Introduction
Retinopathy of Prematurity (ROP) is a vision threatening disease of preterm babies which was first described in 1942. It was defined as a complex disease of retina involving abnormal proliferation of retinal blood vessels in premature infants. Once considered to be a virtually untreatable condition, this condition can be tackled at the earliest stage with proper management guidelines. Neonatal care and socioeconomic status of the country play important role in deciding the visual outcome in babies suffering from this disease. As India is seeing a great deal of preterm births and their increased survival rates immense increase in the ROP burden is expected in near future.

Epidemiology
There have been three distinct periods of “ROP epidemics”. First epidemic was in the early 1950s. Second epidemic occurred in the late 1960s. The third epidemic involved middle to low-income countries and was first recorded in the 1990s and is still on going. India is presently facing the third epidemic of ROP. The phenotype of ROP in Asian countries affects higher birthweight and higher gestational age premature babies. It is estimated that around 14.5 million children are born premature out of which 1,84,700 children develop any stage of ROP out of which 20,000 suffers blindness or severe visual impairment worldwide. It was reported that around 60-65% of premature babies are born in South Asia and Africa. India accounts for 3.5 million preterm births worldwide. According to the United Nations Children’s Fund (UNICEF) survey, it was estimated that around 21 million newborns were having low birth weight (LBW). India is contributing around 1.7 million cases (weight=<2500 g) and 0.4 million (weight=<1500 g), which is third highest incidence rate for LBW.

In high-income countries where most of the babies have an access to neonatal care, ROP-associated blindness is uncommon. But middle-low income countries like India, where there is a lack of infrastructure and capacity ROP related blindness becomes as high as 40% among total cases of childhood blindness, and incidence of ROP may vary between 38%-51.9%. In India, about 2,00,000 are at risk to develop ROP every year considering an incidence of preterm births out of which if about 10% develops treatable ROP, numbers of newborns requiring treatment will be 20,000 every year creating India to be among the worst affected countries with this disease.

Pathogenesis
The ROP pathogenesis is multifactorial where developmental, genetic, and environmental factors come into play. Vascular development in the pathogenesis of ROP is vital. Recently, Flynn et al. divided the retinal vascular development into two phases.

Vasculogenesis The first phase of retinal development begins around gestational age of 14 weeks to 21 weeks. Vascular Precursor Cells (VPCs from mesenchyme) exit the optic nerve and form the four major vessel arcades of the posterior retina.
Angiogenesis The second phase involves the endothelial cells proliferation and capillary formation from the existing blood vessels of first phase. Usually, by 8 months of gestation, the nasal retina gets vascularized and the temporal retina is usually formed by around gestational age of 40 weeks. Thus, at birth preterm babies have a variable extent of incompletely vascularized peripheral retina. After birth, the physiological hypoxia present in-utero is decreased, and after birth the infant is exposed to hyperoxia. The effect of oxygen on the retina on the immature vasculature has been described in two stages-

(1) Primary stage- This is vasoconstrictive stage occurring due to hyperoxia contributing to delayed retinal vascularization and there is reflex vasoconstriction of the capillaries and finally vaso-obliteration. This in turn leads to the suppression of VEGF.

(2) Secondary stage - This is vasoproliferative stage which starts with the shifting of the baby from oxygen to room air. The avascular retina and the developing retinal neurons suffer injury due to hypoxia leading to a sudden surge of VEGF into the vitreous cavity. At this time, there is rise in IGF1 levels which facilitates the effect of VEGF on the retinal angiogenesis resulting in abnormal proliferation of new vessels into the vitreous and tortuosity with dilatation of the retinal vessels with neovascularisation.

Other than VEGF, the role of Cytokines like tumor necrosis factor (TNF-α), interleukin-1β (IL-1β), and IL-6 acting as primary initiators of inflammation following infection or tissue damage were also documented but poorly investigated.

Many house-keeping genes also contribute to the development of the retina and it is suspected that genetic predisposition leads to an increased risk of development of ROP. These genes include angiotensin-converting enzyme (ACE), vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), endothelial nitric oxide synthase (eNOS), familial exudative vitreoretinopathy (FEVR) causing genes- FZD4, LRP5, TSPAN12, and NDP and variants in complement genes - CFH, CFB, FBLN5, CETP and CXCR4.

Risk Factors

ROP is a multifactorial disease where the prematurity itself is the most consistent and major contributing risk factor for ROP.

