# TURKISH NEONATAL SOCIETY & TURKISH OPHTHALMOLOGICAL ASSOCIATION

# Retinopathy of Prematurity (ROP) Guideline

## 2021 Update


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We would like to thank the Turkish Neonatal Society Retinopathy of Prematurity Study Group and the Turkish Ophthalmology Association Retinopathy of Prematurity Commission for their contributions.

# CONTENTS

| | |
|---|---|
| 1. INTRODUCTION | 5 |
| 2. OBJECTIVE | 5 |
| 3. EPIDEMIOLOGY | 5 |
| 4. RISK FACTORS | 6 |
| 5. PATHOGENESIS | 7 |
| 6. CLASSIFICATION | 8 |
| 7. CLINICAL COURSE | 12 |
| 8. OPHTHALMOLOGICAL FOLLOW-UP OF PREMATURE INFANTS | 12 |
| 8.1. DIAGNOSIS AND SCREENING | 12 |
| 8.2. EXAMINATION AND POINTS TO CONSIDER | 14 |
| 8.3. FOLLOW-UP | 17 |
| 8.4. TERMINATION OF SCREENING EXAMINATIONS | 20 |
| 9. TREATMENT | 21 |
| 9.1. LASER PHOTOCOAGULATION | 21 |
| 9.2. ANTI-VEGF (VASCULAR ENDOTHELIAL GROWTH FACTOR) AGENTS | 22 |
| 9.3. SURGICAL TREATMENT | 25 |
| 9.4. TREATMENT ENVIRONMENT | 25 |
| 9.5. ANESTHESIA | 26 |
| 9.6. POST-TREATMENT FOLLOW-UP | 26 |
| 9.7. POST-TREATMENT USE OF EYE DROPS | 27 |
| 10. PROGNOSIS | 28 |
| 11. PREVENTION | 29 |
| 12. REFERENCES | 30 |

## ABBREVIATIONS

| | |
|---|---|
| **A-ROP** | : Aggressive Retinopathy of Prematurity |
| **BEAT-ROP** | : Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity |
| **BOOST** | : Benefits of Oxygen Saturation Targeting Trial |
| **CARE-ROP** | : Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity |
| **COT** | : Canadian Oxygen Trial |
| **BW** | : Birth Weight |
| **ETROP** | : Early Treatment for Retinopathy of Prematurity |
| **EMA** | : European Medicines Agency |
| **FDA** | : Food and Drug Administration |
| **FFA** | : Fundus Fluorescein Angiography |
| **GA** | : Gestational Age |
| **ICROP-3** | : International Classification of Retinopathy of Prematurity, Third Edition |
| **IGF** | : Insulin-like Growth Factor |
| **NeOPRoM** | : Neonatal Oxygenation Prospective Meta-Analysis |
| **ONH** | : Optic Nerve Head |
| **PAR** | : Persistent Avascular Retina |
| **PM** | : Postmenstrual |
| **RAINBOW** | : Ranibizumab versus Laser Therapy for the Treatment of Very Low Birth Weight Infants with Retinopathy of Prematurity |
| **ROP** | : Premature Retinopathy |
| **SUPPORT** | : Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial |
| **TGF-Beta** | : Transformative Growth Factor Beta |
| **TRD** | : Tractional Retinal Detachment |
| **VEGF** | : Vascular Endothelial Growth Factor |
| **WINROP** | : Weight, Insulin-Like Growth Factor, Neonatal Retinopathy of Prematurity |

## 1. INTRODUCTION

In parallel with advances in neonatal care in our country, the survival rates of extremely premature infants with very low gestational age (GA) and birth weight (BW) have increased. As a result, retinopathy of prematurity (ROP)–a condition that can lead to visual impairment or blindness–has emerged as a more frequent problem. Early detection of the disease and timely, appropriate treatment can prevent vision loss, support the child's developmental process, and improve overall quality of life.

## 2. OBJECTIVE

The aim of the national ROP diagnosis and treatment guideline is to provide recommendations –based on current scientific evidence and tailored to the conditions in our country– regarding the diagnosis, treatment, follow-up, and prevention of ROP in premature infants cared for in neonatal intensive care units (NICUs) and identified as at risk. Following the publication of significant studies in the past five years, the 'ROP Diagnosis and Treatment Guideline' originally developed in 2016 required updating. In this 2021 revision, the results of multicenter studies conducted in our country were evaluated, and the recommended screening thresholds for ROP were updated. The guideline adopts the classification system of the *International Classification of Retinopathy of Prematurity, Third Edition (ICROP-3)*, published in July 2021, and incorporates other important and recent studies form the literature.

## 3. EPIDEMIOLOGY

The incidence of retinopathy of prematurity varies according to a country's level of development and the characteristics of its NICUs. In developed countries, ROP predominantly occurs in preterm infants born before 32 weeks' GA, whereas in developing countries, severe ROP has been reported in infants born up to 34 weeks' GA [1–4].

Studies from our country and other developing countries have documented severe ROP requiring treatment in infants with a BW between 1500 and 2500 g [5–7]. In a multicenter study conducted by the Turkish Neonatal Society (TR-ROP study), the incidence of ROP among very low birth weight infants was 42%, and the incidence of advanced-stage ROP was 11%. Among infants with GA 33–35 weeks, the incidence of ROP was 6.1%, with advanced-stage disease in 0.6% (6 per 1000). In infants with a BW between 1500–2000 g at birth, the incidence of ROP was 10.3%, with severe ROP reported in 19 infants (Table I) [8]. These findings highlighting that, in our country, severe ROP can also occur in infants with BW >1500 g.

**Compared with developed countries, advanced-stage ROP requiring treatment continues to be seen in larger and more mature preterm infants in our country**

**Table I: Incidence and Treatment of ROP According to Gestational Age and Birth Weight**

| **Gestational age (weeks)** | **Number of infants screened for ROP (n)** | **ROP (n, %)** | **Severe ROP (n, %)** |
|---|---|---|---|
| ≤28 | 1,539 | 968 (62.9) | 332 (21.6) |
| 29-32 | 3,425 | 666 (19.4) | 76 (2.2) |
| Subtotal (≤32) | 496 | 1,634 (32.9) | 409 (8.2) |
| 33-35 | 1,030 | 56 (6.1) | 6 (0.6) |
| >35 | 121 | 5 (4.1) | - |
| Total | 6,115 | 1,695 (27) | 414 (6.7) |
| **Birth weight (grams)** | **Number of infants screened for ROP (n)** | **ROP (n, %)** | **Severe ROP (n, %)** |
| ≤1000 | 1,109 | 761 (68) | 288 (26) |
| 1001–1250 | 1,085 | 438 (40) | 74 (6.8) |
| 1251-1500 | 1,296 | 269 (20.8) | 33 (2.5) |
| Subtotal (≤1500) | 3,490 | 1,468 (42) | 395 (11) |
| 1501-2000 | 1,944 | 201 (10.3) | 19 (1) |
| >2000 | 681 | 26 (3.8) | - |
| Total | 6115 | 1,695 (27) | 414 (6.7) |
| *Bas AY, Demirel N, Koc E on behalf of the TR-ROP Study Group, et al. Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicenter study in 69 neonatal intensive care units. British Journal of Ophthalmology 2018;102:1711-1716.* | | | |

## 4. RISK FACTORS

Although numerous etiological factors have been implicated in the development of ROP, the most well-established risk factors are low BW and low GA. It is well known that the incidence of ROP rises markedly in infants born weighing less than 1000 g and before 28 weeks' gestation (Table II) [1, 2, 8].

