ORIGINAL ARTICLE

# National variations in retinopathy of prematurity screening criteria in Canada: existent guidelines and actual practice patterns

Vasudha Gupta, MD,[*] Kaitlyn F. Whelan, BSc,[*] Laura Schneider, BSc,[*] Forough Farrokhyar, PhD,[*] Sandesh Shivananda, MD,[†] Shoo Lee, MBBS FRCPC, PhD,[‡] Kourosh Sabri, MBChB[*]

## ABSTRACT • RÉSUMÉ

**Objective:** To survey the current inclusion criteria used for retinopathy of prematurity (ROP) screening across tertiary level 3 neonatal intensive care units (NICUs) in Canada.

**Participants:** Clinical directors from 29 level 3 NICUs in Canada.

**Methods:** Survey of all 29 level 3 NICUs in Canada in September 2010. The survey inquired about the current ROP screening criteria in use in each centre including which neonates are enrolled in the screening program and the timing of when screening begins. The survey was sent via email to the clinical directors at each site. Nonrespondents were contacted by telephone.

**Results:** In total, 23 centres replied, representing a 79% response rate with the survey. Seven different ROP screening inclusion criteria were found to be in use, although one of the centres did not have a clear inclusion protocol. The variation between centres was significant, with some using a combination of birth weight and gestational age and others using birth weight or gestational age alone as their criterion. There was also variation in the timing of initial eye examinations, with 8 different criteria currently in use. Discrepancies were also found among treatment patterns at the centres.

**Conclusions:** Despite the publication of updated Canadian guidelines in 2000, there continues to be significant variation in the actual inclusion criteria being used across the country. Therefore, a need exists for comprehensive, evidence-based Canadian guidelines to optimize the screening inclusion criteria for ROP.

**Objet:** L'objet principal était d'examiner les critéres actuels d'inclusion utilisés dans le dépistage de la rétinopathie des prématurés (RDP) dans les Unités de soins intensifs néonatals (USIN) de 3e niveau au Canada.

**Participants:** Les directeurs de 29 cliniques d'USIN au 3e niveau au Canada.

**Méthodes:** Le sondage des 29 cliniques d'USIN de niveau 3 au Canada s'est déroulé au mois de septembre 2010. Il a porté sur les critéres courants de l'examen de RDP utilisés dans chaque centre, comprenant quels nouveaux-nés sont inscrits au programme d'examen et le moment oú a commencé le dépistage. L'examen a été envoyé par courriel aux directeurs de chacune des cliniques. Les non-répondants ont été rejoints par téléphone.

**Résultats:** En tout, 23 centres ont répondu, soit un taux de réponse de 79 % du sondage. L'on y a trouvé sept critéres d'inclusion différents de sondage du RDP, alors qu'un des centres n'avait pas de protocole de dépistage clair. La variation entre les centres était significative, certains utilisant une combinaison du poids à la naissance et de l'âge gestationnel alors que d'autres utilisaient comme un seul critère, le poids à la naissance ou l'âge gestationnel. Le moment de l'examen oculaire initial variait aussi selon 8 critàres différents actuellement en usage. On a aussi trouvé des divergences dans les modes de traitement des centres.

**Conclusion:** Malgré la publication de la mise à jour des lignes directrices canadiennes en l'an 2000, il y a toujours des variantes significatives dans les critères d'inclusion actuels actuellement utilisés à travers le pays. Il est donc nécessaire d'établir des lignes directrices canadiennes compréhensives, fondées sur les faits pour optimiser l'examen des critères d'inclusion de la RDP.

The Multicentre Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study was the first landmark study in a quest to improve outcomes for neonates experiencing development of severe retinopathy of prematurity (ROP). When the preliminary results were published in 1988, CRYO-ROP clearly identified risk factors for development of severe ROP, and the guidelines it produced regarding the ROP screening inclusion criteria and timing of treatment became internationally accepted.[1] The CRYO-ROP study identified risk factors for development of severe ROP, the most important of which were low birth weight (BW) and low gestational age at birth (GA). Results from the second landmark study regarding ROP, the Early Treatment for Retinopathy of Prematurity (ETROP) Study, were published in 2003.[2] The ETROP study provided evidence-based guidelines for changing the timing of treatment from diagnosis of ''threshold'' disease to the diagnosis of ''prethreshold type 1'' ROP. The new recommendations have subsequently resulted in earlier treatment of severe ROP.

The most recent Canadian Paediatric Society (CPS) guidelines published in 2010 recommend ROP screening

From the [*]Department of Surgery, McMaster University, Hamilton, Ont.; the †Department of Paediatrics, McMaster University, Hamilton, Ont.; and the ‡Department of Paediatrics and Obstetrics and Gynecology, University of Toronto, Toronto, Ont.