One of the largest multicentric trial on ROP, Cryotherapy for Retinopathy of Prematurity Cooperative Group (CRYO-ROP), reported that for every 100 gms increase in birth weight, there is a 27% decrease in the percentage of threshold ROP and also gave incidence among different gestation period (28-29 weeks= 83%; 30-31 weeks=60%; 32-33 weeks=50%). Various other postnatal factors like use of supplemental oxygen, multiplicity, sepsis, apnoea, surfactant therapy, mechanical ventilation, neonatal hyperbilirubinemia, patent ductus arteriosus, intraventricular hemorrhage, double volume exchange transfusion, administration of blood products, thrombocytopenia contribute towards ROP. The weight gain in post-natal life could be a predictor for ROP. WINROP (weight, insulin-like growth factor, neonatal ROP) study revealed that weight gain less than 50% of the birth weight by 6 weeks of life predicts the development of ROP with 100% sensitivity and IGF-1 levels at birth had 90% sensitivity for ROP prediction. The use of oxygen, especially in bigger Asian babies has been reported as a risk factor for developing Aggressive Posterior ROP (APROP) in India.

The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial 11 has suggested that there was no difference in ROP among two groups who were given different concentration of oxygen (96%-99% SaO2 vs 89%-94% SaO2) while the Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial (SUPORT) and Benefits of Oxygen Saturation Targeting Study II (BOOST II) study reported less ROP in 85%-89% SaO2 group as compared to 91%-95% SaO2 group but with increased mortality rates and greater survival rates in 91%-95% SaO2 group. In general consensus is to target oxygen levels greater than 90% saturation in order to reduce morbidity rate. Combination of one or more of the above reported factors maybe be important which requires further studies.

Maternal risk factors - Pre-eclampsia, maternal
essential hypertension, diabetes, and antihistaminics drug use. All these factors require further studies. In a recent meta-analysis any amount of human milk feeding was significantly associated with lower incidence of ROP.

**Screening of ROP**

ROP screening guidelines has aided in detecting newborns who are at risk of developing ROP and helped in closely monitoring their retinal development. These guidelines have helped to identify the severe form of disease requiring treatment and saving children's eyes from the unfavorable outcome which may lead to childhood blindness due to ROP. The screening guidelines are different in different countries depending upon the ROP phenotype.

In India, it has been observed that approximately 13.3% - 22.6% of ROP babies can be missed using the American and British screening guidelines. Hungi et al has reported ROP incidence in India up to 57.6% in older and heavier babies than the American guidelines for ROP screening.

National Neonatology Forum of India gave ROP screening guidelines that are being followed since 2010:

- a) Infants born < 34 weeks of gestation and/or weighing <1750 g or
- b) Heavier (1750-2000 g birth weight) or older babies (34–36 week gestation) if they have attending risk factors like mechanical ventilation, prolonged oxygen therapy, hemodynamic instability, or adverse respiratory or cardiac disease profile.

Rashtriya Bal Swasthya Karyakram (RBSK) formulated by the Ministry of Health and Family Welfare launched in June 2013 is a government initiative which has included ROP screening. In order to ensure screening of all eligible neonates, emphasis is laid on the first screening of ROP by day 30 of life irrespective of the gestational age or initial 3–4 weeks after birth. Infants < 28 weeks or < 1200g should be screened earlier than this, at 2–3 weeks of age to enable early identification and treatment of ROP.

Screening of ROP has to be done by a trained ophthalmologist in the presence of pediatrician under pupillary dilatation. The pupils are dilated using two drops of Phenylephrine 2.5%, Cyclopentolate 0.5% at 20 minutes interval. One must not forget to wipe the access drops as these could be life threatening to small babies due to absorption by the skin. Eye speculum with wire Vectis for globe rotation can be used by a beginner. These are also required for proper documentation of the disease. can

**Telescreening in ROP**

*RetCam*–based screening

Although, in ROP screening indirect ophthalmoscopy remains the gold standard, image-based examination and screening are gaining popularity. The introduction of digital widefield imaging systems has made it possible to perform fundus imaging using RetCam. This technique gives the dynamic image of the retina of the child and facilitates data transfer among ophthalmologists and from technicians to ophthalmologists for early referral. A set of five images of central, extreme nasal, temporal, superior and inferior field to visualize as much retina as possible is sufficient for telescreening. The use of 130 field of view lens usually suffices.

In the Karnataka Internet Assisted Diagnosis of Retinopathy of Prematurity (KIDROP) programme (www.kidrop.org) in India, the Neo camera (developed in India) was used to train doctors, ophthalmic imagers, optometrists, nurses, and paramedics, who were appointed not only to image but also to analyze the images at the first point of contact and it was seen decision making regarding treatment and referral had 93% specificity and 96% sensitivity. Positive predictive value (PPV) was 81.5% as compared to ROP experts. SUNDROP model reported 93.8% PPV. Thus, this recent advancement has provided a distinguished gateway for mass-telescreening in remote locations.