Although some studies have suggested that genetic polymorphism may contribute to the higher incidence of ROP in male infants compared to females, and in white populations compared with black populations, no specific genetic factor has been identified that increases the risk of ROP [9, 10].

**Table II. Major Risk Factors for the Development of ROP**

| |
|---|
| Low gestational age and low birth weight |
| Duration and concentration of oxygen therapy |
| Hemodynamically significant cardiorespiratory problems |
| Patent ductus arteriosus, respiratory distress syndrome |
| Hyperoxia/hypoxia, hypercapnia/hypocapnia, sudden fluctuations in blood gas levels |
| Asphyxia, hypothermia, metabolic acidosis |
| Mechanical ventilation |
| Bronchopulmonary dysplasia |
| Sepsis/meningitis, systemic fungal infections |
| Intracranial hemorrhage |
| Number of blood transfusions, exchange transfusion |
| Hyperglycemia/insulin therapy |
| Early use of erythropoietin for the treatment of preterm anemia |
| Slow postnatal weight gain |
| Multiple gestation |

## 5. PATHOGENESIS

Before the 16th week of gestation, the retina contains no blood vessels. From approximately the 6th week, the anterior segment of the eye is supplied by the hyaloid artery, which passes through the optic disc and vitreous to reach the lens and iris. This artery is normally resorbed by the 34th week of gestation. Retinal vascular development begins between the 15th and 18th weeks, extending outward from the optic disc toward the periphery. Vascularization is usually completed in the nasal retina around 36 weeks and in the temporal retina by about 40 weeks. Consequently, in preterm infants the retina remains incompletely vascularized at birth, leaving a peripheral avascular zone whose extent depends on gestational age. Complete vascularization may not be achieved until 48–52 weeks postmenstrual age. [1, 2].

Although the pathogenesis of ROP is not fully understood, it is thought to occur in two distinct phases. In preterm infants, the retinal vascularization that began in utero may be arrested by various injurious factor. Possible causes of this initial disruption include prolonged hyperoxia, asphyxia, hypothermia, acidosis, vitamin E deficiency, and low levels of omega-3 polyunsaturated fatty acids [1, 2, 9]. Antenatal sensitizing factors such as placental infection and inflammation may also play a role; some authors refer to this period as **'pre-phase'** [11].

**Phase I:** In the early stages of ROP, hyperoxia suppresses the production of oxygen-regulated vascular endothelial growth factor (VEGF) and erythropoietin. The concurrent deficiency of insulin-like growth factor 1 (IGF-1) and inadequate postnatal growth further compromise normal vascular development. In addition, increased free oxygen radicals and oxidative stress cause apoptosis and vaso-obliteration of vascular endothelial cells [1, 9, 12].

**Phase II:** The retina continues to develop; however, impaired vascularization results in unmet oxygen demands and subsequent hypoxia. This hypoxic state initiates Phase II of retinopathy of prematurity, characterized by increased expression of mediators such as VEGF and erythropoietin. As postnatal age advances and IGF-1 levels rise above a critical threshold, growth factors including VEGF exert their angiogenic effects. Consequently, neovascularization emerges at the junction between vascularized and avascular retina.

The newly formed vessels may cluster within the retina, leading to the formation of a thickened ridge. Neovascularization can cause leakage, edema, and, in severe cases, retinal detachment with consequent vision loss. In mild cases, the ridge may regress spontaneously, whereas in severe cases, abnormal, tortuous vessels may extend into the vitreous from the ridge, causing retinal structural distortion, traction, and detachment [2, 9, 12–15].

## 6. CLASSIFICATION

The classification of ROP is based on the ICROP-3 [16]. The disease is described according to location (zones), stage of vascular proliferation, extent, and the presence or absence of plus or pre-plus disease.

**Location (Zones):** The retina is divided into three concentric zones centered on the optic nerve head (ONH) (Figure 1).

- **Zone I:** A circular area with a radius twice the distance from the ONH to optic nerve to the center of the fovea. The ONH is the center of this circle. When examined with a 25D or 28D lens such that the ONH is at the edge of the field, the visible area corresponds to Zone I.
- **Zone II:** The annular region outside Zone I, extending centrifugally from the ONH to the nasal ora serrata.
- **Zone III:** The crescent-shaped residual temporal area anterior to Zone II.

The ICROP-3 update clarified definition of posterior Zone II as the area extending anteriorly from Zone I by two-disc diameters.

