# Retinopathy of prematurity (ROP): Treatment and prognosis

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## INTRODUCTION

Retinopathy of prematurity (ROP) is a developmental vascular proliferative disorder that occurs in the retina of preterm infants with incomplete retinal vascularization. ROP is an important cause of severe visual impairment in childhood. Other ophthalmologic disorders that occur frequently in preterm infants include amblyopia, strabismus, and refractive errors.

The treatment and prognosis of ROP are discussed in this topic. The pathogenesis, epidemiology, classification, and screening for ROP are discussed separately. (See "Retinopathy of prematurity (ROP): Risk factors, classification, and screening".)

Other common eye problems in preterm infants are discussed separately.

- (See "Amblyopia in children: Classification, screening, and evaluation".)
- (See "Evaluation and management of strabismus in children".)
- (See "Refractive errors in children".)

## TREATMENT

Treatment for ROP is based upon disease severity, as defined by the International Classification for Retinopathy of Prematurity (ICROP) ( figure 1). Treatment is initiated when the infant develops type I ROP (also called "high-risk prethreshold ROP"). Type I ROP is defined as any of

the following (see "Retinopathy of prematurity (ROP): Risk factors, classification, and screening", section on 'Classification'):

- Any stage ROP in zone I with plus disease
- Stage 3 ROP in zone I without plus disease
- Stage 2 or 3 ROP in zone II with plus disease

Treatment is generally **not** indicated for eyes that do not meet criteria for type I ROP. (See 'Less severe retinopathy of prematurity' below.)

**Type I ROP** — Treatment is generally indicated for eyes meeting criteria for type I ROP ( figure 1). Treatment may consist of retinal ablative therapy (with laser photocoagulation) or intravitreal injection of an anti-vascular endothelial growth factor (anti-VEGF) agent. (See 'First-line therapies' below.)

Retinal ablative therapy reduces the incidence of adverse structural and functional outcomes [1,2]. Unfortunately, despite appropriate treatment, threshold ROP progresses to retinal detachment in 15 to 20 percent of cases [3]. This was the impetus for the Early Treatment for Retinopathy of Prematurity (ETROP) study [4], which ultimately led to the recommendation to treat the disease at an earlier stage (type I ROP). Treatment should be undertaken as soon as is practicable and, generally, should not be delayed beyond 72 hours following diagnosis [5].

The benefits of retinal ablative therapy in infants with type I ROP were demonstrated in the ETROP trial, which included 317 infants with bilateral type I ROP (also called "high-risk prethreshold ROP") randomly assigned to early treatment in one eye and conventional management in the other [4,6-10]. Early treatment reduced unfavorable visual acuity (14.5 versus 19.5 percent) and unfavorable structural outcomes (9.1 versus 15.6 percent) at nine months corrected age [4]. At age six years, early-treated eyes continued to have fewer unfavorable structural outcomes (8.9 versus 15.2 percent) and relatively preserved peripheral vision [8,9]. At age six years, visual acuity outcomes were no longer statistically superior in the early treatment group (24.6 versus 29.0 percent unfavorable); however, in subgroup analysis, early treatment improved visual acuity outcome for "higher-risk" prethreshold eyes [9,10].

The benefit of early treatment in the ETROP trial was largely driven by improved outcomes in zone I eyes (41 percent of the cohort). Thus, benefits are less well established for infants with borderline treatment indications (eg, zone II eyes starting to show signs of involution).

### First-line therapies

**Choice of therapy** — Effective treatment modalities for ROP include laser photocoagulation and intravitreal injection of anti-VEGF agents (eg, bevacizumab, ranibizumab, aflibercept). Both of these treatment approaches are widely used throughout the world. (See 'Anti-vascular endothelial growth factor therapy' below and 'Laser photocoagulation' below.)

The choice between the two treatment modalities is largely based on the experience and preference of the treating ophthalmologist and the preferences of the patient's caregivers. Randomized trials comparing laser photocoagulation and anti-VEGF therapy, which are discussed below (see 'Anti-vascular endothelial growth factor therapy' below), are limited by small sample size and relatively short follow-up [11-13]. Both therapies have advantages and disadvantages. There is longer experience with laser therapy, and, therefore, the expected effects (including short- and long-term outcomes and adverse events) are generally better established with this modality. However, experience with anti-VEGF therapy continues to grow.