**Classification of ROP**

ROP was first classified in 1987 by The International Classification of Retinopathy Of prematurity (ICROP) to give one common language to the disease. The location of the disease was described on the basis of the three zones (anteroposterior location) all of which were centered around the disc and stages (severity) depending upon the presence of arteriovenous shunt vessels and neovascularisation.
In 2004, The Early Treatment for Retinopathy of Prematurity (ETROP) study grouped ROP into Type 1 and Type 2 ROP. The study concluded that a wait and watch approach with weekly or even twice weekly follow-up of Type 2 ROP eyes. These presently qualify as referral warranted eyes needing close observation. These eyes should be considered for treatment on progression to Type 1 ROP which at present are also called treatment requiring eyes. In 2005 ICROP study was revised and included the aggressive posterior ROP (APROP) to the earlier classification. ROP is divided into zones depending on the location and stage depending on the clinical appearance of the disease. Zone I - Circle centered on the disc with a radius twice the distance from disc to the center of macula. Clinically it is recognized by using +28 Dioptre lens. If the rim of the field of view by +28 D lens touches the nasal rim of the optic disc you are visualizing zone I of the retina. Zone II- A doughnut-shaped area extending from the nasal edge of zone I to ora serrata nasally and up to the anatomic equator temporally. Zone III - The outermost residual temporal crescent of retina anterior to zone II. To be sure of zone III, one must visualize the vessels reaching the nasal ora serrata for at least two clock hours. The stages of ROP define the clinical appearance of the retina at the junction of the vascularized retina and the avascular area. There are 5 stages of ROP – Stage 1- A demarcation line is seen between the vascular and avascular retina. It is a thin structure that lies in the plane of the retina. The vessels are dilated and tortuous (Figure 1a & b).

Stage 2 - The demarcation line grows to occupy a volume and has a height and width to form a ridge above the plane of the retina. Arterio-venous shunts are seen on FFA.

Stage 3 - Ridge with extraretinal fibrovascular proliferation into the vitreous. It may be continuous or non-continuous and is posterior to the ridge. Extraretinal proliferation can be seen as fibrovascular tufts on the ridge or as haemorrhagic spots on the ridge (Figure 3).

Stage 4 – Subtotal retinal detachment (RD) Subtotal retinal detachment may or may not involve fovea and is classified accordingly as shown in Figure 4 (a) and 4 (b).

Stage 5 - Total retinal detachment which could be of 4 types: open funnel, closed funnel, closed anterior funnel with open posterior funnel or open funnel anteriorly and closed funnel posteriorly. ETROP study classified ROP into Type I ROP: Also called high-risk pre-threshold disease (Treatment requiring) a) Zone I, stage 1, 2, or 3 with plus disease b) Zone I, stage 3 with or without plus disease c) Zone II, stage 2 or 3 with plus disease.
d) APROP in any Zone
Type II ROP: Known as low-risk pre-threshold disease (Referral warranted)
a) Zone I stage 1 or 2 without plus disease 
b) Zone II stage 3 without plus disease
Depending upon the vascularity ROP can be divided into. 27

Pre Plus disease - Posterior pole vascular dilation and tortuosity which is more than normal but less than plus disease.
Plus disease – Dilatation of posterior veins and tortuosity of arterioles in at least two quadrants. The arteries show tortuosity in the posterior pole however in the periphery both arteries and veins show tortuosity. There is growing interest in the quantification of the plus disease using Retcam images and artificial intelligence.

Aggressive posterior ROP (APROP) - Rapidly progressive form of ROP with posterior location, severe plus disease, and flat intraretinal neovascularization. This may progress directly to stage 5 ROP if not adequately treated in time as shown in Figure 5 (a) & (b).

Fig. 5 (a) : Fundus picture of APROP
Fig. 5 (b) : FFA in APROP

Threshold ROP was used for treatment in CRYO-ROP study. It is defined as zone I or II Stage 3 ROP, having five contiguous or eight cumulative clock hours with plus disease.
Pre-threshold ROP includes Type 1 ROP (high-risk pre-threshold) and Type 2 ROP (low-risk pre-threshold)
Spontaneously regressed ROP It is defined as “variable changes seen in spontaneously involuted ROP depending on the severity of initial disease”. 24
Changes like abnormally branching or telangiectatic retinal vessels, pigmented changes, lattice-like degeneration, vitreous membranes, localized tractional detachments, and even retinal breaks may be present. The posterior pole may show tortuous vessels, narrow temporal arcade, disk drag, macular heterotropia, and falciform folds.

