MedCrave
Step into the World of Research

Journal of Pediatrics and Neonatal Care

Review Article

Open Access

CrossMark

Management of retinopathy of prematurity: an updated review

Abstract

Retinopathy of prematurity (ROP), previously named retrolental fibroplasia, is a vascular disease of the premature retina that appeared after the advances in preterm neonatal care, potentially causing irreversible vision loss. The most vital part of ROP management is reducing modifiable risk factors such as blending protocols for oxygen delivery, rigorous infection control, restrictive blood transfusion strategies, and parents' education. Laser remains a highly effective therapeutic modality and the gold standard of care in most ROP cases. On the other hand, Anti-VEGF agents emerged as a potential solution to clinical situations where laser delivery is not feasible, as in poor pupillary dilatation with advanced tunica vasculosa lentis (TVL), vitreous haze, corneal opacification, rubeosis iridis, and vitreous hemorrhage. The current recommendations indicate surgery for ROP stages 4-5. For stage 4, surgical modalities incorporate scleral buckling and lens-sparing vitrectomy (LSV).

Keywords: Retinopathy of prematurity, Neonates, Management

Volume 12 Issue 1 - 2022

Khaled El-Atawi,[1] Nayef Alansari,[2] Mahmoud ElHalik,[3] Amani Abdelsamed,[4] Rim Mahfouz[5]

[1]Consultant Neonatologist, Pediatric Department, UAE
[2]Pediatric Ophthalmologist, Dr. Sulaiman Alhabib Hospital, UAE
[3]Consultant Neonatologist, Head of Neonatal Intensive Care Unit, LWCH, UAE, Neonatologist, Pediatric Department, UAE
[4]Senior Specialist, Pediatric Department, NICU, LWCH, UAE
[5]Specialist Registrar, Pediatric Department, UAE

Correspondence: Dr. Khaled El-Atawi, Consultant Neonatologist, Pediatric Department, NICU, LWCH, UAE, Email kelatawi@eim.ae

Received: January 03, 2022 | **Published:** February 22, 2022

Introduction

Retinopathy of prematurity (ROP), previously named retrolental fibroplasia, is a vascular disease of the premature retina that appeared after the advances in preterm neonatal care, potentially causing irreversible vision loss.[1] Increasing numbers of preterm deliveries throughout the world have made ROP a leading cause of childhood blindness.[2] Therefore, detecting ROP in newborns as early as possible is critical. Physicians must be aware of children at risk and ensure that they receive adequate screening, monitoring, and management. In this mini-review, we aimed to shed light on the incidence, pathogenesis, risk factors, and classifications of ROP, as well as the appropriate screening tools and recent management approaches.

Incidence of ROP

In 2010, a large meta-analysis estimated the global prevalence of ROP around 21.7% among preterm infants.[3] The World Health Organization (WHO) defines preterm birth as any birth under 37 weeks of gestation or fewer than 259 days from the last menstrual period, and subdivides it based on gestational age (GA) into: extremely preterm (<28 weeks); very preterm (28-32 weeks); and late preterm (>32 weeks).4 Globally, over 15 million babies are born preterm each year, with resulting complications that disproportionately burden low and middle-income countries (LMIC) relative to high-income countries (HIC).[5]

The incidence of ROP varies significantly across countries depending on the socio-economic developments and healthcare systems quality.[6] Data from HIC report an incidence of 9.9% in very preterm and 56-67.1% in extremely preterm babies.[7,8] Even though ROP shows a growing trend in HIC, it reflects the increasing number of infants born extremely preterm and required advanced management in the Neonatal Intensive Care Unit (NICU).[8] In LMIC, literature estimates ROP prevalence around 20.2-48% in Asia, 6.1- 41.7% in Africa, and 12.7-37% in Latin America.[3,9–12] Among LMIC, the South Asian and Sub-Saharan Afri¬can countries nearly account for two-thirds of the global prevalence of ROP.[3]

Historically, ROP incidence had two prominent peaks. The first one in the 1950s, following the widespread use of supplemental oxygen for pre¬mature babies with the inadequate understanding of ROP pathology.[13] The second peak has grown since 2000 due to the significant increase in survival of very pre¬term infants.[13] However, the two peaks gradually declined only in HIC. While the current challenging peak of ROP incidence in HIC lies with extremely preterm babies, LMIC still faces the old challenges with even more developing premature infants.[14]

ROP risk factors

The most critical risk factors for ROP are advanced prematurity, low birth weight (LBW), and small for gestational age (SGA).[15] Furthermore, several postpartum factors potentially lead to the development of ROP. These factors involve unrestricted use of high saturation supplemental oxygen, continuous positive pressure ventilation, respiratory distress syndrome, apnea, septicemia, intraventricular hemorrhage, blood transfusion, and poor weight gain.[9,16,17] Since the progress in neonatal care did not accompany comparable progress in ROP screening for most LMIC, the lack of standardized screening protocols is becoming a significant risk factor.[14]