Important considerations include:

- Ease of administration – Intravitreal injection of anti-VEGF agents can be performed with topical anesthesia at the bedside, whereas laser photocoagulation requires more time, is typically more stressful to the infant, and is often performed under general anesthesia. Thus, in unstable infants, intravitreal anti-VEGF therapy may be preferred.

- Timing of response – ROP involution is generally more rapid with anti-VEGF therapy.

- Severity of disease – Laser therapy is an established therapy for type I ROP. Strict indications for anti-VEGF therapy are less well established, though the available evidence suggests that anti-VEGF therapy is effective for posterior ROP.

- Long-term ocular outcomes – Long-term ocular outcomes, particularly the effects on visual acuity and visual fields, are not as well established with anti-VEGF therapy. The risk of high myopia appears to be lower with anti-VEGF therapy, and, theoretically, anti-VEGF therapy may limit permanent visual field loss that can occur with peripheral ablative laser therapy. However, this has not been demonstrated in large clinical studies.

- Potential for systemic effects – There is a theoretical concern that anti-VEGF therapy has the potential to lower systemic VEGF levels, which could affect other organs. The available data on short-term safety have not definitively demonstrated an increased risk of adverse systemic effects compared with laser therapy; however, few long-term data are available. While there are no systemic events directly related to laser photocoagulation, unwanted systemic events may occur due to the effects of general anesthesia/sedation and stress associated with the procedure.

**Anti-vascular endothelial growth factor therapy** — Since the early 2000s, anti-VEGF monoclonal antibodies (eg, bevacizumab, ranibizumab, aflibercept) have emerged as an effective treatment for ROP and have been advocated as first-line therapy by many ophthalmologists [11,12,14-20]. The available clinical trial data suggest that anti-VEGF therapy is effective for treating ROP prior to the onset of retinal detachment [11-13].

- **Clinical use** – Anti-VEGF agents may be used as monotherapy or may be used in combination with laser therapy. The minimum effective dose has not yet been established, but it appears to be much less than the doses used in early reports [21-23]. Uncertainties remain regarding the long-term effect of anti-VEGF therapy on visual acuity and visual fields, optimal duration and frequency of follow-up, and management of recurrence [14,20,24-28].

- **Advantages and disadvantages** – Advantages of anti-VEGF therapy over laser photocoagulation for the treatment of ROP include ease of administration (typically at the bedside under local anesthesia) and more rapid response (because it inactivates VEGF directly). In addition, anti-VEGF therapy may be used in infants for whom photocoagulation is difficult or impossible (eg, those with opaque cornea or lens, vitreous haziness, poor pupillary dilation) [11,24].

  Potential disadvantages include interference with normal retinal vascularization (a potential consequence if treatment is administered too early) or hastening retinal detachment (a potential consequence if treatment is given too late) [14,24,25,29-31]. In addition, there is a theoretical possibility of long-term systemic effects from temporarily suppressing serum VEGF levels in the neonatal period, including potential damage to the brain, lungs, liver, and kidneys [32,33]. Based on the available data, these theoretical concerns have not been substantiated. Nevertheless, long-term follow-up data are needed to fully establish the safety of anti-VEGF therapy in this population. Endophthalmitis, though rare, is a potentially devastating complication of intravitreal injection.

- **Agents** – Anti-VEGF agents that have been used to treat ROP include bevacizumab, ranibizumab, and aflibercept. In the United States, aflibercept is approved by the US Food and Drug Administration (FDA) for the treatment ROP [34]. Bevacizumab is FDA-approved for treatment of metastatic colon and other cancers; it has also been used "off-label" to treat neovascular eye conditions, including age-related macular degeneration, diabetic retinopathy, and ROP [14,35]. Ranibizumab is FDA-approved for the treatment of diabetic retinopathy; its use in ROP is "off-label." (See "Diabetic retinopathy: Prevention and treatment", section on 'Anti-VEGF agents'.)

