ARTICLE

Evidence for Changing Guidelines for Routine Screening for Retinopathy of Prematurity

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Context: Existing guidelines recommended by the Canadian Pediatric Society (CPS) and American Academy of Pediatrics (AAP) for routine screening for retinopathy of prematurity (ROP) remain controversial.

Objective: To determine whether current guidelines for routine screening for ROP should be changed.

Design: We examined data that were collected as part of a larger study of 14 neonatal intensive care units (NICUs) in Canada. We examined the effect of strategies using different birth weight (BW) and gestational age (GA) criteria for routine ROP screening, and performed a cost-effectiveness analysis.

Setting: The 14 NICUs (except one) are regional tertiary level referral centres serving geographic regions of Canada, and include approximately 60% of all tertiary-level NICU beds in Canada.

Patients: This large cohort included all 16424 infants admitted to 14 Canadian NICUs from January 8, 1996, to October 31, 1997.

Interventions: None.

Main Outcome Measure: Treatment for ROP.

Results: The most cost-effective strategy was to routinely screen only infants having a BW of 1200 g or less. This included all infants treated for ROP (except 1 outlier at 32 weeks GA and 1785 g BW), at a marginal cost per additional person with improved vision of $513 081 for screening patients between 28 weeks GA and 1200 g BW, compared with $1 800 039 and $2 075 874 for using the current AAP and CPS guidelines, respectively (cryotherapy outcomes). Results for laser therapy were similar, but costs were slightly lower. This strategy reduced the number of infants screened under the current CPS guidelines by 46%.

Conclusion: Screening only infants having a BW of 1200 g or less is the most cost-effective strategy for routine ROP screening.

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ROUTINE SCREENING of preterm infants for retinopathy of prematurity (ROP) is now recommended in many countries. Guidelines published by the Canadian Paediatric Society (CPS) in 1998[1] recommended routine screening for ROP in all infants at or younger than 30 weeks gestational age (GA) or with 1500 g or lower birth weight (BW). Meanwhile, in 1997, those from the American Academy of Pediatrics (AAP)[2] recommended routine screening for all infants younger than 28 weeks GA or with lower than 1500 g BW, as well as those infants with a BW at or above 1500 g with an unstable clinical course felt to be at risk by the attending physician. Previous authors[3-5] have found treatment with either cryotherapy or laser therapy to be effective in reducing the incidence of poor ophthalmic outcomes, and routine screening and treatment for ROP to be cost-effective.[6] However, since screening for ROP requires specialized skills and equipment, has potentially harmful effects on the infant, and carries an associated cost, the appropriateness of current criteria for routine screening has been recently questioned.[7-9] Hussain et al[8] reported that the incidence and severity of ROP have decreased significantly in the present era of surfactant therapy, and that no infant born after 28 weeks GA or having a BW greater than 1000 g required retinal surgery in a cohort of 2528 infants. Wright et al[9] similarly found no cases of threshold ROP or stage 4 ROP[10] among infants of a greater than 1200 g BW in a cohort of 707 infants. Goble[7] examined 1611 infants from 6 neonatal intensive care units (NICUs) in the United Kingdom and found that limiting routine screening of ROP to infants born before 29 weeks GA or with a BW at or below 1250 g did not reduce detection of

The affiliations of the authors appear in the acknowledgment section at the end of the article. Members of the Canadian Neonatal Network appear on page 394.

