Retinopathy of prematurity: An update on screening and management

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Retinopathy of prematurity is a proliferative disorder of the developing retinal blood vessels in preterm infants. The present practice point reviews new information regarding screening and management for retinopathy of prematurity, including the role of risk factors in screening, optimal scheduling for screening examinations, pain management, digital retinal photography and antivascular endothelial growth factor therapy.

Key Words: *Anti-VEGF therapy; Retinopathy of prematurity; ROP screening*

La rétinopathie du prématuré : mise à jour sur le dépistage et la prise en charge

La rétinopathie du prématuré est un trouble prolifératif qui touche les vaisseaux sanguins de la rétine en développement des nourrissons prématurés. Le présent point de pratique traite de nouvelles données sur le dépistage et la prise en charge de la rétinopathie du prématuré, y compris le rôle des facteurs de risque dans le dépistage, le moment optimal pour effectuer les examens de dépistage, la prise en charge de la douleur, la rétinographie numérique et le traitement par anti-facteur de croissance de l'endothélium vasculaire.

Retinopathy of prematurity (ROP), a proliferative disorder of the developing retinal blood vessels in preterm infants, may lead to poor visual acuity or blindness. Data from the Canadian Neonatal Network suggest that for neonates born before 31 weeks' gestational age (GA), approximately 40% to 50% develop some stage of ROP, 7% to 8% develop severe ROP and 5% to 6% require treatment.(1) Health care professionals who care for preterm infants in both neonatal intensive care units and community settings must know who and when to screen for ROP. In 2010, the Canadian Paediatric Society published a practice point summarizing current recommendations for ROP screening.(2) Since then, ROP treatment has progressed, new studies have examined risk factors and selective screening criteria, and revised recommendations have been published by the American Academy of Pediatrics (AAP).(3) The present practice point reviews new information regarding ROP screening and management.

ROP CLASSIFICATION AND DEFINITIONS

The revised 2005 International Classification of Retinopathy of Prematurity, which describes ROP according to location (zones) and severity of abnormal vascularization (stages), is used to classify and record the ophthalmologist's findings based on retinal examination.(4) The zones of the retina are shown in Figure 1, and the stages of ROP and other current terminology are summarized in Table 1. The terms 'type 1' and 'type 2' ROP are now used to differentiate eyes with significant changes of ROP that require treatment (type 1) from eyes with significant changes that do not require treatment but must be carefully monitored (type 2). Current indications for treatment (type 1 ROP) are based on results from the Early Treatment for Retinopathy of Prematurity trial (ETROP)(5) and are:

- Zone I – any stage ROP with plus disease
- Zone I – stage 3 ROP without plus disease
- Zone II – stage 2 or 3 ROP with plus disease

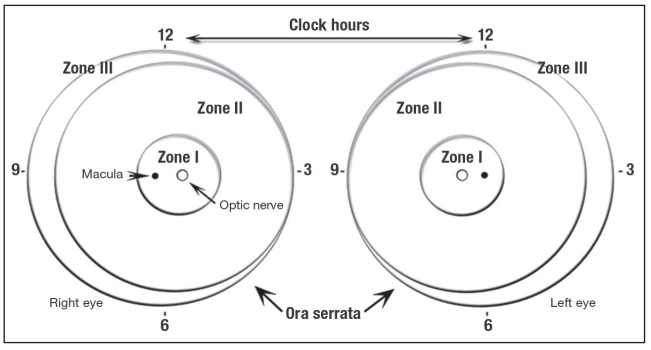

Figure 1) *Retina of the right and left eye, showing borders of the three zones and clock hours used to describe the location and extent of retinopathy of prematurity. Reproduced with permission from reference 3*

The terms 'threshold' and 'prethreshold' are also sometimes used. Threshold ROP is defined as at least five contiguous or eight cumulative clock hours of stage 3 ROP in zones I and II in the presence of plus disease; prethreshold ROP is ROP with a high likelihood of progressing to threshold ROP. Threshold ROP, as well as more severe forms of prethreshold ROP, require treatment and are incorporated in the type 1 ROP category.

SCREENING FOR ROP

Whom to screen

In 2010, the Canadian Paediatric Society suggested that if every infant ≤$30^{6/7}$ weeks' GA regardless of birth weight, as well as any infant with a birth weight ≤1250 g were screened, as recommended by the Royal College of Paediatrics and Child Health, and the Royal College of Ophthalmologists, United Kingdom,(6) the likelihood of an unscreened infant developing advanced ROP that requires treatment would be extremely low.(2) The 2013 AAP policy statement differed somewhat, recommending screening for infants with birth weights ≤1500 g or a GA of 30 weeks or less,

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TABLE 1
Stages (1 to 5) and description of retinopathy of prematurity