Atypical and hybrid forms of ROP: These are not uncommon in the Indian scenario. Eyes with ROP may demonstrate both the flat neovascularization seen in APROP as well as the ridge of staged ROP. 25
The presence of plus disease helps in guiding timely treatment in these eyes. In some cases, only a few vessels arise from the optic disc which does not extend beyond the fovea. This form of severe ROP with poor vascular development is called posterior zone 1 ROP or half zone ROP as shown in Figure 6 (a) & (b).

Fig. 6 (a): Fundus picture in half zone ROP
Fig. 6 (b) : FFA in half zone ROP

• Each preterm baby requires repeated visits before reaching the stage warranting treatment. Each avascular retina needs to be followed up till mature retinal vessels are formed till ora serrata, ROP develops and regresses or ROP develops and is lasered. Only 10% of screened babies require treatment

Fundus fluorescein angiography and ROP
The gold standard of treating and diagnosing ROP continues to be indirect ophthalmoscopy. Fundus fluorescein angiography helps us in understanding the pathogenesis and the course of the disease. Klufas et al in his study concluded that the addition of FFA images to color fundus photographs resulted in significant increase in sensitivity for the diagnosis of ROP. 32
Lepore et al published an atlas of fluorescein angiographic findings in ROP. FFA was seen to clearly delineate the zone I junction between vascularised and non-vascularised retina. The authors also noted the different pattern of vessel branching at the junction between the vascular and avascular retina (AV junction) showing hyperfluorescent cotton wool-like or popcorn-like lesions, focally dilated capillaries, capillary tuft formation, and rosary bead-like lesion
inside vessels of ROP babies. Azad et al have demonstrated the safety of RetCam assisted FFA in babies with ROP in India. They concluded that in addition to being safe intravenous FFA can help in early diagnosis, prompt management and documentation of complete regression of ROP.

**Treatment of ROP**

Two large multicentre trials have been the backbone in the treatment of ROP which includes the CRYO-ROP and ETROP study.

In CRYO–ROP study, Cryotherapy was used for freezing the full thickness of the avascular retina from the external ocular surface, done in patients with threshold ROP. This trial reported that cryotherapy can decrease the unfavorable outcome to 21.8% compared to 43% in eyes who are left untreated. With the introduction of laser treatment in ROP, both cryotherapy and CRYO-ROP guidelines are no longer used. Cryotherapy was to be done under general anaesthesia and lead to a lot of adnexal reaction.

Laser therapy: Confluent laser spots of the avascular retina in ROP is gold standard treatment for ROP. The National Eye Institute in 1999 funded the ETROP trial where the Laser treatment was given to babies with ROP. This proved to be a major help in the treatment of zone 1 ROP. According to the ETROP study, ROP babies falling into High-risk ROP as described following were given treatment:

1. Zone 1, Stage I to III ROP with plus disease
2. Zone 1, Stage III ROP without plus disease
3. Zone II, Stage II to III ROP with plus disease
4. Aggressive posterior ROP

Follow up visits till spontaneous regression of ROP required falling under low risk:

1. Zone 1, Stage I to II ROP without plus disease
2. Zone II, Stage I to III ROP without plus disease
3. Peripheral avascular retina without any stage of ROP

In India, laser therapy of the avascular retina is usually done under topical anaesthesia and a sugar pellet may be used to facilitate the laser treatment. Follow ups are done at least once weekly for zone 1 ROP and one to two weeks for Zone II ROP till ROP regresses or progresses to treatable ROP.

The study concluded that laser therapy in Type I ROP could reduce the unfavorable from 15.6% to 9.1%.

Various studies have reported overall favorable outcome in 86-93% for threshold disease and 100% in pre-threshold disease treated with diode laser.