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Correspondence to Kourosh Sabri, MBChB, HSC 4V19, 1200 Main Street West, Hamilton ON L8N 3Z5; sabrik@mcmaster.ca

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for premature infants who have a GA $\leq$ 30 6/7 weeks (regardless of BW) *and* BW $\leq$ 1250 g.[3] However, it is important to note that at the time the survey was performed, the most current recommended guidelines were to screen neonates with BW $\leq$ 1500 g or GA $\leq$ 30 weeks, or both.[4] In comparison, the American Academy of Pediatrics (AAP) recommends routine screening of all infants born at GA $\leq$ 32 weeks *or* BW $<$ 1500 g, as well as those infants with BW $\geq$ 1500 g but with an unstable clinical course believed to be at risk for severe ROP.[5] The CPS notes that centres may choose to screen up to 1500-g BW based on the AAP guidelines.[3] Recommendations are based on nonrobust studies or consensus. Significant differences exist in inclusion criteria between the AAP[5] and CPS[4] recommendations. This may potentially translate into variation of practice among individual neonatal intensive care units (NICUs) and compromise quality of care.

In 2001, Lee et al.[6] published data showing that among the 14 Canadian level 3 NICUs surveyed, 13 different ROP screening inclusion criteria were in use. This was despite the publication of updated Canadian ROP screening guidelines the previous year.[4] The primary objective of our study was to survey the current inclusion criteria used for ROP screening across all tertiary-level nurseries in Canada, almost a decade after the previously published survey by Lee et al.[6] The results of our study will help form the foundation for a Canadian prospective study aimed at developing evidence-based guidelines for ROP screening inclusion criteria.

## Methods

This study involved a questionnaire survey of all 29 level 3 NICUs in Canada. In September 2010, in collaboration with the Canadian Neonatal Network (CNN), a questionnaire was sent via email to the clinical directors at each of the 29 level 3 NICUs in Canada (since this study was completed, another level 3 NICU has been added resulting in 30 tertiary-level NICUs in Canada). To maximize response rate to the survey, we contacted the nonresponding sites 1 month later with a phone call and follow-up email. The survey inquired about the current ROP screening criteria in use in each centre, including which neonates are enrolled in the screening program, when screening begins, and when it ends. In addition, respondents were asked to give details regarding any circumstances under which neonates who fall outside the screening criteria would be screened for ROP. Furthermore, each CNN site investigator was asked whether his or her centre provides laser or anti–vascular endothelial growth factor treatment or both for severe ROP, and whether the centre had an ophthalmology clinic to continue the ROP screening for those neonates discharged from NICU. The responses were kept confidential. After consultation with McMaster University, the survey was deemed to be exempt from review by the research ethics board at our institution. Results from the survey were entered into a database and analyzed with Microsoft Excel 2007 software (Microsoft Corp, Redmond, Wash.) and SPSS Statistics software (IBM, Armonk, Ny.). Descriptive statistics were performed. Categorical variables were reported as counts and percentages with 95% CIs.

## Results

### Screening inclusion criteria

Of the 29 centres that were contacted across Canada, 23 completed the survey (response rate, 79%). Responses were received from at least 1 centre in each of the 9 provinces housing level 3 NICUs in Canada (there are no level 3 NICUs in Prince Edward Island or any of the Territories). Among the responding centres, 7 different guidelines were found to be in use. Survey results are provided in Table 1. The most commonly used screening criterion was to screen neonates with BW $<$ 1500 g or GA $<$ 30 weeks or both, which was used by 30% (7/23; 95% CI: 16–51%) of centres, which was in keeping with the recommended CPS guidelines.[4] Interestingly, 13% (3/23; 95% CI: 4.5–32%) of centres screened patients based solely on BW, whereas another 13% (95% CI: 4.5–32%) of centres had criteria based only on GA (Table 2). One centre did not clarify what screening guidelines they used. Most centres (18/23 [78%]; 95% CI: 58–93%) made exceptions and also screened at-risk neonates who fell outside their existing screening criteria. Some of the high-risk factors that resulted in these neonates being screened included unstable neonatal course, high oxygen demand, serious respiratory disease, and if the neonatologist believed the neonate to be at greater risk secondary to the complexity of the clinical course.