Pathogenesis of ROP

Under normal circumstances, retinal vasculature develops through vasculogenesis, de novo syntheses of vessels, and angiogenesis, forming newer vessels from preexisting ones.18 During the 12th week's gestation, vasculogenesis begins with vascular precursor cells (VPCs) that create the hyaloid artery, then the posterior retinal arcades and vascular cords with the mesenchymal cells aggregates until the 22nd weeks' gestation.[18] Meanwhile, angiogenesis starts at the 18th weeks' gestation forming perifoveal vasculature, deep plexus vessels, and peripheral retinal capillaries till reaching the ora serrata with the 36th weeks' gestation.[18] Since developing retinal tissues show a higher oxygen demand, leading to relative hypoxia, the local expression of Vascular endothelial growth factor (VEGF) is increased; thus, new vessels grow toward VEGF stimuli in distant hypoxic areas.[18,19]

Accordingly, the process of retinal vasculature is essentially hypoxia–driven and VEGF–mediated. In contrast, preterm infants reach a state of hyperoxia; due to atmospheric and supplemental oxygens, and their serum insulin-like growth factor 1 (IGF1) declines, leading to capillary vaso-obliteration and delayed retinal vascularization (Phase 1 of ROP).[19] Shortly after, the peripheral retina suffers severe hypoxic injury releasing a high amount of VEGF and IGF1, which potentiates angiogenesis further.[19] However, abnormal vessels grow towards VEGF stimuli in the vitreous, and pathological vaso-proliferation overtakes the normal angiogenesis (Phase 2 of ROP).[18,19]

Classification of ROP

The most recent version of the International Classification of ROP (ICROP) classifies ROP based on disease severity (stages), antero-posterior locations (zones), peripheral extent, and presence/absence of plus disease.[20] Typically, ROP passes through five progressive stages. The first stage shows a grayish-white demarcating line along the vascular- avascular retinal junction.[21]

In the second stage, the same line progresses into an elevated ridge. Then, an extra-retinal fibrovascular proliferation appears in the third stage with the former ridge.[21] The fourth stage has two phases; A and B, subtotal retinal detachment sparing the fovea and affecting the fovea, respectively. Eventually, the retina totally detaches during the fifth stage in the form of open or closed funnels. Advanced stages of ROP can present with leukocoria, falciform retinal fold, and shrunken nonfunctional eyes (phthisis bulbi).[20,21]

Likewise, ROP has three zones. Zone 1 lies within an imaginary circle that has a radius between the optic disc and the fovea but twice the distance.[20] In contrast, Zone II extends outside the circle towards the nasal ora serrata, while Zone III reaches the residual crescent of the temporal retina. ROP extents can be measured by numbers of 30-degree sectors or clock hours within retinopathy areas.[20] Accordingly, ICROP defined plus disease as having two or more quadrants of venous dilation (>6 clock hours) and arteriolar tortuosity in the posterior aspect of the retina.[20,22]

Other associations with the plus disease include pupil rigidity, vitreous haze, and iris neovascularization. ICROP also described another critical form of ROP, identified as Aggressive Posterior ROP (APROP), which progresses directly to the last stage without passing through the intermediate stages.[22] Notably, APROP correlates with a fast-evolving plus disease, posterior Zone II locations, vascular loops, and intraretinal neovascularization.[23]

Screening of ROP

Current North American and European guidelines recommend ROP screening for all newborns with LBW ≤1500g or SGA ≤30 weeks besides those of LBW 1500-2000g or SGA >30 weeks who require cardiopulmonary support.[24–26] However, following these recommendations, the literature revealed that ROP incidence in infants >1250 g was 5–44.9%, while 6.2% of visual impairment occurred in those >32 weeks gestation.[27,28] Further studies in the Asian population showed that the American and European suggested cut-off missed 17.7-22.6% of preterm babies with severe ROP, and 57.6% of the diagnosed infants were heavier and older than their western counterparts.[29,30]

Therefore, many LMICs have developed different ROP-screening protocols based on their regional variation.14 For instance, updated Indian guidelines recommend early ROP screening (within the first four weeks of life) for all newborns with LBW ≤2000g or SGA ≤34 weeks besides those of SGA 34-36 weeks with additional risk factors.[31] Likewise, Chinese guidelines suggested a cut-off of SGA <34 weeks or LBW<2000g, while in Turkey and Egypt, the cut-off of LBW was < 1700g and < 1500g, respectively.[32–34]

Typical ROP screening needs an experienced ophthalmologist to perform dilated eye examinations through a binocular indirect ophthalmoscope (BIO), which is the standard method.[35] Despite the growing number of preterm infants who require ROP screening, only a limited number of trained ophthalmologists is present, resulting in an enormous workload and delayed surveillance.[14] For instance, the United States has only 1504 ophthalmologists, and only 11% of them can perform ROP screenings, while Canada has only 100 subspecialists responsible for more than 12,150 ROP examinations each year.[35]