Anti–VEGF therapy - Introduction of anti-VEGF treatment has shifted the trend of treatment for ROP towards pharmacotherapy. Giving Intravitreal bevacizumab as an initial monotherapy can cause regression in 88% cases of type I ROP with only 9% requiring additional laser treatment and 1% requiring additional injection. Another randomized clinical trial, Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) results were compared between the anti-VEGF (bevacizumab- 0.625 mg in 0.025 ml used) group and conventional laser group for treating stage 3 + ROP having zone I or II posterior disease and has shown the superiority of anti-VEGF treatment over conventional laser therapy for infants for zone I but not in zone II disease. The rate of recurrence was 26% vs 6% between laser and anti-VEGF groups. The role of more and more anti-VEGF agents are being investigated as an adjunctive or alternate therapy. Ranibizumab 0.2mg was found to be superior than laser therapy with fewer unfavorable ocular outcomes in multicentric RAINBOW study. In one comparative study, the efficacy of intravitreal pegaptanib and laser photocoagulation was investigated and it was seen that 89.7% of injection treated eyes had favorable anatomic outcomes with stable regression of ROP as compared to only 60.8% of laser-treated eyes. Recently, one-year outcomes of intravitreal aflibercept injection were evaluated in one of prospective nonrandomized interventional case series study in 26 eyes with type 1 pre-threshold ROP and it found that favorable anatomical and visual outcome were present in 96% and 80% of eyes respectively. Ranibizumab and bevacizumab have been compared and similar efficacy was found in causing regression of ROP.

But numerous studies in the literature have reported late recurrence even after pharmacotherapy as anti-VEGF effects remain for 6 weeks post intravitreal injection. Reactivation has been reported even after 3 years of treatment. It has been now used as primary therapy for APROP, Aggressive anterior ROP, or poor media clarity due to posterior disease to improve visualization for laser treatment or persistent
neovascularization, tractional elements, and tractional retinal detachment before surgery which occurs following failed laser treatment.

Surgery - Surgical modalities including scleral buckling, lens-sparing vitrectomy, and lensectomy with vitrectomy are indicated for Stage 4A, Stage 4B, and Stage 5 ROP depending upon stage, extent, and location of the traction. Lens-sparing vitrectomy (LSV) is the most commonly performed and preferred surgery for Stage 4 ROP giving gratifying results. Lensectomy with vitrectomy is the surgery for stage 5 ROP. Best anatomical and functional outcome seen in stage 5 ROP are in open funnel configuration. The visual outcome for stage 5 is very poor and can lead to permanent visual impairment. Various studies in the literature have reported anatomical success ranging from 84 – 100% after LSV for Stage 4A ROP and 14.3% - 45.5% in Stage 5 ROP. Follow-up - The therapy for ROP goes much beyond the management in infancy. Once the baby develops ROP, a long term follow-up is required in these babies to give them useful vision. These babies have high incidence of sequelae like refractive error, strabismus, anisometropia, amblyopia, glaucoma, cataract, disc and macular drag, retinal breaks, retinal detachment etc.

Conclusion
Retinopathy of prematurity has become a modern epidemic that recently emerged as a worldwide health problem. Since improvements in neonatal care in recent decades, the rise in ROP has been noted recently. New operational guidelines have provided a more comprehensive approach to managing the disease. But still, there is more research is required in the field of ROP to decrease the overall financial burden on the country.

References


### WHICH INFANTS NEED TO BE TREATED
Infants developing signs of sight threatening ROP in one or both eyes

### WHEN SHOULD TREATMENT BE GIVEN
Within 48 hours as the disease can progress very fast to retinal detachment

### WHO SHOULD TREAT
An ophthalmologist trained and competent in treating sight threatening ROP

### METHOD OF TREATMENT
Laser treatment delivered by indirect ophthalmoscope to the avascular peripheral retina
Pain control and /or sedation are required. Staff trained in neonatal resuscitation must be present
Note: Once retinal detachment has occurred, complex vitreoretinal surgery by an expert can prevent blindness in some cases

### WHERE TO TREAT
In the SNCU/NICU if an Inpatient.
If discharged from the SNCU/NICU: in an eye department if infrastructure and personnel are available

### FOLLOW UP AFTER TREATMENT
Ophthalmologist should follow up at one week. Further laser treatment may be required

### LONG TERM FOLLOW UP
Infants treated for sight threatening ROP are at high risk of refractive errors and other eye conditions. They should be follow up until at least 5 years of age

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**Figure 3:** Ocular and cortical mortality in preterm infants — follow-up evaluation guidelines. (Reproduced with permission from “Project operational guidelines. Prevention of Blindness from Retinopathy of Prematurity in Neonatal Care Units,” https://ophiusagroup.com/uploads/2018/04/ROP-operational-guidelines.pdf)

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**Figure 4:** Ophthalmic evaluation guidelines for preterm infants. (Reproduced with permission from “Project operational guidelines. Prevention of Blindness from Retinopathy of Prematurity in Neonatal Care Units,” https://ophiusagroup.com/uploads/2018/04/ROP-operational-guidelines.pdf)

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