- **Efficacy** – The efficacy of anti-VEGF therapy for ROP is supported by randomized trials and meta-analyses [11-13,36,37]. Taken together, they suggest that anti-VEGF therapy is effective in arresting ROP, is well tolerated in the short term, and may be associated with lower risk of unfavorable structural eye outcomes and high myopia compared with laser therapy.

  In a meta-analysis of three trials comparing anti-VEGF therapy with laser therapy, progression to stage 4 or 5 ROP (ie, partial or complete retinal detachment) occurred at similarly low rates (approximately 1 percent) in both treatment groups [12]. Recurrence rates were also similar in both groups (18 percent for anti-VEGF versus 20 percent for laser therapy; relative risk [RR] 0.88, 95% CI 0.47-1.63). However, in subgroup analyses, the recurrence rate for zone I eyes was lower with anti-VEGF treatment compared with laser therapy, whereas for zone II eyes, the recurrence rate was lower with laser therapy.

  The largest trial included in the meta-analysis was the Bevacizumab Eliminates the Angiogenic Threat for ROP (BEAT-ROP) trial, a multicenter randomized trial involving 150 infants with stage 3+ ROP in zone I or posterior zone II who were randomized to treatment with intravitreal bevacizumab (IVB) or laser phototherapy [11]. At 54 weeks postmenstrual age, infants treated with IVB had fewer recurrences (6 versus 26 percent) and fewer structural abnormalities (eg, macular dragging, retinal detachment). The difference was most pronounced in zone I eyes. Recurrence occurred later among infants treated with IVB than infants treated with laser therapy (mean of 16.0 versus 6.2 weeks after treatment), suggesting that infants treated with IVB may require prolonged follow-up. In a follow-up study of 109 infants enrolled in BEAT-ROP who were evaluated at a mean age of 2.5 years, very high myopia was observed less commonly in IVB-treated eyes compared with laser-treated eyes (3 versus 42 percent) [38].

  In the subsequent RAINBOW trial, which was not included in the meta-analysis, 225 infants with type I ROP (excluding stage 2+ in zone II) were randomized in a three-way fashion to high- or low-dose intravitreal ranibizumab (IVR) or laser therapy [13]. Among the 202 surviving infants who underwent eye examination at 24 weeks, ROP completely regressed in 100 percent in the high-dose IVR group, 96 percent in the low-dose IVR group, and 100 percent in the laser therapy group. Unfavorable structural eye findings (eg, retinal vessel dragging, retinal fold, partial or complete retinal detachment) were noted in 1, 6, and 9 percent, respectively. The number of patients requiring additional therapies after initial treatment was similar in all three groups (31, 31, and 30 percent, respectively).

  In a follow-up report of 153 infants from the RAINBOW trial who were evaluated at age 20 to 28 months, ocular structural abnormalities were seen less commonly in ranibizumab-

treated infants (2 percent in both the high- and low-dose groups) compared with laser therapy-treated infants (9 percent); however, the difference was not statistically significant [39]. High myopia was less common in infants who received high-dose ranibizumab compared with laser therapy (5 versus 20 percent; odds ratio 0.19, 95% CI 0.05-0.69). Vision-related quality of life scores were slightly higher in the high-dose ranibizumab group compared with laser therapy (mean score 84 versus 77), but the finding did not achieve statistical significance.

In the FIREFLEYE trial, which was also not included in the meta-analysis, 113 infants (218 eyes) with type I ROP were randomly assigned to intravitreal aflibercept (n = 75 infants; 146 eyes) or laser therapy (n = 38 infants; 72 eyes) [36]. Both treatments achieved similar success rates (86 percent with intravitreal aflibercept versus 82 percent with laser therapy, a difference that was not statistically significant). The number of eyes requiring additional therapies after initial treatment (either retreatment with the same modality or with the alternate treatment) was similar in both groups (23 and 18 percent, respectively). Serious ocular side effects were more common in the aflibercept group, while systemic side effects occurred less frequently. An interim analysis showed no clear differences in outcomes between aflibercept and laser therapy at two-year follow up [40].

Infants enrolled in the RAINBOW and FIREFLEYE trials are being followed to five years of age, which will provide important information regarding the long-term safety of intravitreal anti-VEGF therapy in this population.

Observational studies also suggest a high rate of ROP regression following treatment with anti-VEGF agents (including bevacizumab, ranibizumab, aflibercept, or conbercept) [14,16,17,19,41-45].