Stage 1	Demarcation line separating avascular from vascularized retina
Stage 2	Ridge arising in region of demarcation line
Stage 3	Extraretinal fibrovascular proliferation/neovascularization extending into the vitreous
Stage 4	Partial retinal detachment
Stage 5	Total retinal detachment
Plus disease	Increased vascular dilatation and tortuosity of posterior retinal vessels in at least two quadrants of the retina
Pre-plus disease	More vascular dilatation and tortuosity than normal but insufficient to make the diagnosis of plus disease
Type 1 ROP	Zone I – any stage ROP with plus disease as well as stage 3 ROP without plus disease
	Zone II – stage 2 or 3 ROP with plus disease
Type 2 ROP	Zone I – stage 1 or 2 ROP without plus disease
	Zone II – stage 3 ROP without plus disease

as well as screening selected infants with birth weights between 1500 g and 2000 g or a GA >30 weeks who had an unstable clinical course and were believed to be at high risk for ROP.(3)

In 2014, an updated (2009 to 2014) literature search was conducted. This review found that the risk for severe ROP was greatest in infants ≤28 weeks' GA or weighing <1000 g at birth. Of 2593 infants screened in three recent cohorts from developed countries, no infants who were both ≥31 weeks' GA and >1250 g at birth met ETROP treatment criteria.(7-9) Canadian Neonatal Network data from 2009 to 2014 revealed that 1340 infants ≥31 weeks' GA were screened for ROP and four (0.30%) were treated; 2171 infants weighing >1250 g at birth were screened and three (0.14%) were treated.(1) Data are not available to determine whether any of the treated infants were both >1250 g at birth and ≥31 weeks' GA. Three studies specifically examined the incidence of ROP in infants ≥30 weeks' GA and/or having a birth weight ≥1250 g.(10-12) Of 1749 infants screened, only four (0.2%), all born before the year 2000, developed severe ROP. However, all four were outside of both the GA and birth weight parameters specified.

In the past several years, investigators have explored whether using additional screening criteria would permit early diagnosis of ROP requiring treatment, while decreasing the number of examinations for infants who will not require treatment. Slow postnatal weight gain has been associated with a higher risk for developing severe ROP(13,14) and several screening algorithms that compare actual weight gain with expected growth curves, in addition to incorporating factors such as insulin-like growth factor, have been developed.(15) The validity and generalizability of these models is currently under study.

Studies are underway through the Canadian Neonatal Network to analyze data with the intent of developing evidence-based recommendations for ROP screening of Canadian preterm infants. In the meantime, a practice of screening all infants born ≤$30^{6/7}$ weeks' GA (regardless of birth weight) as well as infants having a birth weight ≤1250 g and more mature infants believed to be at high risk for ROP, has a very small likelihood of an unscreened baby having treatable ROP.

When to screen

The scheduling of ROP screening examinations should ensure that eyes likely to need treatment are identified in a timely manner while, at the same time, minimizing the number of examinations for infants at low risk. Because ROP takes longest to develop in very immature infants, timing of the first examination should be based on postmenstrual age (GA plus chronological age) rather than postnatal age. Data from two large clinical trials – the Multicenter Trial of Cryotherapy for ROP and the Effects of Light Reduction on ROP – have been used to suggest an evidence-based schedule for the first eye examination, as shown in Table 2.(16) A contemporary observational study supports this schedule when type 1 ROP is used as a treatment criterion.(17) Because there is less evidence to base screening of infants <25 weeks' GA on, the AAP has suggested that these infants should be considered for earlier screening (ie, at six weeks chronological age) when comorbidities, such as necrotizing enterocolitis, sepsis, or the need for assisted ventilation or inotropes, are present. Nevertheless, prospective studies that included infants 22 to 25 weeks' GA reported that stage 3 ROP did not occur before 31 weeks' postmenstrual age.(18,19)

TABLE 2
Timing of the first retinopathy of prematurity screening examination

Gestational age at birth, weeks	Age at initial examination, weeks	
	Postmenstrual age	Chronological age
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

Follow-up screening examinations should be recommended by the examining ophthalmologist. The AAP has modified its suggestions for follow-up examinations and cessation of examinations, as reported in Table 3.

Other issues in screening

Eye examinations cause distress and pain, and may be associated with adverse physiological effects, including apnea, that are distressing to parents and may require modification of the infant's daily care.(20) Topical anesthetics, pacifiers, swaddling and sucrose are used to reduce discomfort. Systematic reviews suggest that no agent is highly effective in reducing pain scores; data are conflicting as to which agent is most effective in this setting.(21-23)

Availability of appropriately trained ophthalmologists may be a challenge when developing ROP screening programs, particularly in community settings that care for preterm infants following transfer from tertiary level units or after discharge. The use of specialized digital retinal photography (RetCam), which captures images that can be transmitted electronically, improves availability of screening in the community,(24) a practice that is family-centred and may be cost efficient. A recent report concluded that digital retinal photography has high accuracy for detection of clinically significant ROP.(25) The sensitivity for detection of mild ROP is less certain. Infants who are screened using digital photography should have at least one indirect ophthalmoscopic examination by an ophthalmologist before treatment or cessation of screening.