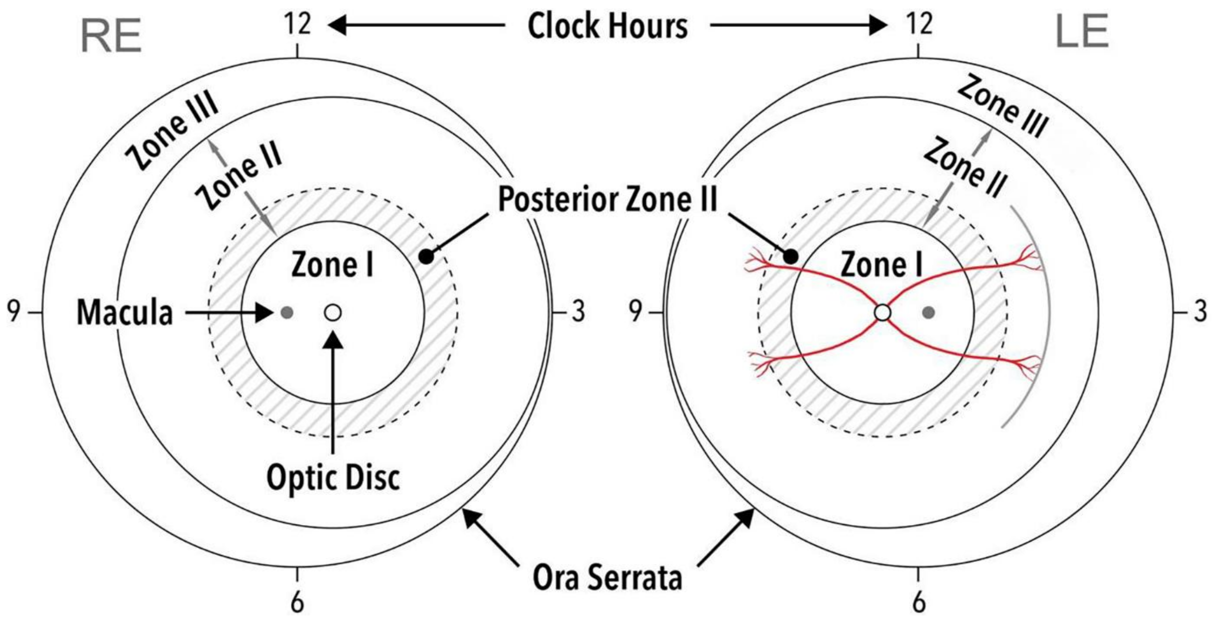


Figure 1. Location of the disease

**Stage of Vascular Proliferation:** ROP is classified into five stages based on the degree of vascular proliferation. If ROP has not yet developed, the zone of the avascular retina should be specified.

- **Stage 1:** A demarcation line between the vascularized and avascular retina.
- **Stage 2:** Ridge; a slightly elevated, prominent neovascular proliferation extending above the surface (indicating acquisition of a three-dimensional structure).
- **Stage 3:** Extraretinal fibrovascular proliferation arising from the ridge (flat neovascularization seen in aggressive ROP is also classified as Stage 3 in ICROP-3).

- **Stage 4A:** Partial retinal detachment not involving the macula.
- **Stage 4B:** Partial retinal detachment involving the macula.
- **Stage 5:** Total retinal detachment.

In ICROP-3, Stage 5 is further subcategorized.

- **Stage 5A:** Total tractional retinal detachment (TRD) with the posterior pole visible on ophthalmoscopy.
- **Stage 5B:** Total TRD with the retina completely folded behind the lens, presenting as leukocoria, usually with closed funnel detachment.
- **Stage 5C:** Leukocoric TRD with anterior chamber narrowing and irido-corneo-lenticular synechiae, progressing to corneal opacification.

**Extent:** The retinal is divided into 30° sectors, analogous to clock hours, to describe the circumferential extent of disease. The stage may vary between sectors.

**Plus Disease:** Defined as increased arteriolar tortuosity and venular dilation in at least two quadrants around the ONH, often accompanied by vitreous haze, iris vessel engorgement, and reduced pupillary reactions.

**Pre-plus disease** refers to vessel changes thar are more marked than normal but insufficient for a diagnosis of plus disease. ICROP-3 describes plus and pre-plus disease as a part of continuum.

**Disease Categories**

Combining the above parameters, each eye is categorized as [1, 2, 16]:

- **Threshold Disease:** Stage 3 ROP in Zone I or Zone II with plus disease, involving five contiguous or eight cumulative clock hours.
- **Pre-threshold Disease:**
    - Any stage in Zone I without threshold disease
    - Stage 2 ROP with plus disease in Zone II
    - Stage 3 ROP in Zone II
    - Stage 3 ROP in Zone II with less than threshold extent but with plus disease

- **Type 2 ROP (low-risk pre-threshold):**
    - Stage 1 or 2 in Zone I without plus disease
    - Stage 3 ROP in Zone II without plus disease
- **Type 1 ROP (high-risk pre-threshold):**
    - Any stage in Zone I with plus disease
    - Stage 3 in Zone I
    - Stage 2 or 3 in Zone II with plus disease
- **Aggressive ROP (A-ROP):** A-ROP is a rapidly progressive, severe form of ROP that, if untreated, often advances to Stage 5. Formerly termed 'Rush Disease' or 'APROP', the 2021 ICROP-3 revision adopted the term A-ROP to include aggressive cases that may also occur more anteriorly (e.g. oxygen-induced ROP).

In A-ROP, plus disease is striking in all four quadrants and is disproportionate to the peripheral stage. The disease is usually in Zone I or posterior Zone II, but the avascular border may be indistinct, **making staging difficult**. **Flat neovascularization** is seen at the vascular-avascular junction without the typical white fibrotic ridge. Capillary nonperfusion may also be present posterior to the ridge. Fundus fluorescein angiography (FFA) can be very helpful for diagnosis.

**In A-ROP, flat neovascularization at the border of the avascular retina may not be elevated above the retinal the surface, leading to missed diagnosis. Another characteristic feature is that the disease can progress directly to Stage 4 or 5 without following the typical sequential progression from Stage 1 to Stage 3. Once A-ROP is diagnosed, medical intervention should be initiated immediately, subjecting the case to staging according to the degree of vascular proliferation [1, 16].**

- **Severe ROP:** Both Type 1 ROP and A-ROP are considered severe and require treatment.
- **Regression:** Spontaneous or post-treatment resolution of active ROP findings, which may be complete or partial. Partial regression often leaves areas of **persistent avascular retina (PAR)** and peripheral vascular anomalies, which should be documented [16].

- **Reactivation:** Recurrence of active ROP after regression, occurring at the original ridge or vascular-avascular junction. **It should be documented in reports** (e.g., 'Reactivated Zone II Stage 2 ROP') [16].
- **Long-term Sequelae:** These may include vitreoretinal interface abnormalities, epiretinal membranes, localized TRD, ectopic macula, peripheral retinal degenerations/holes/tears, rhegmatogenous retinal detachment, PAR, peripheral vascular anastomoses/loops, and glaucoma [16].

## 7. CLINICAL COURSE

The clinical course of ROP is determined more by PM age and the location of the disease rather than postnatal age. The disease may appear as early as PM 30-32 weeks, although it most commonly begins around PM 34 weeks. The disease progresses irregularly until 40–45 weeks of gestation and usually regresses spontaneously. Among infants with a birth weight ≤1250 grams, two-thirds develop ROP, and 6% of these require medical intervention due to severe disease. [17–20].

## 8. OPHTHALMOLOGICAL FOLLOW-UP OF PREMATURE INFANTS

### 8.1. DIAGNOSIS AND SCREENING

According to the 2018 recommendations of the American Academy of Pediatrics and the American Academy of Ophthalmology, all infants with a BW ≤1500 g and/or GA ≤30 weeks should be screened for ROP. Screening is also recommended for with GA >30 weeks and BW 1500–2000 g who have clinical problems requiring cardiopulmonary support [21].

When the results of the TR-ROP study conducted by the Turkish Neonatal Society are evaluated, severe ROP cases have been detected in larger and more mature infants. In this study, treatment-requiring severe ROP was identified in infants with BW ≤1700 g and GA up to 34 weeks [8]. Based on these findings, the screening criteria presented in Table III are considered appropriate for our country.