- **Adverse effects** – Serious adverse ocular effects occur in approximately 5 to 10 percent of treated eyes and may include retinal hemorrhage, retinal detachment, macular traction, cataract, increased intraocular pressure, and endophthalmitis [46]. These complications are more common when anti-VEGF therapy is used in combination with laser therapy [46,47]. Systemic side effects are uncommon. In a meta-analysis of three trials (544 eyes) comparing anti-VEGF therapy with laser therapy, local adverse effects were rare in both groups [12]. No infants in the anti-VEGF therapy group experienced corneal clouding, endophthalmitis, or systemic adverse effects. In the subsequent RAINBOW trial, in which 225 infants were randomly assigned to high- or low-dose ranibizumab or laser therapy, rates of systemic and ocular side effects were similar in all three treatment arms [13]. One infant in the high-dose ranibizumab group developed a cataract thought to be caused by

lens damage from the injecting needle; another infant in the low-dose ranibizumab group developed endophthalmitis requiring vitrectomy.

**Laser photocoagulation** — Laser photocoagulation, using the diode or argon laser, is an established standard treatment for ROP. The laser, mounted on an indirect ophthalmoscope, is aimed through the pupil and focused on the avascular retina using a condensing lens like the one used for retinal viewing.

- **Efficacy** – Based on the available clinical trial data described above (see 'Anti-vascular endothelial growth factor therapy' above), laser photocoagulation appears to have similar efficacy compared with anti-VEGF therapy, though laser therapy may be associated with a higher risk of unfavorable structural eye outcomes and high myopia [11-13,38,39].

  Laser photocoagulation has superior efficacy and better tolerability compared with cryotherapy, as supported by randomized controlled trials and observational studies [48-55]. In these studies, laser therapy achieved higher rates of resolution or regression of ROP, less retinal detachment, better visual acuity, and less myopia compared with cryotherapy.

- **Complications** – Laser treatment is generally well tolerated. Compared with older cryotherapy procedures, infants undergoing laser therapy are less likely to have conjunctival chemosis, inflammation, pain, or apnea and bradycardia following the procedure.

  Cataracts may develop after laser treatment, but visually significant lens opacities appear to be rare. In the BEAT-ROP trial, three infants (4 percent) required surgery for cataract removal after treatment with laser therapy [11]. Cataracts may be less likely to occur following photocoagulation with a diode compared with argon laser. In one study of 293 eyes, no visually significant cataracts occurred after diode laser treatment [56]. In contrast, cataracts formed in 1 to 6 percent of eyes following argon laser treatment [57,58]. A rare complication of laser treatment is angle-closure glaucoma seen two to five weeks after treatment [59]. (See "Overview of glaucoma in infants and children", section on 'Retinopathy of prematurity' and "Cataract in children", section on 'Radiation'.)

### Therapies not commonly used

- **Cryotherapy** – In contemporary practice, cryotherapy is rarely used and is generally limited to settings where laser photocoagulation and anti-VEGF therapy are unavailable. Cryotherapy was the only proven treatment for ROP until the early 1990s, but it has been

largely replaced by laser photocoagulation and anti-VEGF therapy due to improved outcomes with those modalities [60-63]. (See 'First-line therapies' above.)

- **Beta blockers** – Limited evidence from a few small randomized trials and observational studies suggests administration of oral beta blockers (eg, propranolol) prior to the onset of or in the earlier stages of ROP may reduce progression towards severe ROP and decrease the need for laser photocoagulation or anti-VEGF therapy [64,65]. Additional data regarding efficacy, dosing, timing, safety, and long-term visual outcome are needed before using this approach clinically.

**Treatment failure and recurrence** — For patients who fail to achieve ROP regression with the initial therapy and for those in whom vision-threatening ROP recurs, further therapy generally consists of a second treatment using either the same modality or a different modality.

Therapy with laser photocoagulation or intravitreal anti-VEGF injection results in regression of ROP in the majority of treated patients (≥85 to 90 percent in most reports) [3,11,48,51,53]. Regression may occur over several weeks with laser therapy, whereas the response is usually more rapid with anti-VEGF therapy. However, even if the ROP regresses, recurrences may occur. Some studies have reported recurrence in as many as one-quarter of treated patients. Reported recurrence rates vary considerably depending on the timing of treatment, the laser treatment technique, the specific anti-VEGF agent and dose used, and/or the definition used to identify recurrence.