Treatment of ROP

Conventional treatment of ROP is retinal ablation, directed toward the avascular part of the retina, with the goal of decreasing production of angiogenic growth factors. The effectiveness of laser

TABLE 3
Suggested follow-up schedule for retinopathy of prematurity (ROP) screening

Follow-up	Indications	Modifications
1 week or less	• Immature vascularization, zone I – no ROP • Immature retina extends into posterior zone II, near boundary of zone I • Stage 1 or 2 ROP, no plus disease, zone I • Stage 3 ROP, no plus disease, zone II • Presence or suspected presence of aggressive posterior ROP • Inability to determine zone due to hazy view	Added immature vascularization, immature retina and aggressive posterior ROP
1 to 2 weeks	• Immature vascularization, posterior zone II • Stage 2 ROP, no plus disease, zone II	
2 weeks	• Stage 1 ROP, no plus disease, zone II • Immature vascularization, zone II – no ROP • Unequivocally regressing ROP, zone II	Added immature vascularization
2 to 3 weeks	• Stage 1 or 2 ROP, no plus disease, zone III • Regressing ROP, zone III	
Stop screening	• Vascularization in zone III without previous zone I or II ROP • Full retinal vascularization in close proximity to the ora serrata for 360° • Postmenstrual age of 50 weeks and no prethreshold or worse ROP • Regression of ROP (no abnormal vascular tissue capable of reactivation and progression present in zone II or III)	Changed postmenstrual age from 45 weeks to 50 weeks

Adapted from reference 3

photocoagulation is well established.(26) Ideally, treatment should be initiated for type 1 ROP within 72 h of its detection.(5)

Antivascular endothelial growth factor (anti-VEGF) therapy is a recent development in the treatment of ROP. In a randomized trial, intravitreal injection of bevacizumab, a recombinant humanized monoclonal antibody, was shown to be more effective than conventional laser therapy in decreasing the recurrence of zone I but not posterior zone II ROP.(27) A follow-up study examining refractive outcomes at 30 months demonstrated that the prevalence of myopia was significantly higher in eyes treated with laser therapy.(28) Nevertheless, there are concerns about anti-VEGF therapy, including reports that results may be transient with later recurrence of ROP,(29) lack of knowledge about its effect on normal angiogenesis in the organs of the developing preterm infant and potential adverse effects on the neural retina. For these reasons, the AAP suggests that detailed informed consent should be obtained if anti-VEGF therapy is contemplated. Long-term follow-up studies with adequate numbers are needed to establish safety.

Follow-up of treated infants should be recommended by the treating ophthalmologist. A longer period of follow-up is required when anti-VEGF therapy has been used.

Responsibilities in ROP screening

All nurseries that provide care for preterm infants at risk for ROP must have criteria and procedures to ensure appropriate ROP screening by an ophthalmologist skilled in its identification. Results must be documented and communicated to parents by the health care team. Parents should be aware that there is a chance of poor visual outcome even with therapy. When infants are transferred from one unit to another, arrangements must be made by the neonatal team for appropriate ophthalmological follow-up at the receiving centre. Results of ROP screening and the plan for ongoing screening must be accurately communicated to receiving health care providers. The neonatal team must include arrangements for any indicated ophthalmological examinations in discharge planning and ensure that parents understand the importance of follow-up. Discharged infants with ROP often have ongoing ophthalmological problems, such as strabismus, cataracts, amblyopia and refractive errors, regardless of whether treatment was required, and should be followed by an ophthalmologist. Even preterm infants without ROP are more likely than term infants to experience visual problems. Follow-up programs should include visual examination for all preterm infants who have been screened as part of the follow-up process.

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REFERENCES

1. Canadian Neonatal Network Annual Reports: www.canadianneonatalnetwork.org/portal/ (Accessed December 12, 2015).
2. Jefferies AL; Fetus and Newborn Committee, Canadian Paediatric Society. Retinopathy of prematurity: Recommendations for screening. Paediatr Child Health 2010;15(10):667-74.
3. Fierson WM; American Academy of Pediatrics, Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2013;131(1):189-95.
4. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005;123(7):991-9.
5. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol 2003;121(12):1684-94.
6. Royal College of Ophthalmologists; Royal College of Paediatrics and Child Health. Guideline for the screening and treatment of retinopathy of prematurity; UK retinopathy of prematurity guideline, May 2008: www.rcpch.ac.uk/system/files/protected/page/ROP%20Guideline%20-%20Jul08%20final.pdf (Accessed January 13, 2016).
7. Amer M, Jafri WH, Nizami AM, Shomrani AI, Al-Dabaan AA, Rashid K. Retinopathy of prematurity: Are we missing any infant with retinopathy of prematurity? Br J Ophthalmol 2012;96(8):1052-5.