### Timing of initial eye examination

The timing of initial eye examination varied between the participating centres. Eight different criteria were found to be in use by these centres (Tables 1 and 3). Eleven of the 23 centres (48%; 95% CI: 29–67%) began screening at 31 weeks GA for those born at GA 23 to 27 weeks and at 4 weeks postnatal age for those born at GA 28 to 31 weeks (Table 3). Approximately 39% (95% CI: 26–63%) of the centres began screening between 4 and 6 weeks postnatal age (Table 3). Of interest, there did not appear to be a correlation between screening criteria used and the timing of the initial examination.

### Treatment

Only 17 of the 23 centres (74%; 95% CI: 53.5–87.5%) provided treatment for ROP. Of these, 15 (88%; 95% CI: 66–97%) offered treatment using laser, whereas only 8 (47%; 95% CI: 26–69%) offered anti–vascular endothelial growth factor treatment (Table 4). In approximately half (47%; 95% CI: 29–67%) of the centres, all

**Table 1—Screening characteristics at each centre**

| Centre number | NICU level | ROP screening criteria | Timing of initial eye examination | Screening outside criteria? |
|---|---|---|---|---|
| 1 | Modified III | <1500 g BW and (or) <30 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |
| 2 | III | <1500 g BW and (or) <30 weeks GA | At 4 weeks postnatal age | Yes |
| 3 | III | <1500 g BW and (or) <30 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | No |
| 4 | III | <1501 g BW and (or) <31 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | No |
| 5 | III | <1500 g BW and (or) 32 weeks GA | At 4 weeks postnatal age | Yes |
| 6 | III | <1500 g BW and (or) 32 weeks GA | At 4 weeks postnatal age | Yes |
| 7 | III | <1250 g BW | At 6 weeks postnatal age | Yes |
| 8 | III | No details given | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |
| 9 | III | <1500 g BW and (or) <30 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |
| 10 | III | <1500 g BW and (or) <30 weeks GA | Between 4 and 6 weeks postnatal age | Yes |
| 11 | III | <32 weeks GA | Other (discretion of ophthalmologist, usually no later than 4 weeks postnatal age) | Yes |
| 12 | Modified III | <1500 g BW and (or) <32 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |
| 13 | II/III | <1500 g BW | At 6 weeks postnatal age | Yes |
| 14 | III | <1500 g BW and (or) <31 weeks GA | At 5 weeks postnatal age | Yes, rarely |
| 15 | III | <1500 g BW | At 32 weeks GA for those born GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 | Yes |
| 16 | III | <1500 g BW and (or) <32 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |
| 17 | III | <1500 g BW and (or) <30 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | No |
| 18 | III | <36 weeks GA | At 6 weeks postnatal age | No |
| 19 | III | <1500 g BW and (or) <32 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |
| 20 | III | <1500 g BW and (or) <30 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |
| 21 | III | 1500 g BW and (or) <32 weeks GA | At 4 weeks postnatal age | Yes |
| 22 | III | Only <32 weeks GA | At 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |
| 23 | III | <1501 g BW and (or) <31 weeks GA | At 31 weeks GA for those born at GA 22–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | Yes |

BW, birth weight; GA, gestational age at birth; NICU, neonatal intensive care unit; ROP, retinopathy of prematurity.

treatment was performed within the operating room setting, whereas 29% (95% CI: 13–53%) of centres treated patients only in the NICU. In most centres (11/16 [69%]; 95% CI: 44–86%), anaesthesia or sedation for the treatment was administered by anaesthetists (Table 4).

**Table 2—Distribution of ROP screening criteria in use**

| Inclusion criteria | Centres (% of total respondents) |
|---|---|
| <1500 g BW and (or) <30 weeks GA | 7 (30.4) |
| <1500 g BW and (or) <31 weeks GA | 3 (13.0) |
| <1500 g BW and (or) <32 weeks GA | 6 (26.1) |
| <1500 g BW | 2 (8.7) |
| <1250 g BW | 1 (4.3) |
| <36 weeks GA | 1 (4.3) |
| <32 weeks GA | 2 (8.7) |
| Unknown | 1 (4.3) |

BW, birth weight; GA, gestational age at birth; ROP, retinopathy of prematurity.