**Table III: Recommended Screening Criteria for Retinopathy of Prematurity in Our Country**

| |
|---|
| • Screening is recommended for all infants with GA <34 weeks or BW ≤1700 g.<br>• Screening is also appropriate for preterm infants with GA ≥34 weeks or BW >1700 g who have received cardiopulmonary support therapy, or whom the attending clinician considers at risk for ROP development* |

*The quality of care in neonatal intensive care units varies between units. Each unit should determine its upper screening limits for GA and BW based on its own epidemiological data.

**Table IV: Timing of the First ROP Examination According to Gestational Age [21]**

| GA (weeks) | PM Age at First Examination (weeks) | Chronological Age at First Examination (weeks) |
|---|---|---|
| **22*** | 31 | 9 |
| **23*** | 31 | 8 |
| **24*** | 31 | 7 |
| **25** | 31 | 6 |
| **26** | 31 | 5 |
| **27** | 31 | 4 |
| **28** | 32 | 4 |
| **29** | 33 | 4 |
| **30** | 34 | 4 |
| **31** | 35 | 4 |
| **32**** | 36 | 4 |

* In infants with GA <25 weeks, the first examination may be performed at postnatal 6 weeks without waiting for PM 31 weeks
** In infants with GA > 32 weeks, the first examination should be performed at postnatal week 4 [22].

**The first ophthalmological examination should be performed at PM 30-31 weeks in infants born at GA <27 weeks, and at postnatal week 4 in infants born at GA ≥27 weeks (Table IV). The examination schedule is based on PM age which is calculated as GA + chronological age.**

## 8.2. EXAMINATION AND POINTS TO CONSIDER

Retinal examination should be performed by an **ophthalmologist who is competent and experienced in ROP**, using a lid speculum, binocular indirect ophthalmoscope with 20D and 28D lenses, and scleral indentation, with the infant in a **supine position**. While the infant remains hospitalized, the examination should ideally be performed in NICU, with continuous monitoring and in the presence of intensive care physicians.

- **Families should be informed verbally and in writing about the ROP examination and follow-up. Informed consent must be obtained before the first examination**.
- **If consent is not granted, permission from the court should be obtained for medical examination and procedures, based on the principle that the infant's right to life is paramount. If the parental wishes are not aligned with medical recommendations for the infant's health and right to life, the consent is considered invalid.**
- **The consultation request date for the ROP examination should be recorded on the consultation form. The name of the ophthalmologist performing the examination and the date of examination should be documented.**
- **In the examination notes, the ophthalmologist should record in detail: pupil status; zone, stage, and extent of disease; presence or absence of plus disease; treatment plan and the date of the next examination**

**Pupil dilation:** For proper retinal assessment, the pupil must be dilated. Adequate dilation allows examination of the peripheral retina and facilitates the staging of ROP. [22, 23].

- **Mydriasis should be initiated 1 hour before the examination.**
- **Recommended regimen: instill one drop each of 2.5% phenylephrine and 0.5% tropicamide, repeated every 5 minutes for a total of 2-3 applications.**
- **The optimal time for examination is generally 45–60 minutes after the last drop.**
- **If the pupils are inadequately dilated, mydriatic drops may be repeated, but this should be avoided whenever possible due to potential systemic side effects.**
- **Poor dilation may occur in severe ROP.**

Ocular manipulation and the use of eye drops may lead to complications including bradycardia, tachycardia, cardiac arrhythmia, apnea, desaturation, hypertension, vomiting, gastric residuals, transient paralytic ileus, and, rarely, death [22, 23].

Mydriatic drops can be absorbed via the periocular skin, cornea, conjunctiva, nasal mucosa, and nasolacrimal duct. Reducing systemic absorption minimize the risk of adverse effects [22, 23].

**To reduce systemic absorption and potential side effects of eye drops:**

- **Apply drops in small volumes,**
- **Wipe away any excess medication from around the eye,**
- **Close the eyelids after instillation**
- **Apply gentle pressure to the lacrimal sac and inner canthus for 2 minutes after instillation,**
- **Ensure the examination is performed at the scheduled time to avoid repeated drug administration.**

**Pain Control and Positioning**

ROP examination –particularly with the use of a speculum– is a painful procedure. It is important to provide topical anesthesia and, when possible, sedation [24–26].

• **During the examination:**

- **The infant's head and arms should be stabilized by a nurse,**
- **Hands and feet should be gently flexed or loosely swaddled,**
- **Use of a pacifier, breast milk, or oral sucrose during and after the examination may help reduce discomfort.**

**Recommended topical anesthesia: Instill one drop of 0.5% proparacaine hydrochloride into each eye 3–5 seconds before the examination. The effect lasts for approximately 15–20 minutes.**

**Infection Prevention**

Eye examinations can cause infectious conjunctivitis and, rarely systemic infections. Ophthalmologists must wash their hands appropriately before each examination and comply with all hygiene protocols. A sterile eyelid speculum and scleral indentor should be used for each patient [27].

- **Instruments used during the examination should be sterilized in an autoclave.**
- **Isopropyl alcohol or chlorhexidine is not sufficient for sterilization.**

### 8.3. FOLLOW-UP

The follow-up schedule for premature infants with ROP is determined based on the findings of the first examination. If retinopathy is detected, the follow-up interval should be planned according to the severity of the disease and its rate of progression.

Depending on the ocular findings, one of the following decisions should be documented:

1. **No further screening examinations are required** – if retinal vascularization is complete.
2. **Follow-up required** –at intervals of 3-4 days, 1 week, or 2 weeks, depending on the specific conditions described below.
3. **Urgent treatment required** – if the decision for treatment has already been made.

If retinal vascularization is in Zone III, examinations are repeated every 2–3 weeks; if in Zone II, at least every 2 weeks; if **in Zone I, at least weekly, depending on whether progression is observed. If worsening of findings or pre-plus disease is detected, the frequency of examinations should be increased at the discretion of the attending ophtalmologist** [28, 29]. The follow-up algorithm for ROP is presented in **Figure 2**.

- **The first examination is the responsibility of the neonatologist/pediatrician. The ophthalmologist determines the follow-up interval, duration of screening, and treatment decisions.**
- **Screening should continue until ROP has regressed or complete retinal vascularization is achieved.**
- **The ophthalmologist is responsible for referring patients requiring further follow-up or treatment to the appropriate physician/clinic.**

**Digital Imaging in Follow-up**

Devices capable of capturing retinal images digitally are now in use. This method is very useful for:

- Recording retinal findings in digital environment,
- Comparing with previous examinations,
- Education in ROP diagnosis
- Teleconsultation.