In the BEAT-ROP trial, recurrences occurred less commonly with IVB compared with laser therapy (6 versus 27 percent) [11]. However, higher recurrence rates with anti-VEGF therapy have been reported in observational studies and in the RAINBOW trial [13,15,16,41,66-68]. Reported recurrence rates in these studies ranged from 15 to 30 percent. The timing of recurrence is later with anti-VEGF therapy compared with laser therapy. In the BEAT-ROP trial, recurrence occurred at a mean of 16 weeks after IVB versus 6.2 weeks after laser treatment [11]. Most recurrences after IVB treatment occur at 45 to 55 weeks adjusted age [69]. Risk factors for recurrence include lower birth weight, longer hospitalization, and aggressive posterior ROP.

**Less severe retinopathy of prematurity** — Treatment is generally **not** indicated for eyes that do not meet criteria for type I ROP ( figure 1), though such infants should be monitored until the criteria for discontinuation of screening have been met. (See "Retinopathy of prematurity (ROP): Risk factors, classification, and screening", section on 'Examination schedule'.)

In certain circumstances, it may be reasonable to treat eyes that do not meet criteria for type I ROP. For example, if one eye has type I or more severe ROP and is undergoing treatment and

the fellow eye has active ROP that does not meet criteria for type I ROP, it may be reasonable to treat both eyes at the same time, particularly if there are concerning or persistent findings in the less severe eye [70]. Such decisions should be made on a case-by-case basis.

**Retinal detachment** — When ROP progresses to partial or total retinal detachment (stage 4 or 5), surgical intervention may be attempted to promote reattachment of the retina and preservation of vision. The procedures typically used include scleral buckling or vitrectomy. In one series, these techniques resulted in light perception or better vision in 72 percent of eyes and achieved visual acuity of 20/300 or better in 15 percent [71].

With scleral buckling, a silicone band is placed around the eye and tightened so that the wall of the eye is reapposed to the retina, allowing reattachment to occur. Vitrectomy involves surgical removal of the vitreous and excision of the fibrous tissue that is placing traction on the retina. Upon removal of the vitreous and its associated traction, the retina may settle back into position, with resulting reattachment. Despite successful reattachment of the retina, patients who have detachments involving the fovea often have extremely poor vision [72-76].

Predictors of retinal detachment after laser treatment for threshold ROP were identified in a retrospective case series of 262 eyes in 138 infants [77]. Retinal detachment developed in 14 percent of eyes by 6 to 12 weeks [3]. Retinal detachment was more frequent in eyes with vitreous hemorrhage severe enough to completely obscure visualization of the retina and in eyes with clinically important vitreous organization. Vitreous organization was defined by the presence of white, fibrous-appearing opacification of the vitreous above the vascular/avascular junction. It was considered clinically important when it spanned ≥2 contiguous clock hours or was dense enough to moderately or severely reduce visualization of the retina but also to have been unassociated with retinal detachment at the time of initial discovery. The development of retinal detachment was not associated with prolonged activity of stage 3 disease or plus disease more than 21 days after treatment.

## FOLLOW-UP

**Treated patients** — Follow-up is suggested within one week after laser photocoagulation or anti-vascular endothelial growth factor (anti-VEGF) injection to ensure that additional treatment is not necessary [5]. Subsequent follow-up depends on the clinical course. We typically see patients every one to two weeks initially, with less frequent evaluations as the clinical course improves. Infants treated with anti-VEGF injections require a longer duration of follow-up since late recurrences can occur [5] (see 'Treatment failure and recurrence' above). In addition, for anti-VEGF-treated eyes that have significant residual avascular retina, ongoing peripheral retinal

evaluation beyond the first decade of life is important to detect potential late retinal complication.

Infants with ROP are at increased risk for developing myopia, astigmatism, anisometropia, and strabismus [78-80]. Infants and children with a history of severe ROP therefore may require regular follow-up with an ophthalmologist to monitor for long-term vision problems. The evaluation and management of refractive errors and strabismus in children are discussed separately. (See "Refractive errors in children" and "Evaluation and management of strabismus in children".)