PATIENTS AND METHODS

STUDY POPULATION

The study population comprised all 16 424 infants admitted to 14 NICUs in the Canadian Neonatal Network[11,12] during a 22-month period from January 8, 1996, to October 31, 1997. The 14 hospitals (except one) are regional tertiary-level referral centers and include about 60% of all tertiary-level NICU beds in Canada (**Table 1**). Each NICU served a distinct geographic region and coordinated infant transfer and care within the region. Infants moved out of their region only for specific care that could not be provided by the regional hospital, or if excess patient census prevented admission to the regional hospital. In the latter event, patients were usually transferred back to the regional hospital as soon as patient census permitted. There were 267 NICU beds total (range, 2-45 beds) and 262 intermediate-level and continuing care beds (range, 0-45 beds) among the 14 NICUs. The mean number of annual admissions to a NICU was 673 (range, 133-1129 admissions). Cryotherapy and laser therapy for ROP were available in 8 hospitals. At the other 6 hospitals, infants were transferred to other hospitals for treatment of ROP. The data were collected as part of a larger study of practices and outcomes of NICUs[12] across Canada, which had a population of nearly 30 million people[13] and more than 357 000 births[14] in 1996. The 14 NICUs in this study served a population of about 18 million people.

DATA ABSTRACTION

Trained research assistants prospectively abstracted patient information from the mothers' and infants' medical records at each hospital on a daily basis. Data were directly entered into laptop computers using a customized data entry program with built-in error checking and a standard manual of operations and definitions.[15] Data were electronically transmitted to the Canadian Neonatal Network Coordinating Center at the British Columbia Research Institute for Children's and Women's Health, Vancouver, British Columbia, for verification. Potential data errors were rechecked by site research assistants. Data management was conducted by the Canadian Neonatal Network Coordinating Center, in concert with a Steering Committee composed of experienced researchers and neonatologists representing each of the 5 geographic regions (British Columbia, Prairie Provinces, Ontario, Quebec, Maritime Provinces) in Canada, and with site investigators representing each of the participating hospitals. Patient information was collected until death or until discharge from the NICU. For patients transferred to a community hospital prior to discharge home, written recommendations for ROP screening accompanied the patients on transfer, and ROP screenings were performed at the community hospitals. In Canada, ROP treatment is only performed at tertiary-level referral hospitals. All patients diagnosed with threshold ROP at community hospitals were transferred to a regional tertiary-level hospital for treatment. To ensure inclusion of patients referred from community hospitals for ROP treatment, we identified all patients treated for ROP in regional tertiary-level hospitals (including the NICU, pediatric intensive care unit, operating theater, and general pediatric wards) located in the geographic regions included in the study during the study period between 1996 and 1997 and for 1 year subsequently, and matched them against subjects in our study.

PATIENT INFORMATION AND VARIABLE DEFINITIONS

Patient information included information on ROP (stage, zone, and treatment given)[10] and treatment for ROP. Institutional criteria for routine screening for ROP in 1996 and 1999 were obtained from each institution. Study variables were defined according to the Canadian Neonatal Network SNAP Project Abstractor Manual.[15] Gestational age was defined as the best obstetric estimate based on early prenatal ultrasound, obstetric examination, and obstetric history unless the postnatal pediatric estimate of gestation differed from the obstetric estimate by more than 2 weeks. In that case, the pediatric estimate of GA based on the best estimate of the attending neonatologist or the Ballard Score[16] was used instead. Survival was defined as survival to discharge home from the NICU or from another hospital to which the patient had been transferred. Retinopathy of prematurity was defined according to the International Classification for Retinopathy of Prematurity[10] and the Reese Classification[17] of cicatrical disease.

OUTCOME DEFINITION

We chose treatment for ROP (ie, "threshold" disease) as the primary outcome. The currently accepted indication for treatment is "threshold" disease (ie, stage 3 ROP extending for longer than at least 5 contiguous clock hours or at least 8 cumulative clock hours in zone I or zone II, with plus disease). At this stage, the risk of blindness is around 50%, and treatment of threshold disease using cryotherapy has been shown to reduce unfavorable outcome (visual acuity worse than 20/200 OU) from 61.7% to 47.1% at 5½ years of age.[5] More recently, laser therapy has been reported to improve visual outcomes by 10% to 50% when compared with cryotherapy.[18-21] Many previous studies used severe ROP (≥ stage 3 ROP) as the end point.[1,3,6] However, not all patients with stage 3 disease require treatment, and evidence from the Multicenter Trial of Cryotherapy for ROP[5] suggests that treatment for ROP that does not reach threshold may have the adverse severe ROP (≥ stage 3 ROP)[10] or detection of those requiring treatment. However, since these studies involved small sample sizes, larger and more definitive population-based evidence is needed. The purpose of this study is to examine recent data from a large cohort of Canadian infants to determine whether there is evidence to support changing the present guidelines for routine screening for ROP.