**However, the decision regarding follow-up intervals, termination of screening, or initiation of treatment must be based on binocular indirect ophthalmoscopy.**

In the multicenter e-ROP study, the sensitivity of images obtained with a digital camera was reported as 90% and the specificity as 87% [30]. Further research is needed to evaluate the sensitivity, advantages, and practical implementation of such devices [21]. Although indirect ophthalmoscopy is sufficient for diagnosis and follow-up, digital imaging devices are valuable for direct comparison between visits and can serve as medicolegal evidence. Devices capable for performing fundus fluorescein angiography (FFA) may also help in the differential diagnosis of ROP from other conditions such as familial exudative vitreoretinopathy and incontinentia pigmenti.

**Prediction Algorithms**

Recently, algorithms have been developed to predict the development of severe ROP based on postnatal weight gain, aiming to reduce the number of examinations. In developed countries, these algorithms have shown 100% sensitivity in infants with GA <32 weeks [31–33]. However, in developing countries –where severe ROP is more common in larger infants– the sensitivity of the 'Weight, Insulin-like Growth Factor, Neonatal Retinopathy of Prematurity' (WINROP) algorithm, as reported in the original study, was found to be low. Currently, there is no international recommendation for its routine use or validation [34, 35]

# RETINOPATHY OF PREMATURITY (ROP) FOLLOW-UP ALGORITHM

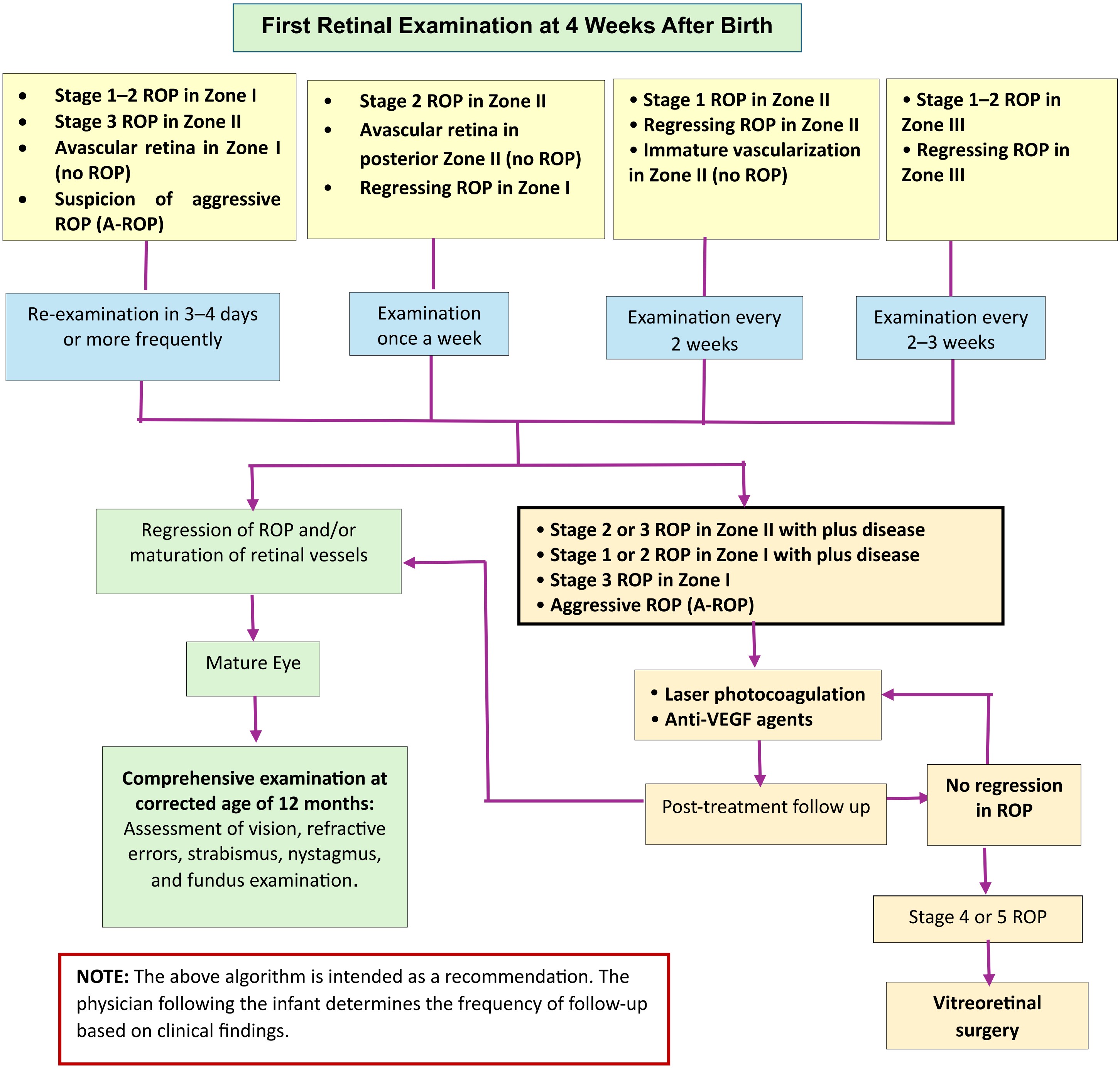


**Figure 2:** Retinopathy of Prematurity (ROP) Follow-up Algorithm

### 8.4. TERMINATION OF SCREENING EXAMINATIONS

In infants without ROP, once the retinal vessels have reached Zone III, the risk of developing sight-threating ROP is very low. However, determining the vessels have truly reached Zone III can be challenging. The decision to terminate screening should always be made **only after complete retinal vascularization** is confirmed.

In infants with ROP but without an indication for treatment, once it is clearly established that the disease has stopped progressing and has begun to regress, follow-up examinations may be performed at longer intervals. **Situations in which screening examinations may be terminated are listed below** [21, 22]:

- **Complete retinal vascularization (This criterion is particularly important in patients who have received anti-VEGF agents).**
- **No Zone I or Zone II ROP detected in previous screening examination and retinal vascularization has reached Zone III (If the ophthalmologist is uncertain about the zone or if the infant is <PM 35 weeks, repeat examinations are recommended).**
- **No pre-threshold or worse ROP detected in any previous screening examinations and the infant has reached PM 45 weeks.**
- **Regressing ROP with no abnormal vascular tissue that could carry a risk of reactivation or progression**
- **In patients who have received anti-VEGF therapy, close follow-up is required between PM 44 and 55 weeks, when the risk of reactivation is highest.**
- **In patients who have received anti-VEGF therapy, screening should not be terminated before at least PM 60 weeks. Very late proliferative ROP recurrences have been reported in such cases. Termination of follow-up in these infants should be performed with caution and individualized clinical judgment. Increasingly, it is accepted that these infants should undergo FFA at around PM 60 weeks, and if avascular areas persist, laser photocoagulation should be performed. This approach can help late recurrences and complications and is also considered more practical given the increasing difficulty of performing peripheral retinal examinations as the infant grows.**

## 9. TREATMENT

The criteria for laser photocoagulation in ROP were established by the multicenter Early Treatment for Retinopathy of Prematurity (ETROP) study group. These criteria also consider high-risk pre-threshold ROP findings (Type 1 ROP) [36]. It has been reported that early treatment improves visual acuity and reduces adverse structural outcomes [37].