**Untreated patients** — The optimal approach to follow-up in patients with ROP that does not meet criteria for treatment is uncertain. Late retinal complications (eg, retinal tears or detachment) can occur in some patients [81]. We suggest follow-up for patients who were noted to have a large amount of avascular retina at the time of cessation of ROP screening. Follow-up may also be appropriate for patients with lesser degrees of avascular retina. The optimal timing of follow-up is uncertain but should probably continue beyond the first decade of life for most patients.

In a retrospective multicenter series of 186 patients (363 eyes) with ROP that did not require treatment, retinal abnormalities were commonly noted over follow-up to a mean age of 35 years, [81]. Peripheral retinal anomalies included lattice degeneration in 52 percent, atrophic holes in 35 percent, retinal tears in 31 percent, and retinal detachment in 39 percent of eyes. While the study represents a selected group of patients under the care of vitreoretinal surgeons, the study does raise important concerns about the long-term care of patients who did not require treatment for ROP and it supports the notion that long-term follow-up is needed for a subset of these patients.

## OUTCOME

Long-term visual impairment occurs in 7 to 15 percent of children with moderate to severe ROP [82-85]. The risk of visual impairment is greatest in children with severe ROP (ie, stage ≥3). Poor visual acuity is rare when ROP is observed only in zone III ( figure 1) [86].

The incidence of visual impairment due to ROP has decreased considerably since the 1990s, most likely as a result of improved screening for ROP and advances in treatment, including laser photocoagulation and anti-vascular endothelial growth factor (anti-VEGF) agents [85]. In a retrospective study, the incidence of complete blindness due to ROP decreased from 27.5 percent in the period from 1994 to 2000 to 7.1 percent in the period from 2000 to 2009 [84].

Similarly, in another retrospective cohort study, the incidence of visual impairment from ROP fell from 26 percent in the period from 1991 to 2004 to 7.3 percent in the period from 2005 to 2012 [85]. During this same period, rates of detection of ROP increased substantially, suggesting that the improved outcomes are due to improvements in treatment rather than prevention [87].

Severe ROP is also a predictor of nonvisual functional disabilities [88,89]. In a cohort study of 1582 preterm infants with birth weights ≤1250 g born between 1999 and 2004 and followed up at age five years, 40 percent of children with severe ROP had at least one nonvisual disability compared with 16 percent of children without severe ROP [88]. Motor impairment, cognitive impairment, and severe hearing loss were three to four times more common in children with severe ROP than in those without. Long-term complications of prematurity are discussed in greater detail separately. (See "Overview of the long-term complications of preterm birth".)

## PREVENTION

Based upon the available evidence, we recommend that efforts to reduce ROP focus on prompt detection and treatment. In addition, episodes of physiologic instability that may increase the risk of ROP should be avoided if possible. (See "Retinopathy of prematurity (ROP): Risk factors, classification, and screening", section on 'Risk factors'.)

- **Breast milk feeding** – Breast milk feeding appears to play a protective role in preventing ROP and should be encouraged for this benefit and because of other well-established benefits of breast milk [90,91]. (See "Infant benefits of breastfeeding".)

- **Docosahexaenoic acid (DHA) supplementation** – DHA and other omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) are integral components of the brain and retinal phospholipid membrane. Preterm infants miss some of the fetal accretion of DHA, which normally occurs during the third trimester of pregnancy. Clinical trials suggest that DHA supplementation has modest beneficial effects on visual acuity and may reduce the risk of ROP in very preterm neonates [92-94]. The effects of LCPUFA supplementation on other outcomes (eg, cognitive development, BPD, other neonatal comorbid diseases) and recommendations regarding maternal and infant dietary intake and supplementation are provided separately. (See "Long-chain polyunsaturated fatty acids (LCPUFA) for preterm and term infants".)

- **Interventions to prevent bronchopulmonary dysplasia (BPD)** – Interventions aimed at preventing or reducing the severity of BPD theoretically have potential to reduce ROP by limiting exposure to mechanical ventilation and supplemental oxygen, which are

important risk factors for ROP. Prevention of BPD is discussed in greater detail separately. (See "Bronchopulmonary dysplasia (BPD): Prevention".)