8. Isaza G, Arora S, Bal M, Chaudhary V. Incidence of retinopathy of prematurity and risk factors among premature infants at a neonatal intensive care unit in Canada. J Pediatr Ophthalmol Strabismus 2013;50(1):27-32.
9. Holmström GE, Hellström A, Jakobsson PG, Lundgren P, Tornqvist K, Wallin A. Swedish national registry for retinopathy of prematurity (SWEDROP) and the evaluation of screening in Sweden. Arch Ophthalmol 2012;130(11):1418-24.
10. Hutchinson AK, O'Neil JW, Morgan EN, Cervenak MA, Saunders RA. Retinopathy of prematurity in infants with birth weights greater than 1250 grams. J AAPOS 2003;7(3):190-4.
11. Yanovitch TL, Siatkowski RM, McCaffree M, Corff KE. Retinopathy of prematurity in infants with birth weight >or= 1250 grams-incidence, severity, and screening guidelines cost-analysis. J AAPOS 2006;10(2):128-34.
12. Ahmed MA, Duncan M, Kent A; NICUS Group. Incidence of retinopathy of prematurity requiring treatment in infants born greater than 30 weeks' gestation and with a birthweight greater than 1250 g from 1998 to 2002: A regional study. J Paediatr Child Health 2006;42(6):337-40.
13. Hellström A, Hård AL, Engström E, et al. Early weight gain predicts retinopathy in preterm infants: New, simple, efficient approach to screening. Pediatrics 2009;123(4):e638-45.
14. Binenbaum G, Ying GS, Quinn GE, et al; Premature Infants in Need of Transfusion Study Group. A clinical prediction model to stratify retinopathy of prematurity risk using postnatal weight gain. Pediatrics 2011;127(3):e607-14.
15. Binenbaum G. Algorithms for the prediction of retinopathy of prematurity based on postnatal weight gain. Clin Perinatol 2013;40(2):261-70.
16. Reynolds JD, Dobson V, Quibb GE, et al; CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: Natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmol 2002;120(11):1470-6.
17. Kennedy KA, Wrage LA, Higgins RD, et al; SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Evaluating retinopathy of prematurity screening guidelines for 24- to 27-week gestational age infants. J Perinatol 2014;34(4):311-8.
18. Austeng D, Källen KB, Hellström A, et al. Natural history of retinopathy of prematurity before 27 weeks' gestation in Sweden. Arch Ophthalmol 2010;128(10):1289-94.
19. Austeng D, Källen KB, Hellström A, et al. Screening for retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. Arch Ophthalmol 2011;129(2):167-72.
20. Mitchell AJ, Green A, Jeffs DA, Roberson PK. Physiologic effects of retinopathy of prematurity screening examinations. Adv Neonatal Care 2011;11(4):291-7.
21. Sun X, Lemyre B, Barrowman N, O'Connor M. Pain management during eye examinations for retinopathy of prematurity in preterm infants: A systematic review. Acta Pediatr 2010;99(3):329-34.
22. Kandasamy Y, Smith R, Wright IM, Hartley L. Pain relief for premature infants during ophthalmology assessment. J AAPOS 2011;15(3):276-80.
23. Samra HA, McGrath JM. Pain management during retinopathy of prematurity eye examinations: A systematic review. Adv Neonatal Care 2009;9(3):99110.
24. Abdul Aziz AA, Isaac M, Tehrani NN. Using telemedicine to screen for retinopathy of prematurity. CMAJ 2014;186(13):1012-4.
25. Chiang MF, Melia M, Buffenn AN, et al. Detection of clinically significant retinopathy of prematurity using wide-angle digital retinal photography: A report by the American Academy of Ophthalmology. Ophthalmology 2012;119(6):1272-80.
26. Ng EY, Connolly BP, McNamara JA, Regillo CD, Vander JF, Tasman W. A comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years: Part 1. Visual function and structural outcome. Ophthalmology 2002;109(5):928-35.
27. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. New Engl J Med 2011;364(7):603-15.
28. Geloneck MM, Chuang AZ, Clark WL, et al; BEAT-ROP Co-operative Group. Refractive outcomes following bevacizumab monotherapy compared with conventional laser treatment: A randomized clinical trial. JAMA Ophthalmol 2014;132(11):1327-33.
29. Hu J, Blair MP, Shapiro MJ, Lichtenstein SJ, Galasso JM, Kapur R. Reactivation of retinopathy of prematurity after bevazicumab injection. Arch Ophthalmol 2012;130(8):1000-6.

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