Meanwhile, novel screening methods through telemedicine-captured retinal images and digital retinal photography (DRP) emerged as potential alternatives. After the successful experience with tele-screening programs in LMIC, such as the KIDROP model in India, the recent United Nations Development Program (UNDP) report strongly suggested DRP as a new gold standard tool for ROP screening.[36] Unlike BIO, DRP does not require advanced experience; and by utilizing a 130° wide-angle hand-held camera over the cornea, it potentially diagnoses over 90% of ROP cases.[37] A recent meta-analysis estimated DRP sensitivity and specificity over 80%, with positive and negative predictive values of 79% and 88.4%, respectively.[38]

Treatment of ROP

The most vital part of ROP management is reducing modifiable risk factors such as blending protocols for oxygen delivery, rigorous infection control, restrictive blood transfusion strategies, and parents' education.[39]

A. Blended oxygen supplementation

In the Neonatal Oxygen Prospective Meta-analysis (NeOProM) study, infants who received lower oxygen saturation >89% had a significantly lower incidence of severe ROP (RR=0.72) but a higher incidence of death (RR=1.16).[40] A recently updated meta-analysis reported the same findings, with emphasis on mortality risk.[41] Therefore, the current American guidelines recommend an oxygen saturation target >90% in extremely LBW neonates.[42]

However, the question remained: What is the oxygen saturation target that can reduce both ROP and mortality risks, if any. In an attempt to find the answer, two recent studies recommended a balanced strategy that significantly decreased the incidence of severe ROP without increasing mortality.[43,44] This dynamic strategy involves a gradual elevation of oxygen saturation ranges, thus preventing early hyperoxia and succeeding retinal hypoxia relative to the static oxygen titration strategies.[43,44]

B. Laser photocoagulation and cryotherapy

Current laser recommendations in ROP evolved from the findings of Early Treatment for Retinopathy of Prematurity Cooperative Group (ETROP) trials. ETROP recommends laser photocoagulation treatment in any of the following: ROP type I; APROP; ROP zone I in stage 1-3 with plus; ROP zone I in stage 3 without plus; or ROP zone II in stage 2-3 with plus disease.[45]

Technically, indirect infrared diode lasers or four-frequency doubled Nd: YAG lasers are applied through the Laser indirect ophthalmoscope (LIO) as a delivery media.[45] Furthermore, the laser ablates the whole avascular retina up to the ora serrata.46. Multiple

centers in HIC replaced the diode laser with the 532 nm green laser.[47] A modified laser version also became convenient for usage inside transparent incubators for the critically ill neonates who highly depend on NICU for survival.[46]

Laser remains a highly effective therapeutic modality and the gold standard of care in most ROP cases.[41] Nearly 93% and 100% of threshold and pre-threshold ROP, respectively, regress after laser therapy.[48,49] Even in APROP, it reaches an efficacy range of 71.4–84%.[50] Likewise, laser therapy showed highly favorable outcomes in LMIC, with over 96% success rates for type 1 ROP.[49]

Although the laser effect on APROP is rela¬tively poor, recent studies reported better safety and structural outcomes in treated eyes.[51] Literature also identified individual risk factors that can hinder the laser effect and induce retinal detachments despite confluent photocoagulation.[51] These risk factors involve the presence of posterior ROP Zone 1, SGA < 29.5 weeks, pre-retinal hemorrhage, and preexisting fibrovascular proliferation.[51,52]

On the other hand, laser therapy significantly increases the risk of peripheral vision loss, cataracts, myopia, and phthisis bulbi.[53] In a recent meta-analysis, laser therapy correlated with shallower diameters of the anterior chamber, reduced spherical equivalent, and higher incidence of myopia and astigmatism.[54] Accordingly, long-term follow-ups of treated children are essential to evaluate possible refractive errors. Myopia and strabismus, the commonest, showed a significant association with severe ROP and notable structural sequelae.[55]

Cryotherapy appeared in line with laser photocoagulation, consisting of scleral, choroidal retina freezing, and resulted in a nearly 50% reduction in retinal detachments.[56] However, cryotherapy had multiple drawbacks, such as being relatively difficult, time-consuming, and demanding general anesthesia.[56] Updated guidelines, therefore, minimized its role after the findings of ETROP trials, where pe-threshold laser showed a better reduction in unfavorable structural sequelae from 15.6% to 9.1% relative to thresholds.[45]

C. VEGF inhibitors

Anti-VEGF agents emerged as a potential solution to clinical situations where laser delivery is not feasible, as in poor pupillary dilatation with advanced tunica vasculosa lentis (TVL), vitreous haze, corneal opacification, rubeosis iridis, and vitreous hemorrhage.[57] They have the advantage of feasibility, less structural complication, minimal risks for refractive errors, and reaching the ischemic posterior pole.[57] Being the first suggested anti-VEGF for ROP, Bevacizumab is a recombinant monoclonal antibody used to treat several cancers such as glioblastoma, renal, colon, and lung carcinomas when given systematically; and macular degeneration or retinopathy, when given intravitreally.[58,59] Other Anti-VEGF agents include intravitreal ranibizumab (IVR) and intravitreal aflibercept (IVA).[60]