- **Ineffective and unproven interventions** – Other interventions aimed at preventing ROP have generally not been effective [95]:

  - **Antioxidant therapies** – Antioxidant therapies (eg, vitamin E, D-penicillamine, and limited exposure to light) have been proposed as specific interventions to prevent or limit the progression of ROP; however, these therapies have been unsuccessful:

    - A meta-analysis of randomized trials found that vitamin E supplementation was associated with a nonsignificant trend toward reduced risk of severe ROP (relative risk [RR] 0.72, 95% CI 0.41-1.25); however, it increased the risk of sepsis (RR 1.52, 95% CI 1.13-2.04) [96].

    - A meta-analysis of three randomized trials (369 patients) of D-penicillamine in preterm infants did not detect a significant reduction in severe ROP (RR 0.38, 95% CI 0.03-4.26) [97].

    - A meta-analysis of four randomized or quasi-randomized trials (897 patients) of ambient light reduction found that the intervention did not reduce the incidence of ROP (RR 1, 95% CI 0.89-1.13) [98].

  - **Oxygen targets** – Both high and low oxygen levels have been tested as strategies to prevent ROP or limit progression; neither strategy appears to be effective.

    Supplemental oxygen therapy has been tested as a strategy to prevent progression of ROP, with the rationale that retinal hypoxia contributes to neovascularization. In the STOP-ROP trial, 649 infants with prethreshold ROP were randomly assigned to maintain oxygen saturation at 96 to 99 (supplemental) or 89 to 94 (conventional) percent [99]. The rate of progression to threshold ROP was lower in the supplemental oxygen group compared with the conventional group, but the finding did not reach statistical significance (41 versus 48 percent; odds ratio 0.72, 95% CI 0.52-1.01). In a prespecified subgroup analysis of the effect in infants without plus disease, the rate of progression to threshold ROP was significantly reduced (39 versus 46 percent). Rates of adverse ophthalmologic outcomes (including partial or total retinal detachment, retinal folds, obstruction of the visual axis, or macular ectopia) were similar in the supplemental oxygen and conventional groups (8 versus 8.3 percent, respectively). Adverse pulmonary effects occurred more frequently in the supplemental oxygen group than in the conventional group. Treated infants were more likely to have pneumonia and/or

exacerbations of chronic lung disease (13.2 versus 8.5 percent) and to remain hospitalized, on oxygen, and on diuretics at 50 postmenstrual weeks. Thus, if there is a beneficial effect of supplemental oxygen on ROP, it appears to be small and the risk of adverse events likely outweighs the benefit.

Similarly, efforts to prevent ROP by avoiding high oxygen levels have also been unrewarding. In a 2015 meta-analysis that included data from five randomized trials comparing restricted oxygen therapy (target oxygen saturation 85 to 89 percent) and liberal oxygen therapy (target oxygen saturation 91 to 95 percent), the restrictive strategy was associated with a nonsignificant reduction in ROP (RR 0.72, 95% CI 0.50-1.04; three trials) but an increased risk of in-hospital mortality (RR 1.18, 95% CI 1.03-1.36; two trials) [100]. There was no difference in mortality or severe disability at 18 to 24 months (RR 1.02, 95% CI 0.92-1.14; four trials). In a subsequent meta-analysis that included observational studies and clinical trials, lower oxygen saturation target was associated with a lower risk of developing ROP (RR 0.86, 95% CI 0.77-0.97) but an increased risk of mortality (RR 1.15, 95% CI 1.04-1.29) [95].

The optimal target for oxygen saturation in extremely preterm infants remains uncertain. This is discussed in greater detail separately. (See "Neonatal target oxygen levels for preterm infants", section on 'Oxygen target levels'.)