RESULTS

In 1996, 13 different criteria were used by the 14 hospitals in the study (Table 1). In 2000, only 4 hospitals had adopted the CPS guidelines[1] published in 1998. Of the 16 424 infants in the study, 2077 were screened in the NICU prior to discharge or transfer. Under the CPS

effect of reducing the prospect for normal vision. We also examined cost-effectiveness of screening and treatment for ROP.

DATA ANALYSIS

We examined the implications of 3 different strategies for routine screening for ROP using (1) GA criteria, (2) BW criteria, and (3) combined GA-BW criteria. For each strategy, we chose a range of criteria to ensure inclusion of all infants treated for ROP. Since the most mature and largest infant treated for ROP in the study cohort was born at 32 weeks GA, with a 1785 g BW, we examined GA criteria up to 32 weeks, BW criteria up to 1800 g, and combined GA-BW criteria up to 32 weeks GA or 1800 g BW. We cross-tabulated the number of infants who were screened, who had higher than stage 3 ROP, and who were treated for ROP against the GA, BW, and combined GA-BW criteria (**Table 2**). We used the table to identify the criterion that included all infants treated for ROP but screened the least number of infants.

ASSUMPTIONS FOR COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis was undertaken from the viewpoint of the provincial payer. Canada has a tax-funded universal health insurance system that pays physicians according to a set schedule of fees. Hospitals are given a global budget. Patients do not pay out of pocket for health care. Therefore, costs relevant to the health care system are the provincial payer reimbursement schedule and the allocated hospital costs. Charges and other payments are not available or relevant. **Table 3** shows the cost inputs used in the calculations. Costs of screening were estimated by applying the British Columbia provincial payer reimbursement schedule[22] to screening guidelines published by Schalij-Delfosetel[23] and recommended by the CPS.[1] Under this guideline, screening was first performed at 32 weeks corrected GA, and then at 2 weekly intervals until 40 weeks GA. A screening test fee of $117.84 was paid for each eye examination. For infants screened and found to have stage 3 or higher ROP, we assumed that screening was subsequently conducted at weekly intervals until 40 weeks corrected GA or until treatment. A consultation fee of $64.70 was paid when an infant was referred for ROP treatment. A treatment fee of $464.72, which includes postsurgery examinations, was paid for each eye treatment performed. Data from the Cryotherapy for Threshold ROP Trial[6] showed that 27.5% of eye treatments were administered using general anesthesia, so we factored in an anesthesia fee (a $64.01 consultation fee plus a $212.80 anesthesia fee) for 27.5% of treatments. Costs of hospital treatment were estimated using hospital accounts data based on the number of tests and treatments carried out. This included an operating theater fee of $400 for each operation, one additional night of NICU stay ($709.41) if the patient was readmitted for surgery, and a laser therapy equipment depreciation charge of $617.74 per eye treated (based on initial equipment cost of $80 000, straight-line amortization throughout 10 years, discount rate of 5%, zero salvage value, and one-third usage by patients other than infants requiring treatment for ROP, which is the norm at the Children's and Women's Health Centre of British Columbia). For readmitted infants, the cost of transfer by air and by land were obtained from the British Columbia Ambulance Service (S.K.L., unpublished data, 1996). For infants receiving treatment before being discharged from the hospital providing the intensive care, we assumed that no additional hospital stay was incurred. Costs to hospitals that may have delayed transfer to less costly level I or level II nurseries because of ROP screening were not included. Costs to parents were not considered.