## Discussion

Our survey, the largest of its kind with a high response rate of 79%, found that significant variation exists in the actual inclusion criteria and timing of the first ROP screening examination across the country. It is evident that there is low compliance with recommended guidelines, and these guidelines do not take into account severity of illness and poor neonatal course. This is an important finding, because evidence-based, uniformly accepted guidelines are likely to

**Table 3—Distribution of timing of first screening eye examination**

| Timing of First Screening | Centres (% of Total Respondents) |
|---|---|
| 31 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | 11 (47.8) |
| 31 weeks GA for those born at GA 22–27 weeks and at 4 weeks postnatal age for those born at GA 28–31 weeks | 1 (4.3) |
| 32 weeks GA for those born at GA 23–27 weeks and at 4 weeks postnatal age for those born at GA 28–21 weeks | 1 (4.3) |
| 4 weeks postnatal age | 4 (17.5) |
| Between 4 and 6 weeks postnatal age | 1 (4.3) |
| 5 weeks postnatal age | 1 (4.3) |
| 6 weeks postnatal age | 3 (13.1) |
| Other (discretion of ophthalmologists, usually no later than 4 weeks postnatal age) | 1 (4.3) |

GA, gestational age at birth.

reduce the overall burden of screening and patient-related morbidity.

As a result of the aforementioned CRYO-ROP[1] and ETROP[2] studies, many countries developed screening programs to identify and treat those neonates at risk for sight-threatening ROP. Importantly, the demographic characteristics of the "at-risk" group of infants, such as BW and GA, show significant variation between developed countries and so-called middle-income countries (Table 5). However, even among the developed countries, there are differences in the ROP screening criteria, as highlighted in Table 6. Although there are inevitable differences regarding postnatal care of preterm infants among the developed countries, some of the variations listed in Table 6 are due to a lack of up-to-date, comprehensive, national, prospective studies examining the characteristics of screened and treated infants. Although only a small minority of screened neonates experience development of severe enough disease requiring treatment, many national and local ROP screening guidelines are set to cast a wide net, screening more rather than fewer neonates, to ensure that no infant with severe disease is missed.

**Table 4—ROP treatment availability per centre**

| Centre Number | Laser Treatment | Anti-VEGF | Sedation | Location of Treatment |
|---|---|---|---|---|
| 1 | — | — | — | — |
| 2 | No | Yes | Anaesthetists | OR |
| 3 | — | — | — | — |
| 4 | Yes | No | Anaesthetists | NICU |
| 5 | — | — | — | — |
| 6 | Yes | Yes | Others (local) | NICU |
| 7 | Yes | Yes | Anaesthetists | NICU |
| 8 | Yes | No | Anaesthetists | OR |
| 9 | Yes | No | Anaesthetists | OR |
| 10 | — | — | — | — |
| 11 | Yes | No | Anaesthetists | OR |
| 12 | — | — | — | — |
| 13 | Yes | No | Anaesthetists | OR |
| 14 | Yes | No | Anaesthetists | OR |
| 15 | Yes | Yes | Neonatologists | NICU |
| 16 | Yes | Yes | Neonatologists or Laser Nurse | OR/NICU |
| 17 | No | Yes | — | — |
| 18 | — | — | — | — |
| 19 | Yes | No | Anaesthetists | OR/NICU |
| 20 | Yes | No | Anaesthetists | OR |
| 21 | Yes | Yes | Nurse | NICU |
| 22 | Yes | Yes | Neonatologists/ Anaesthetists | OR/NICU |
| 23 | Yes | No | Anaesthetists | OR |

Anti–VEGF, anti–vascular endothelial growth factor; NICU, neonatal intensive care unit; OR, operating room; ROP, retinopathy of prematurity.

Jeffries et al.[3] published the new CPS screening guidelines in 2010 that aim to modify the existing Canadian ROP screening guidelines to include only premature infants with a GA $\leq$ 30 6/7 weeks *and* BW $\leq$ 1250 g. They do, however, recommend that patients with a BW between 1251 and 2000 g who have had a difficult clinical course should also be screened.[3]

The primary objective of our study was to survey the current inclusion criteria used for ROP screening across all tertiary-level nurseries in Canada. We found that the majority of centres did not comply with the most up-to-date CPS ROP screening guidelines[3] in existence at the time of the survey. We speculate that the lack of acceptance of recommended guidelines may be because of lack of high-level evidence, a variation in recommendations between associations such as the CPS and AAP, and a nonavailability of recommendations based on risk stratification. The most recent CPS guidelines were based on a combination of retrospective data and past international studies. Although we did examine data from the CNN, which provides data from all level 3 NICUs across Canada, it was collected and analyzed retrospectively.[3] Therefore, the data were not monitored for completeness or accuracy at the time of collection and, therefore, these data may not be used as the basis of definitive new guidelines. It is for the same reasons that past and present CPS guidelines have failed to provide universally accepted and adhered to recommendations for ROP screening in Canada. The most recent ROP screening guidelines for the United Kingdom were published in 2008, through the workings of a multidisciplinary guideline development group consisting of experts from the Royal College of Ophthalmologists, Royal College of Paediatrics & Child Health, and the British Association of Perinatal Medicine.[11] The guideline provides several *different* screening recommendations and good practice points, giving each recommendation a grading based on the strength of evidence underpinning it. This document highlights the lack of evidence-based, prospective studies that would help reduce these variations and create one universally accepted and *adhered to* screening set of guidelines acceptable to developed countries with similar standards of health care such as the United Kingdom and Canada.[11]