- **Inositol** – Inositol is an essential nutrient involved in surfactant production. It has been postulated that inositol supplementation in preterm infants at risk for BPD may improve respiratory status and other related outcomes, including ROP. Based on the available data, we suggest **not** supplementing inositol in preterm infants at risk for BPD and ROP. In a multicenter randomized trial in 638 preterm neonates, rates of type 1 ROP were similar in infants who received inositol supplementation compared with placebo (16 versus 11 percent; RR 1.38, 95% CI 0.91-2.1) [101]. Rates of BPD were also similar (58 versus 57 percent; RR 1.03, 95% CI 0.91-1.16). The trial was stopped early due to increased mortality in the inositol group (RR 1.66, 95% CI 1.14-2.43). An earlier meta-analysis of three trials (336 patients) found lower rates of ROP in infants treated with inositol, though the finding did not achieve statistical significance (12 versus 20 percent; RR 0.62, 95% CI 0.38-1.01) [102]. Mortality was also reduced (RR 0.53, 95% CI 0.31-0.91), but the incidence of BPD was not (RR 1.30, 95% CI 0.64-2.64). The trials included in the meta-analysis were deemed to be at high risk of bias, thus limiting the certainty in these findings. In addition, the apparent effect of inositol on lowering mortality and ROP were difficult to reconcile with its lack of effect in reducing BPD.

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword[s] of interest.)

- Basics topic (see "Patient education: Retinopathy of prematurity (ROP) (The Basics)")

## SUMMARY AND RECOMMENDATIONS

- **Importance** – Retinopathy of prematurity (ROP) is a developmental proliferative vascular disorder that occurs in the retina of preterm infants with incomplete retinal vascularization. It is a common cause of potentially preventable childhood blindness in the United States. (See 'Introduction' above and "Retinopathy of prematurity (ROP): Risk factors, classification, and screening".)

- **Indications for treatment** – Treatment for ROP is based on disease severity ( figure 1) (see 'Treatment' above):

  - For patients with type I ROP or more severe disease, we recommend treatment rather than ongoing surveillance (**Grade 1B**). (See 'Type I ROP' above.)

  - For patients with ROP who do not meet criteria for type I ROP, we suggest ongoing surveillance rather than providing specific ROP therapy (**Grade 2B**). These infants should be monitored until the criteria for discontinuation of screening have been met. (See 'Less severe retinopathy of prematurity' above and "Retinopathy of prematurity (ROP): Risk factors, classification, and screening", section on 'Discontinuation'.)

- **Choice of therapy** – Effective treatments for ROP include laser photocoagulation and intravitreal injection of an anti-vascular endothelial growth factor (anti-VEGF) agent (eg,

bevacizumab, ranibizumab, aflibercept). The choice of therapy depends upon the medical condition of the infant, experience and preference of the treating ophthalmologist, and preferences of the patient's caregivers. (See 'First-line therapies' above and 'Choice of therapy' above.)

- **Management of treatment failure or recurrence** – Therapy with laser photocoagulation or intravitreal anti-VEGF injection results in regression of ROP in most patients. Regression may occur over several weeks with laser therapy, whereas the response is usually more rapid with anti-VEGF therapy. However, even if the ROP regresses, recurrences may occur.

  For patients who fail to achieve ROP regression with the initial therapy and for those in whom vision-threatening ROP recurs, further therapy may consist of a second treatment using the same modality or may involve using a different modality. (See 'Treatment failure and recurrence' above.)

- **Retinal detachment** – When ROP progresses to partial or total retinal detachment (stage 4 or 5), surgical intervention may be attempted to prevent progression, promote reattachment of the retina, and preserve vision. (See 'Retinal detachment' above.)

- **Follow-up** – After treatment, follow-up examinations are required for infants who remain at risk for ROP progression and for infants with treated ROP who are at risk for recurrence. (See 'Follow-up' above.)

- **Outcome** – Long-term visual impairment occurs in 7 to 15 percent of children with moderate to severe ROP. The risk of visual impairment is greatest in children with severe ROP (ie, stage ≥3). The incidence of visual impairment due to ROP is decreasing, most likely as a result of advances in treatment of severe disease. (See 'Outcome' above.)

- **Prevention** – Efforts to prevent severe ROP should focus on prompt detection and treatment. Episodes of physiologic instability that may increase the risk of ROP should be avoided if possible. Breast milk feeding appears to play a protective role in preventing ROP and should be encouraged for this benefit and because of other well-established benefits of breast milk. Other interventions aimed at preventing ROP have generally not been effective. (See 'Prevention' above.)

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