age. It is recommended that if the progression of retinal vessels has stopped at 2-3 disc diameters from initial retinal vessel edge, examinations should continue until complete retinal vascularization occurs at around 70 weeks adjusted age.

Laser versus Bevacizumab. A retrospective review[44] compared the long-term outcomes of patients treated with laser and IVB. Refractive errors were seen in 28% of the lasered group versus 9% of the IVB group. Time to maturation of the retinal vasculature was delayed at 53 weeks in the IVB group while one child in the laser group required strabismus surgery and another needed retreatment. It was concluded that anti-VEGF therapy appeared to be as effective as laser in the treatment of ROP and may have better long-term outcomes but required longer follow up. A higher degree of myopia was also observed in the lasered group with no unfavorable structural outcomes. Similarly, Isaac and colleagues[45] also reported that there was no statistically significant difference in visual acuity at 2 years among preterms treated with IVB and laser. Li et al[46] also supported that there were no statistically significant differences in neurodevelopmental outcomes, along with VA, in IVB and lasered infants at 3 years after treatment. Contrastingly, Morin[47] described higher rates of neurodevelopmental impairment in the laser-treated group at 18-22 months.

Intravitreal anti-VEGF remains to be off-label for ROP. Although its efficacy for ROP has been documented, concerns for its long-term safety, timing and dosing remain to be resolved with future research.[48]

Summary and Future Directions

A global movement geared towards increasing awareness and preventing ROP is rising. As the demographic of infants with ROP changes over time, new data from middle-income countries are emerging as increasing number of babies with ROP are recognized to have long-term visual disability. The advent of new imaging technologies aids in the understanding on the pathology, pathophysiology, management, and long-term sequelae of this blinding disease. A potential shift in management toward the increasing use of anti-VEGF needs to be approached carefully as more studies are conducted with regard to its efficacy and safety in ROP. Ultimately, knowledge and a better understanding of ROP will allow ophthalmologists to combat this debilitating disease and prevent children from suffering from a lifetime of blindness.

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