After the findings of the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study, anti-VEGF agents gained more credentials in treating ROP.[57] In the BEAT-ROP study, intravitreal bevacizumab (IVB significantly reduced the recurrence rate (4%) compared to conventional laser (22%), particularly for ROP Zone I.[57] Furthermore, IVB can be used as monotherapy, or combined with laser therapy, as a rescue medication after failed laser. In advanced ROP stages 3-4, a combined laser with IVB significantly reduced arteriolar tortuosity and venous dilatation without recurrence.[61] Likewise, IVR used for APROP with vitreous hemorrhage significantly improved the fundus visibility for the following laser therapy with 92% more favorable anatomical outcomes.[62]

Unfortunately, the literature has no definite agreement on optimal dosage and follow-up strategy, but most studies administered a dose of 0.625 mg/0.025 ml for IVB and 0.25 mg/0.025 ml for IVR for each eye.[14] Since anti-VEGF inhibitors do not entirely terminate pathological angiogenesis, the persistence of peripheral avascular retina can develop late recurrences of ROP.[63] Recent studies reported late reactivation after a period that ranges from 4 weeks to 2.5 years following anti-VEGF monotherapy.[63,64] Also, because of the vital role of VEGF in the tissue development of preterm infants, anti-VEGs may increase the risk of neurodevelopmental delays; yet current studies fail to affirm or refute the risk.[65,66] Accordingly, anti-VEGF therapy should be administered in selected cases as rescue treatment combined with laser photocoagulation until further evidence arises.

When compared with laser treatment, a meta-analysis of ten studies showed that the incidence of retreatment was significantly higher in anti-VEGF group (OR= 2.52, 95% CI: 1.37 - 4.66; p= 0.003) compared to the laser treatment, while the incidences of myopia and eye complications were significantly lower with anti-VEGF compared to the laser treatment (OR= 0.29, 95% CI: 0.10 - 0.82; p=0.02). However, there was no difference in the recurrence incidence (p=0.45) and time between treatment and retreatment (p =0.12).[67] Another meta-analysis demonstrated that using anti-VEGF instead of laser photocoagulation may lower the chance of refractive errors. Anti-VEGF therapy was associated with low retinal detachment, lens or corneal opacity requiring surgery, and post-discharge mortality. Finally, the data are insufficient to determine if anti-VEGF, compared to laser photocoagulation, enhances the recurrence of ROP.[68]

D. Surgical interventions

Current recommendations indicate surgery for ROP stages 4-5. For stage 4, surgical modalities incorporate scleral buckling and lens-sparing vitrectomy (LSV).[24,69] While stage 5 requires further lensectomy along with vitrectomy (LV) or open-sky vitrectomy (OSV).69,70. The risk of poor surgical outcomes is higher in infants with no prior laser or VEGF treatment, narrow-narrow funnel configuration, and late presentation, which has the worst prognosis once retrolental fibroplasia develops.[71]

While the success rates of these modalities in stage 4 range from 84-100%, it only reaches 14.3-45.5% in stage 5.69,70 Likewise, the recurrence rate of retinal detachment in stage 5 extends to over 22% of cases compared to 5% in stage 4.[72] Recent studies suggested the use of pre-operative IVB, which significantly shortened the operation time by 26 min, reduced the recurrence by 30%, and induced better visual outcomes in 88% of cases.[73] Otherwise, currently studied novel techniques such as plasmin-assisted vitrectomy show promising results, awaiting future evidence and recommendations.[74]

E. Adjuvant therapy; beta-blockers, human milk, vitamin A and E

A recent Cochrane systematic review and meta-analysis revealed that oral beta-blockers significantly reduced the need for anti-VEGF agents (RR=0.32) and laser therapy (RR=0.54), with a number needed to treat around only 12-18 cases of ROP.[75] Besides, oral beta-blockers significantly hindered the progression to stage 3 (RR=0.60).[75]

Another meta-analysis on the benefits of human milk showed an overall reduction in the risk of ROP development for extremely premature infants compared to formula feeding (OR=0.31).[41]

Similarly, meta-analyses on Vitamin A and E supplementations reported a significant reduction in ROP incidence with better retinal functions in premature infants (OR=0.27 and 0.30, respectively).[41] At the moment, these therapeutic modalities can be used as adjuvants to the standard therapy until further evidence emerges.