Although the current screening programs successfully identify severe cases of ROP in need of treatment, less than 10% of the neonates screened experienced development of severe disease.[6] Our survey showed that there were significant differences in screening criteria between

**Table 5—International variations in the birth weight and gestational age at birth of infants with severe ROP**

| | | Infants with Severe ROP | | | | | |
|---|---|---|---|---|---|---|---|
| | | BW (g) | | | GA (weeks) | | |
| Study country | Infants (N) | Mean | Range | SD | Mean | Range | SD |
| Canada[7] | 117 | 759 | 440–1785 | 182 | 25.6 | 22–32 | 1.7 |
| United States[7] | 36 | 763 | 415–1255 | 175 | 25.4 | 23–29 | 1.5 |
| United Kingdom[7] | 109 | 737 | 450–1260 | 174 | 25.3 | 23–32 | 1.6 |
| Argentina[7] | 47 | 1051 | 550–1680 | 279 | 30.0 | 24–34 | 2.2 |
| India[8] | 144 | 1410 | 650–2310 | NG | 30.2 | 25–35 | NG |
| China[9] | 114 | 1432 | 760–2500 | 319 | 29.8 | 26–34 | 1.9 |

BW, birth weight; GA, gestational age at birth; ROP, retinopathy of prematurity.

**Table 6—ROP screening inclusion criteria by country**

| Country | BW (g) | | GA (weeks) |
|---|---|---|---|
| Singapore[10] | $<1250$ | and (or) | $<32$ |
| Canada[4] | $\leq 1500$ | and (or) | $\leq 30$ |
| United States[5] | $<1500$ | and (or) | $\leq 32$ |
| United Kingdom[11] | $\leq 1500$ | and (or) | $<32$ |
| Denmark[12] | $<1750$ | and (or) | $\leq 32$ |
| Sweden[13] | | | $\leq 31$ |
| Germany[14] | | | $<32$ |

BW, birth weight; GA, gestational age at birth; ROP, retinopathy of prematurity.

centres ranging from BW $\leq$ 1250 g to BW $\leq$1500 g and (or) GA $<$ 32 weeks. Small differences in BW or GA cutoffs at a local level result in differences of several hundred infants being enrolled into screening at a national level. Because each infant receives at least 3 to 4 eye examinations, these local differences in screening criteria result in differences of several hundred, if not thousand, eye examinations at a national level each year. There are many reasons why it is desirable to minimize the overall burden of ROP screening. ROP examinations increase the risk for patient morbidity, causing pain, distress, apnea, and bradycardia in patients,[15–17] and undue stress on parents. Requiring ROP examination often necessitates newborns having to be transported across cities and regions to tertiary centres that can perform the necessary eye examinations. Such transfers cause morbidity to the child and drain valuable health care resources both in terms of cost and nursing staff/ambulance crew time. Eye examinations also cost the health care service in terms of ophthalmologists and nursing staff time and resources. Several studies[6,18–20] have indicated that more restrictive inclusion criteria could decrease the overall number of screening procedures, while nonetheless ensuring the detection of all cases of ROP in need of treatment.

The results of this survey have helped build the foundation for the development of SCREEN-ROP, a Canadian Institutes of Health Research–funded, nationwide, prospective study designed to formulate evidence-based ROP screening guidelines, which can be embraced by all Canadian nurseries and ophthalmologists involved with ROP. This study has been designed so that new screening recommendations will be based on complete and accurate data on all infants screened for ROP in all 30 tertiary nurseries across Canada and all infants treated for ROP nationwide. The study will examine many factors that may contribute to the development of severe ROP besides GA and BW. It is the intention of the study to develop a more specific evidence-based, stratified screening set of guidelines whereby depending on factors including but not exclusive to BW and GA, infants will be enrolled into 1 of 2 or 3 specific screening protocols. The aim of the study is to recommend screening guidelines that will reduce the overall number of infants enrolled into screening to minimize the number of eye examinations per child and yet capture all cases of severe ROP in need of treatment. Availability of such evidence-based ROP screening guidelines may reduce variation in practice and improve efficiency of ROP screening programs. The SCREEN-ROP study will begin data collection in early 2012 and aims to have its preliminary results published in 2013.

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