**Accordingly, the conditions requiring treatment are as follows:**

- **Stage 1 or stage 2 ROP in Zone I with plus disease**
- **Stage 3 ROP in Zone I,**
- **Stage 2 or stage 3 ROP in Zone II with plus disease**
- **A-ROP**

- **In A-ROP cases, treatment should be initiated as soon as possible; in less aggressive cases, treatment should be started within 48–72 hours.**

The treatment algorithm for ROP is presented in Figure 3.

### 9.1. LASER PHOTOCOAGULATION

Laser photocoagulation is the standard treatment method for ROP. The avascular retina produces angiogenic factors that stimulate abnormal vascularization. The aim of treatment is the ablation of the avascular peripheral retinal areas. This procedure is performed using diode laser or argon laser photocoagulation. Laser treatment is applied not on the abnormal vessels themselves, but to all avascular areas anterior to these vessels. Retinal ablation therapy is indicated in 'threshold disease' and in high-risk 'pre-threshold' disease [36, 38]. The procedure can be performed under general anesthesia or under remifentanil/fentanyl sedation. Depending on the extent of the avascular area, the duration of the procedure ranges from 15 minutes to 1 hour.

Possible complications after laser treatment include pain, apnea, bradycardia, chemosis, vitreous hemorrhage, infection, iris and lens burns, cataract, posterior synechiae, glaucoma, and a decrease in visual acuity, often accompanied by visual field loss. Cataract formation is less common after diode laser treatment compared to argon laser treatment. In A-ROP cases, intensive laser application may rarely cause anterior segment ischemia with hypotony, which is a serious complication that may result in loss of the eye [39]. For this reason, laser treatment is generally not the first choice in A-ROP or Zone I disease.

**Despite laser treatment, some patients may progress to stage 4 with retinal detachment.** The risk of retinal detachment increases in the presence of vitreous hemorrhage or white fibrous tissue within the vitreous [40]. In such cases, vitreoretinal surgery may be required.

### 9.2. ANTI-VEGF AGENTS

Bevacizumab, ranibizumab, and aflibercept are anti-VEGF monoclonal antibodies that act by blocking VEGF. The infant is appropriately positioned and stabilized. The procedure is then performed under topical anesthesia after ocular surface sterilization with povidone-iodine. An intravitreal injection is administered via the pars plicata, approximately 1 mm posterior to the limbus, preferably with a short 4 mm 30-gauge needle. The procedure typically takes about 10–15 minutes.

Anti-VEGF agents are widely used in adults for various retinal vascular pathologies, most commonly age-related macular degeneration, diabetic retinopathy, retinal vein occlusions, and, in preterm infants, for the treatment of ROP [41, 42].

Although laser photocoagulation remains the gold standard for ROP treatment, anti-VEGF agents have certain advantages:

- easier administration,
- no requirement for general anesthesia,
- rapid clinical response,
- feasibility in cases with corneal/lens opacity, vitreous haze, or poor pupillary dilation,
- preservation of peripheral visual field [43–45].

Potential risks include transient reduction of serum VEGF levels and the possibility of brain, lung, and kidney injury [46]. Following treatment, rapid regression of plus disease is usually observed starting from the next day. However, vascularization of the avascular retina occurs slowly over an extended period and may remain incomplete in some eyes. In severe stage 3 or Stage 4 cases, intravitreal anti-VEGF injection may induce rapid progression to stage 5 due to contraction of the fibrotic component, known as **'crunch phenomenon'**. This is thought to result from the natural increase of transforming growth factor-beta (TGF-beta), a VEGF antagonist, around PM 36–40 weeks, which becomes more dominant after VEGF supression [47].

In the multicenter 'Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity' (**BEAT-ROP**) trial, bevacizumab treatment for Zone I stage 3 ROP or posterior Zone II ROP was associated with lower recurrence and fewer structural abnormalities (retinal detachment, macular ectopia) compared to laser photocoagulation [43].

**Although the minimum effective dose is unknown, typically half of the adult dose is used (Bevacizumab: 0.675 mg/0.025 mL; Ranibizumab: 0.25 mg/0.025 mL).** In the multicenter 'Ranibizumab versus Laser Therapy for the Treatment of Very Low Birthweight Infants with Retinopathy of Prematurity" (**RAINBOW**) trial, intravitreal high-dose intravitreal ranibizumab (0.2 mg), low-dose ranibizumab (0.1 mg), and laser photocoagulation were compared. Systemic plasma VEGF levels did not decrease at weeks 2 and 4 following intravitreal ranibizumab [48].

In the same study, 'treatment success' was defined as the absence of active ROP, absence of unfavorable ocular structural outcomes, and no need for retreatment. Treatment success rates were 80%, 75%, and 66% for high-dose intravitreal ranibizumab, low-dose intravitreal ranibizumab, and laser photocoagulation, respectively [48].

The multicenter 'Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity" (**Care-ROP**) trial compared ranibizumab doses of 0.12 mg and 0.2 mg and found similar efficacy [49].

**Treatment failure after laser therapy usually becomes evident within 2–3 weeks, whereas late recurrences have been reported after bevacizumab treatment. Therefore, follow-up should be longer after bevacizumab administration** [50, 51]. Peripheral retinal vascularization is very slow –and often incomplete– in infants treated with anti-VEGF agents. Monitoring should continue until vascularization is complete, which may take up to 2-3 years. Late reactivations have been reported, so long-term follow-up is essential. Examination under general anesthesia may be required in older infants whose peripheral retina cannot be adequately visualized. A practical approach to avoid prolonged follow-up is to perform FFA when vascularization reaches anterior Zone II or at PM 60 weeks, and to apply laser photocoagulation to any remaining avascular area [52].

Some reports suggest increased rates of neurodevelopmental problems in infants treated with anti-VEGF agents compared to laser treatment [53, 54]. A meta-analysis reported lower Bayley III cognitive and language scores after intravitreal bevacizumab compared to laser photocoagulation [55]. Well-designed long-term studies are needed to evaluate neurodevelopmental outcomes following intravitreal ranibizumab.