F. The limitations of currently available therapy options

There are currently no approved drugs for treating ROP in neonates, and the usual treatment for severe ROP depends on surgical techniques such as laser therapy or cryotherapy. Surgical techniques save vision in most of the visual field but not in the periphery. General anesthesia may be required in premature infants.[76] Limited surgical options and a growing understanding of ROP pathophysiology have prompted research into pharmacologic treatments, such as anti-VEGF, which are routinely used to treat severe ROP.[77] Compared to traditional surgical techniques, this drug class has revolutionized the treatment of neovascular retinopathies.[78] However, anti-VEGF therapies have limitations in patients with ROP. For example, VEGF is a neuroprotective factor, and its loss in the retina may disrupt the neurovascular homeostasis, causing retinal injury.[79] Furthermore, anti-VEGF diffusion into the blood may reduce serum VEGF levels, affecting physiological angiogenesis or tissue growth.[80] However, the ideal VEGF serum level in preterm newborns is undetermined. Some of the mentioned limitations of anti-VEGF usage may be addressed by medications acting upstream of VEGF and targeting mechanisms influencing VEGF synthesis. In this regard, propranolol looks favorable. Its safety profile in premature infants has to be evaluated more thoroughly, although it seems promising. First, it prevents ROP development when used topically, eliminating intravitreal injections and their associated adverse effects.[75,81] Second, propranolol does not reduce VEGF levels in the retina, but rather restores them to normal levels, indicating no neurovascular adverse effects.[82] Third, propranolol had no effect on VEGF levels in organs other than the retina in the oxygen-induced retinopathy mouse model, indicating a safe systemic profile for developing organs and tissues.[82] Most of the above-mentioned pharmaceutical treatments target the second phase of ROP when hypoxia-induced increased production of proangiogenic factors induces pathologic angiogenesis. As a result, the potential benefit of medications like anti-VEGF, propranolol, and others is generally lower than anticipated. Treatment of ROP pharmacologically may be improved if it is possible to intervene early in the disease.

G. Future directions

The ROP treatment paradigm should shift from curative (second phase) to preventative (treatment during the first phase). Preclinical investigations have shown the usefulness of preventative measures. For example, studies on animal models showed that administration of systemic retinoic acid dosing during the hyperoxic phase of ROP help in controlling VEGF levels, preventing VEGF overexpression and retinal neovascularization. Similar findings were achieved with 17ß-estradiol.[83] Adenosine A2A receptor antagonists appear to work differently, preventing retinal neovascularization by decreasing reactive oxygen species.[84] Moreover, reduced vaso-obliteration during the first hyperoxic phase may reduce neovascularization (and the resulting visual damages) during the second hypoxic phase. Lowering hyperoxic phase strength to reduce disease effect may be useful in other retinal disorders besides ROP. Although further research is needed in animal models and randomized human trials to assess the safety of medications targeting the early phase of ROP, the results so far are encouraging and suggest that treating extremely low birth weight preterm infants before ROP manifests may be helpful.

References

1. World Health Organization. Born too soon: the global action report on preterm birth. 2012.
2. Bashinsky AL. Retinopathy of Prematurity. *N C Med J.* 2017;78:124–128.
3. Blencowe H, Lawn JE, Vazquez T, et al. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. *Pediatr Res.* 2013;74Suppl 1:35–49.
4. Quinn J-A, Munoz FM, Gonik B, Frau L, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine.* 2016;34:6047–6056.
5. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet (London, England).* 2016;388:3027–3035.
6. 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 for screening programs. *Pediatrics.* 2005;115:e518–525.
7. Venincasa VD, Bugg V, Dvorak J, et al. Temporal Profile of Retinopathy of Prematurity in Extremely Premature Compared to Premature Infants. *J Pediatr Ophthalmol Strabismus.* 2019;56:116–123.
8. Isaza G, Donaldson L, Chaudhary V. Increased incidence of retinopathy of prematurity and evolving treatment modalities at a Canadian tertiary centre. *Can J Ophthalmol.* 2019;54:269–274.
9. Azami M, Jaafari Z, Rahmati S, et al. Prevalence and risk factors of retinopathy of prematurity in Iran: a systematic review and meta-analysis. *BMC Ophthalmol.* 2018;18:83.
10. Edy Siswanto J, Sauer PJ. Retinopathy of prematurity in Indonesia: Incidence and risk factors. *J Neonatal Perinatal Med.* 2017;10:85–90.
11. Onyango O, Sitati S, Amolo L, et al. Retinopathy of prematurity in Kenya: prevalence and risk factors in a hospital with advanced neonatal care. *Pan Afr Med J.* 2018;29:152.
12. Fortes Filho JB, Borges Fortes BG, Tartarella MB. Incidence and main risk factors for severe retinopathy of prematurity in infants weighing less than 1000 grams in Brazil. *J Trop Pediatr.* 2013;59:502–506.
13. Quinn GE. Retinopathy of prematurity blindness worldwide: phenotypes in the third epidemic. *Eye Brain.* 2016;8:31–36.
14. Sen P, Wu W-C, Chandra P, et al. Retinopathy of prematurity treatment: Asian perspectives. *Eye (Lond).* 2020;34:632–642.
15. Chang JW. Risk factor analysis for the development and progression of retinopathy of prematurity. *PLoS One.* 2019;14:e0219934.
16. Lin L, Binenbaum G. Postnatal weight gain and retinopathy of prematurity. *Semin Perinatol.* 2019;43:352–9.
17. Chen ML, Guo L, Smith LEH, et al. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. *Pediatrics.* 2010;125:e1483–492.
18. Heidary G, Vanderveen D, Smith LE. Retinopathy of prematurity: current concepts in molecular pathogenesis. *Semin Ophthalmol.* 2009;24:77–81.
19. Smith LE, Hard A-L, Hellström A. The biology of retinopathy of prematurity: how knowledge of pathogenesis guides treatment. *Clin Perinatol.* 2013;40:201–214.
20. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol (Chicago, Ill 1960).* 2005;123:991–999.
21. Miri M, Amini Z, Rabbani H, Kafieh R. A Comprehensive Study of Retinal Vessel Classification Methods in Fundus Images. *J Med Signals Sens.* 2017;7:59–70.

Citation: El-Atawi K, Alansari N, ElHalik M, et al. Management of retinopathy of prematurity: an updated review. *J Pediatr Neonatal Care.* 2022;12(1):24–29. DOI: 10.15406/jpnc.2022.12.00452

22. Ghergherehchi L, Kim SJ, Campbell JP, et al. Plus Disease in Retinopathy of Prematurity: More Than Meets the ICROP? *Asia-Pacific J Ophthalmol (Philadelphia, Pa).* 2018;7:152–155.

23. Hewing NJ, Kaufman DR, Chan RVP, et al. Plus disease in retinopathy of prematurity: qualitative analysis of diagnostic process by experts. *JAMA Ophthalmol.* 2013;131:1026–1032.

24. Fierson WM. Screening Examination of Premature Infants for Retinopathy of Prematurity. *Pediatrics.* 2018;142.

25. Jefferies AL. Retinopathy of prematurity: An update on screening and management. *Paediatr Child Health.* 2016;21:101–108.

26. Maier RF, Hummler H, Kellner U, et al. [Guidelines for ophthalmological screening of premature infants in Germany (S2k level, AWMF guidelines register no. 024/010, March 2020) : Joint recommendation of the German Ophthalmological Society (DOG), Retinological Society (RG), Professional Association of Ophthalmologists in Germany e. V. (BVA), German Society of Paediatrics and Adolescent Medicine (DGKJ), Professional Association of Pediatricians (BVKJ), Federal Association "The Premature Child" , Society for Neonatology and Paediatric Intensive Care Medicine (GNPI)]. *Ophthalmologe. 2021*;118:117–131.

27. Jalali S, Matalia J, Hussain A. Modification of screening criteria for retinopathy of prematurity in India and other middle-income countries. *Am J Ophthalmol.* 2006;141:966–968.

28. Lawn JE, Davidge R, Paul VK, et al. Born Too Soon: Care for the preterm baby. *Reprod Health.* 2013;10:S5.

29. Vinekar A, Dogra MR, Sangtam T, et al. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: ten year data from a tertiary care center in a developing country. Indian J *Ophthalmol.* 2007;55:331–336.

30. Hungi B, Vinekar A, Datti N, et al. Retinopathy of Prematurity in a rural Neonatal Intensive Care Unit in South India--a prospective study. *Indian J Pediatr*. 2012;79:911–915.

31. Singh AK, Kumar R, Mishra CK, et al. Moving from Survival to Healthy Survival through Child Health Screening and Early Intervention Services Under Rashtriya Bal Swasthya Karyakram (RBSK). *Indian J Pediatr.* 2015;82:1012–1018.

32. Xu Y, Zhou X, Zhang Q, et al. Screening for retinopathy of prematurity in China: a neonatal units-based prospective study. *Invest Ophthalmol Vis Sci.* 2013;54:8229–8236.

33. Bas AY, Demirel N, Koc E, et al. Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. *Br J Ophthalmol.* 2018;102:1711–1716.

34. Hadi AMA, Hamdy IS. Correlation between risk factors during the neonatal period and appearance of retinopathy of prematurity in preterm infants in neonatal intensive care units in Alexandria, Egypt. *Clin Ophthalmol.* 2013;7:831–837.

35. Karunatilake M, Daspal S, Mugarab Samedi V, et al. Screening for Retinopathy of Prematurity Through Utilization a Pediatric Retinal Camera at Jim Pattison Children's Hospital: A Vision for Improved Care. *Glob Pediatr Heal.* 2021;8:2333794X211039642.

36. Dogra MR, Katoch D, Dogra M. An Update on Retinopathy of Prematurity (ROP). *Indian J Pediatr.* 2017;84:930–936.

37. Wilson CM, Ells AL, Fielder AR. The challenge of screening for retinopathy of prematurity. *Clin Perinatol.* 2013;40:241–259.

38. Athikarisamy SE, Patole S, Lam GC, et al. Screening for retinopathy of prematurity (ROP) using wide-angle digital retinal photography by non-ophthalmologists: a systematic review. *Br J Ophthalmol.* 2015;99:281–288.