**Despite these uncertainties, situations where anti-VEGF therapy may be preferred are listed below:**

- **Zone I or posterior Zone II ROP,**
- **Presence of A-ROP**
- **Posterior disease with an avascular macula (to avoid laser)**
- **Conditions limiting retinal visualization: poor pupillary dilation (rigid pupil), corneal/lens opacities, vitreous hemorrhage or haze**
- **Critically ill infants unable to tolerate general anesthesia for laser treatment**

The American Academy of Pediatrics has stated that bevacizumab may be considered in Zone I Stage 3 ‘plus’ disease, but further studies are needed to determine optimal dosing, timing, safety, and efficacy [21]. Currently, the United States Food and Drug Administration (FDA) and the Turkish Ministry of Health have not approved anti-VEGF agents for ROP, and their use is off-label. **Written informed consent from parents must be obtained before treatment.**

**The European Medicines Agency (EMA) approved ranibizumab in September 2019** for treatment of ‘Zone I Stage 1+, 2+, 3, or 3+ ROP, Zone II Stage 3+ ROP, or A-ROP [56]. **FDA granted orphan designation (July23, 2019) of aflibercept for the treatment of ROP**.

**Neither laser nor anti-VEGF agents can always prevent retinal detachment; in cases of total or subtotal retinal detachment, vitreoretinal surgery is performed.**

### 9.3. SURGICAL INTERVENTION

If ROP progresses to subtotal or total retinal detachment (Stage 4 or Stage 5), urgent vitreoretinal surgical interventions are performed to prevent retinal separation and preserve vision. **These treatment methods have been reported to preserve 'light perception' in approximately 72% of patients and to achieve a visual acuity of 20/300 or better in about 15% of cases** [57–59].

Vitrectomy involves the surgical removal of the vitreous followed by excision of the fibrovascular tissue causing traction on the retina. This technique relieves the retina and allows it to reattach. In cases where the retina is severely drawn anteriorly, the lens may sometimes need to be sacrificed to achieve retinal reattachment. Even when treatment is anatomically successful, many patients may still develop poor vision or blindness. While better outcomes, both anatomically and functionally, can be achieved in Stage 4A disease, success rates are much lower in Stage 4B or Stage 5 [57–59].

In stage 5, surgery is generally not recommended. However, in bilateral and very recent stage 5 cases, an attempt may be made. In such cases, the primary aim is to prevent anatomical deformation of the globe (such as phthisis bulbi or corneal opacification) and, if possible, to achieve light perception or hand motion vision. Light perception is important for regulating the body's diurnal rhythm and for orientation. Although rare, some Stage 5 patients may also achieve ambulatory vision [57, 59].

- **The advantages and potential complications of each treatment modality should be clearly explained to the family, and informed consent must be obtained prior to initiation of therapy**

### 9.4. TREATMENT ENVIRONMENT

It is important to protect the infant from hypothermia and to monitor vital signs during laser treatment. The procedure can be performed under operating room conditions or in a separate, darkened area within the NICU. Vitreoretinal surgery is carried out under operating room conditions, whereas anti-VEGF agents can be administered in appropriately prepared settings for injection. Monitoring should be continued both during and after the procedures.

### 9.5. ANESTHESIA

When operating room conditions are not available, laser photocoagulation can be performed within the NICU under intravenous sedation and analgesia administered in the presence of a neonatologist. Topical anesthesia alone does not provide adequate analgesia and is therefore not recommended for laser treatment [22, 60].

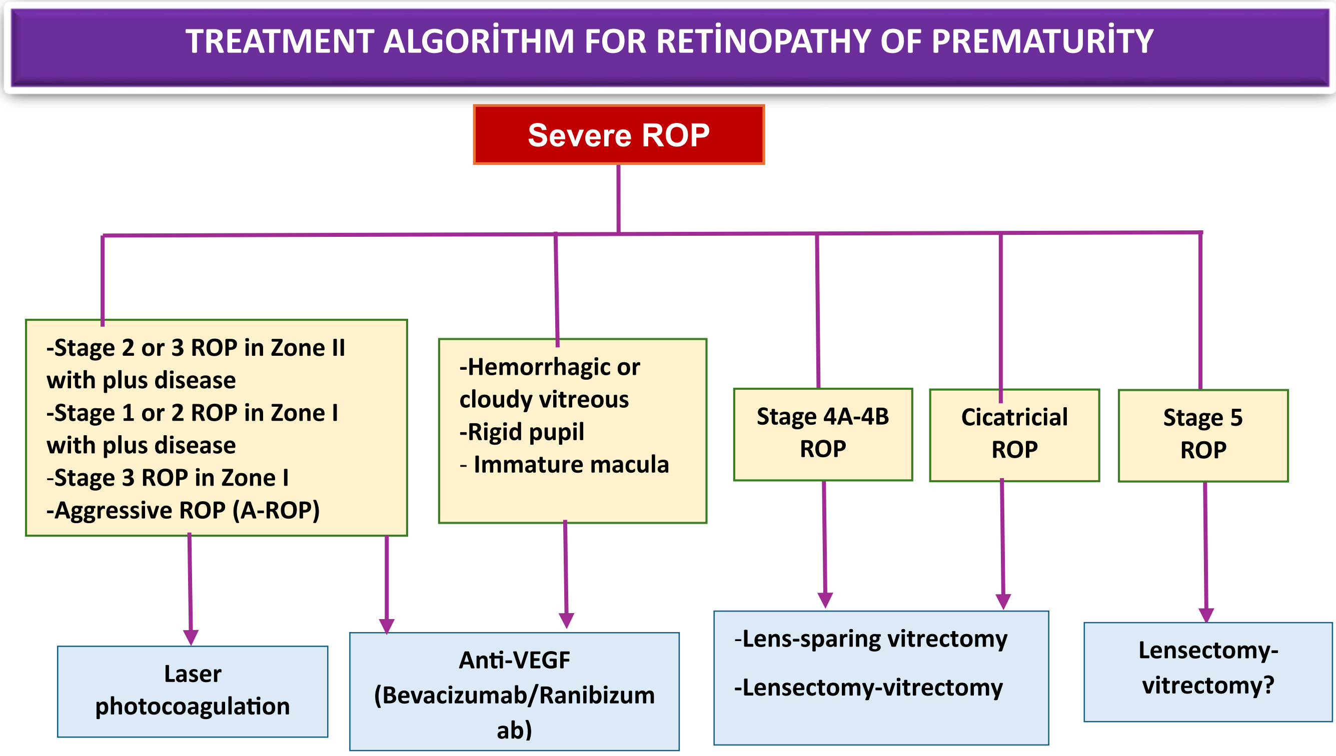


Figure 3: Treatment algorithm for retinopathy of prematurity

### 9.6. POST-TREATMENT FOLLOW-UP

**Following laser treatment, follow-up examinations should be performed on day 1 and day 7 and then repeated weekly until the disease regresses.** Regression after laser photocoagulation is typically observed within 1–2 weeks. If no regression is seen within this period or if progression is detected, incomplete laser application to certain areas should be suspected, or new avascular areas may have emerged due to regression of flat neovascularization. In such cases, a second laser treatment should be administered within a short time frame, as determined by the ophthalmologist.

After anti-VEGF treatment, recovery is faster, and a marked regression of vascular findings is expected within 1–3 days. Plus disease regresses, neovascularization subsides, and the ridge flattens. However, vascularization of the avascular areas is slow, and it should be remembered that it may remain incomplete despite weeks of follow-up. Regression should be observed by the 2nd–3rd day after injection; if the expected regression has occurred, re-evaluation should be performed at the 1st week. The infant should then be followed according to the surveillance algorithm shown in Figure 2 as "regressed ROP," until vascularization is completed, or, if not achieved, until prophylactic laser therapy is applied [42].

**Even if severe ROP requiring treatment does not develop, all infants with ROP should be re-examined within 6 months to 1 year after regression of the acute phase for a detailed ophthalmologic examination.** Families should be informed that these individuals are at risk of ophthalmological problems such as amblyopia, strabismus, high myopia and astigmatism, anisometropia, cataract, retinal detachment, and glaucoma, and they should be encouraged to remain vigilant. Patients should be evaluated annually until school age [21, 22, 61].

**In patients who developed severe ROP or have undergone treatment, lifelong follow-up is crucial, particularly for screening ophthalmological complications that may appear during adolescence and adulthood [61].**

### 9.7. POST-TREATMENT USE OF EYE DROPS

Prophylactic steroid and mydriatic eye drops may be used for up to 7 days following laser therapy to prevent hyphema, posterior synechia, and transient cataract formation., Prophylactic antibiotic eye drops can be administered four times daily for up to one week after intravitreal anti-VEGF injection. Following vitreoretinal surgery, topical eye drops containing steroids, antibiotics, and cycloplegics should be used for the duration determined by the surgeon (up to 4–6 weeks) [22].

## 10. PROGNOSIS

The course of the disease is variable; onset in Zone I, rapidly progression, ‘plus’ disease, and retinal detachment are poor prognostic indicators. Disease starting in Zone II with a slow course generally results in complete recovery or partial retinal scarring, a process that may take up to 1 year. Cases starting in Zone III have the best prognosis and typically achieve complete recovery [18]. No cases starting in Zone III have been reported to develop partial or total retinal detachment [38].

Regression of ROP has been observed in 90% of patients at an average of 38-44 weeks PM age. In patients regressing from Zone II to Zone III, prognosis is excellent in 99% of cases, and no partial or total retinal detachment has been reported when limited to Zone III [19].

The exact frequency of blindness and severe visual impairment due to ROP is unknown. However, ophthalmological problems develop within 6–10 years in 55% of patients who show regression. [20]. In infants who develop mild ROP (Stage 1 or Stage 2 without associated plus disease) and do not have retinal scarring, the incidence of myopia, strabismus, nystagmus, and amblyopia is higher compared to term infants[18].Long-term visual problems have been reported in 7–15% of cases in severe ROP cases with ‘plus’ disease or Stage 3 and above [62–65].

Severe ROP and/or its treatment may lead to ophthalmologic morbidities such as glaucoma, retinal detachment, nystagmus, cataract, optic atrophy, macular problems, microcornea, phthisis bulbi, and refractive errors [66].Severe ROP may be an early marker of neurodevelopmental morbidities. Cognitive, motor, and hearing problems have been found to be 3–4 times more common in cases with severe ROP [67].

- **Families should be informed that, despite appropriate follow-up and treatment, visual problems that may result in blindness can still develop in preterm infants.**
- **A detailed post-discharge follow-up plan should be explained to the family and documented in the patient’s medical record.**
- **All preterm infants should be monitored for vision, refractive errors, and strabismus until the preschool period. Neurodevelopmental follow-up should not be neglected in these patients.**

## 11. PREVENTION

Although the development of ROP is multifactorial, oxygen therapy and its duration remain among the main risk factors. Preventing hyperoxia and recurrent hypoxia–hyperoxia episodes, together with careful monitoring and restriction of administered oxygen concentration, are the most important protective strategies to reduce the incidence and severity of ROP.

There is high-level evidence from randomized controlled trials regarding the target oxygen saturation levels in preterm infants born at a GA of less than 28 weeks, from birth until PM age 36-40 weeks, while supplemental oxygen is still required [68–70].

Randomized, double-blind trials such as SUPPORT, BOOST II (Australia, New Zealand, UK), and COT, which classified target oxygen saturations as low ($SaO_2$: 85-89%) or high ($SaO_2$: 91-95%), were evaluated in the 'Neonatal Oxygenation Prospective Meta-analysis' (**NeOProM**). In this meta-analysis, the low oxygen saturation group had a reduced incidence of severe ROP but higher mortality and necrotizing enterocolitis (NEC) rates [71].

**It is recommended to maintain a target oxygen saturation range of 90–94% for preterm infants requiring supplemental oxygen with monitor alarm limits set at 89–95% to help maintain the target range** [72]. Strategies to prevent bronchopulmonary dysplasia will also reduce oxygen and mechanical ventilation exposure, thereby decreasing the risk of ROP [38].

Meta-analyses comparing preterm infants predominantly fed with breast milk to those fed with formula have shown that breast milk reduces the incidence of any-stage and severe ROP. The antioxidant, immunomodulatory, and neuroprotective properties of breast milk are thought to contribute to its protective effect [73, 74]. The inclusion of omega-3 (fish oil) in total parenteral nutrition (TPN) has been reported to reduce the incidence of ROP [75–77].

Vitamin E supplementation has been reported to reduce the severity of ROP, however it also increases the risk of sepsis and NEC. Antioxidant therapies such as D-penicillamine, reduction of light exposure, IGF-1 replacement, and intravenous or enteral inositol have not been shown to decrease the incidence of ROP [78–83].

Beta-blockers, which possess antiproliferative and antiangiogenic properties, have been reported in some studies to halt progression in infants with ROP. However, there is insufficient data regarding the efficacy, safety, and long-term systemic effects of beta-blocker use in preterm infants [84–87].

• **Antenatal steroid administration, optimal antenatal care,** appropriate delivery room management and good clinical practices during the course of infants' stay in neonatal intensive care units**, protection of TPN sets from light to prevent lipid peroxidation, thermoregulation, pain management, kangaroo care, ensuring appropriate postnatal weight gain, and monitoring, measuring and controlling the oxygen concentration delivered to infant–are important factors in reducing the incidence of ROP. Education and awareness of both nurses and physicians on these aspects are essential.**

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