39. Mutlu FM, Sarici SU. Treatment of retinopathy of prematurity: a review of conventional and promising new therapeutic options. *Int J Ophthalmol.* 2013;6:228–236.

40. Askie LM, Darlow BA, Davis PG, et al. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database Syst Rev.* 2017;4:CD011190.

41. Raghuveer TS, Zackula R. Strategies to Prevent Severe Retinopathy of Prematurity: A 2020 Update and Meta-analysis. *Neoreviews.* 2020;21:e249–63.

42. Cummings JJ, Polin RA. Oxygen Targeting in Extremely Low Birth Weight Infants. Pediatrics. 2016;138(2):e20161576. *Pediatrics.* 2016;138.

43. Cayabyab R, Arora V, Wertheimer F, et al. Graded oxygen saturation targets and retinopathy of prematurity in extremely preterm infants. *Pediatr Res.* 2016;80:401–406.

44. Colaizy TT, Longmuir S, Gertsch K, et al. Use of a Supplemental Oxygen Protocol to Suppress Progression of Retinopathy of Prematurity. *Investig Opthalmology Vis Sci.* 2017;58:887.

45. Good W V. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc.* 2004;102:233–250.

46. Singh SR, Katoch D, Handa S, et al. Safety and efficacy of 532 nm frequency-doubled Nd-YAG green laser photocoagulation for treatment of retinopathy of prematurity. *Indian J Ophthalmol*. 2019;67:860–865.

47. Dikci S, Demirel S, Fırat PG, et al. Comparison of Nd:YAG laser (532 nm green) vs diode laser (810 nm) photocoagulation in the treatment of retinopathy of prematurity: an evaluation in terms of complications. *Lasers Med Sci.* 2020;35:1323–1328.

48. Dhawan A, Dogra M, Vinekar A, et al. Structural sequelae and refractive outcome after successful laser treatment for threshold retinopathy of prematurity. *J Pediatr Ophthalmol Strabismus.* 2008;45:356–61.

49. Katoch D, Sanghi G, Dogra MR. Structural sequelae and refractive outcome 1 year after laser treatment for type 1 prethreshold retinopathy of prematurity in Asian Indian eyes. Indian J *Ophthalmol.* 2011;59:423–426.

50. Kumawat D, Sachan A, Shah P, et al. Aggressive posterior retinopathy of prematurity: a review on current understanding. *Eye (Lond).* 2021;35:1140–1158.

51. Sanghi G, Dogra MR, Katoch D, et al. Aggressive posterior retinopathy of prematurity in infants ≥ 1500 g birth weight. *Indian J Ophthalmol.* 2014;62:254–257.

52. Ahn YJ, Hong KE, Yum HR, et al. Characteristic clinical features associated with aggressive posterior retinopathy of prematurity. *Eye (Lond).* 2017;31:924–930.

53. Gunay M, Sekeroglu MA, Celik G, et al. Anterior segment ischemia following diode laser photocoagulation for aggressive posterior retinopathy of prematurity. *Graefe's Arch Clin Exp Ophthalmol = Albr von Graefes Arch Fur Klin Und Exp Ophthalmol.* 2015;253:845–848.

54. Liang J. Systematic review and meta-analysis of the negative outcomes of retinopathy of prematurity treated with laser photocoagulation. *Eur J Ophthalmol.* 2019;29:223–228.

55. Quinn GE, Dobson V, Davitt B V, et al. Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity study: findings at 4 to 6 years of age. *J AAPOS Off Publ Am Assoc Pediatr Ophthalmol Strabismus.* 2013;17:124–128.

56. Palmer EA, Hardy RJ, Dobson V, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol (Chicago, Ill 1960).* 2005;123:311–318.

57. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med.* 2011;364:603–315.

58. Abdel-Maboud M, Menshawy E, Bahbah EI, et al. Intravitreal bevacizumab versus intravitreal triamcinolone for diabetic macular edema-Systematic review, meta-analysis and meta-regression. PLoS *One.* 2021;16:e0245010.

59. Garcia J, Hurwitz HI, Sandler AB, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. *Cancer Treat Rev.* 2020;86:102017.

60. Huang C-Y, Lien R, Wang N-K, et al. Changes in systemic vascular endothelial growth factor levels after intravitreal injection of aflibercept in infants with retinopathy of prematurity. *Graefe's Arch Clin Exp Ophthalmol = Albr von Graefes Arch Fur Klin Und Exp Ophthalmol.* 2018;256:479–487.

61. Raizada S, Al Kandari J, Al Foudari A. Early experience with intravitreal bevacizumab combined with laser treatment for retinopathy of prematurity. *Middle East Afr J Ophthalmol.* 2011;18:196–197.

62. Xu Y, Kang X, Zhang Q, et al. Combination of Intravitreal Injection of Ranibizumab and Photocoagulation for the Treatment of Aggressive Posterior Retinopathy of Prematurity with Vitreous Hemorrhage. J *Ophthalmol.* 2016;2016:5029278.

63. Hu J, Blair MP, Shapiro MJ, et al. Reactivation of retinopathy of prematurity after bevacizumab injection. *Arch Ophthalmol (Chicago, Ill 1960).* 2012;130:1000–1006.

64. Snyder LL, Garcia-Gonzalez JM, Shapiro MJ. Very Late Reactivation of Retinopathy of Prematurity After Monotherapy With Intravitreal Bevacizumab. *Ophthalmic Surg Lasers Imaging Retina.* 2016;47:280–283.

65. Wu W-C, Shih C-P, Lien R, et al. SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR AFTER BEVACIZUMAB OR RANIBIZUMAB TREATMENT FOR RETINOPATHY OF PREMATURITY. *Retina.* 2017;37:694–701.

66. Morin J, Luu TM, Superstein R, et al. Neurodevelopmental Outcomes Following Bevacizumab Injections for Retinopathy of Prematurity. *Pediatrics.* 2016;137.

67. Li Z, Zhang Y, Liao Y, et al. Comparison of efficacy between anti-vascular endothelial growth factor (VEGF) and laser treatment in Type-1 and threshold retinopathy of prematurity (ROP). *BMC Ophthalmol.* 2018;18:19.

68. González C R, Díaz C M, Garretón C R. Anti-vascular endothelial growth factor (VEGF) drugs compared to laser photocoagulation for treatment of type 1 retinopathy of prematurity. *Medwave.* 2022;22:e8507.

69. Bhende P, Gopal L, Sharma T, et al. Functional and anatomical outcomes after primary lens-sparing pars plana vitrectomy for Stage 4 retinopathy of prematurity. *Indian J Ophthalmol.* 2009;57:267–271.

70. Shah PK, Narendran V, Kalpana N. Anatomical and visual outcome of stages 4 and 5 retinopathy of prematurity. *Eye (Lond).* 2009;23:176–80.

71. Sen P, Jain S, Bhende P. Stage 5 retinopathy of prematurity: An update. *Taiwan J Ophthalmol.* 2018;8:205–15.

72. Kondo H, Arita N, Osato M, et al. Late recurrence of retinal detachment following successful vitreous surgery for stages 4B and 5 retinopathy of prematurity. *Am J Ophthalmol.* 2009;147:661–666.e1.

73. Xu Y, Zhang Q, Kang X, et al. Early vitreoretinal surgery on vascularly active stage 4 retinopathy of prematurity through the preoperative intravitreal bevacizumab injection. *Acta Ophthalmol.* 2013;91:e304–10.

74. Lee Y-S, Wang N-K, Chen Y-P, et al. Plasmin Enzyme-Assisted Vitrectomy in Pediatric Patients with Vitreoretinal Diseases. *Ophthalmic Res.* 2016;56:193–201.

75. Kaempfen S, Neumann RP, Jost K, et al. Beta-blockers for prevention and treatment of retinopathy of prematurity in preterm infants. *Cochrane Database Syst Rev.* 2018;3:CD011893.

76. Sinha R, Talawar P, Ramachandran R, et al. Perioperative management and post-operative course in preterm infants undergoing vitreo-retinal surgery for retinopathy of prematurity: A retrospective study. *J Anaesthesiol Clin Pharmacol.* 2014;30:258–262.

77. Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. *Cochrane Database Syst Rev.* 2018;1:CD009734–CD009734.

78. Seery CW, Betesh S, Guo S, et al. Update on the Use of Anti-VEGF Drugs in the Treatment of Retinopathy of Prematurity. *J Pediatr Ophthalmol Strabismus.* 2020;57:351–62.

79. Froger N, Matonti F, Roubeix C, et al. VEGF is an autocrine/paracrine neuroprotective factor for injured retinal ganglion neurons. *Sci Rep.* 2020;10:12409.

80. Stewart MW. The expanding role of vascular endothelial growth factor inhibitors in ophthalmology. *Mayo Clin Proc.* 2012;87:77–88.

81. Filippi L, Cavallaro G, Berti E, et al. Propranolol 0.2% Eye Micro-Drops for Retinopathy of Prematurity: A Prospective Phase IIB Study. *Front Pediatr.* 2019;7:180.

82. Cammalleri M, Locri F, Catalani E, et al. The Beta Adrenergic Receptor Blocker Propranolol Counteracts Retinal Dysfunction in a Mouse Model of Oxygen Induced Retinopathy: Restoring the Balance between Apoptosis and Autophagy. *Front Cell Neurosci.* 2017;11:395.

83. Zhang H, Wang X, Xu K, et al. 17β-estradiol ameliorates oxygen-induced retinopathy in the early hyperoxic phase. *Biochem Biophys Res Commun.* 2015;457:700–705.

84. Zhou R, Zhang S, Gu X, et al. Adenosine A2A receptor antagonists act at the hyperoxic phase to confer protection against retinopathy. *Mol Med.* 2018;24:41.