The estimates of outcome in terms of poor ophthalmic outcomes avoided were obtained from recent data on efficacy of treatment published by the Multicenter Trial of Cryotherapy for ROP[5] and from review of recent publications comparing laser treatment with cryotherapy, which suggested that laser treatment may improve visual outcomes by 10% to 50% compared with cryotherapy.[18-21] We assumed that symmetric eye disease occurred in 82.5% of patients, as reported by Palmer et al,[24] and retreatment was required in 6.4%.[6]

For each of the 3 screening strategies (GA, BW, and combined GA-BW) considered, we derived a total cost of screening and treatment using each criteria (Table 3). Using data from the Multicenter Trial of Cryotherapy for ROP,[5] which showed a reduction in unfavourable visual acuity outcomes from 61% to 47%, we estimated the number of persons with improved vision as a result of surgery, and the average cost per person with improved vision. We assumed that laser treatment would improve cryotherapy outcomes by between 10% and 50%, and we estimated costs associated with these outcomes. With progressive moves from one screening criterion to the next screening criterion (eg, moving from screening only infants at ≤26 weeks GA to screening all infants ≤27 weeks GA, and so on), we also estimated the number of additional persons with improved vision and the marginal cost per additional person with improved vision (MC/APIV).

Sensitivity analysis was conducted using 2 scenarios: (1) all eligible infants were screened, additional cases of stage 3 or higher ROP and treatment for ROP were detected in the same proportions by GA and BW, as infants who received screening in the study cohort; (2) infants with a 1200 g or lower BW were screened as per Scholij-Delfosetel's criteria,[23] plus infants between 1200 g and 1800 g BW were screened once only at 37 weeks gestation. This is a low-cost strategy designed to capture the outlier (largest treated infant in the cohort).

guidelines,[1] 3408 live-born infants would have been eligible for screening, but only 1939 of these infants were screened prior to discharge or transfer from the NICU. Of the remaining 1469 infants, 386 died in the NICU, 409 were discharged home without screening, and 674 were transferred to another hospital prior to discharge home. Table 2 presents the results of screening and treatment given, stratified by GA, BW, and a combination of GA-BW. One treated infant, who was born at 32 weeks and 1785 g, was an outlier who would not have been eligible for screening under existing CPS[1] and AAP[2] guidelines. However, screening was requested by the attending neonatologist for this infant because of an extremely difficult clinical course with a prolonged

Table 1. Inclusion Criteria for Routine ROP Screening in 1996 and 2000*

Hospital	Screening Criteria During 1996		CPS Guidelines in Use During 2000
	BW, g	GA, wk	
Victoria General (Victoria, BC)	≤1500	≤32	No
Children's & Women's (Vancouver, BC)	<1250	None	No
Royal Columbian (North West, BC)	<1500	<32	Yes
Royal Alexandra (Edmonton, AB)	<1500	None	No
Foothill's (Calgary, AB)	None	<32	Yes
Royal University (Saskatoon, SK)	<1500	None	No
Health Sciences (Winnipeg, MB)	<1500	<30	Yes
St Joseph's (London, ON)	<1500	<36†	No
Mount Sinai (Toronto, ON)	≤1250	≤30	No
Hospital for Sick Children (Toronto)	<1250	<30	No
Women's College (Toronto)	≤1500	≤30	Yes
North York (North York, ON)	Variable	Variable	No
Grace-IWK (Halifax, NS)	≤1500	≤30	No
Charles Janeway (St John's, NF)	None	≤32	No
Total	NA	NA	4 Yes

*ROP indicates retinopathy of prematurity; BW, birth weight; GA, gestational age; CPS, Canadian Pediatric Society; BC, British Columbia; AB, Alberta; SK, Saskatchewan; MB, Manitoba; ON, Ontario; NS, Nova Scotia; NF, Newfoundland; and NA, not applicable.

†Other screening criteria were used.

period of exposure to high oxygen concentrations. Since this infant had risk factors that were different from the usual for ROP, we analyzed the data both excluding and including this infant.

Table 2 presents the most efficient screening strategy to include all infants treated for ROP (excluding the outlier infant): to screen only infants with a BW of 1200 g or lower. This requires the screening of 1631 eligible infants in the study cohort. The CPS[1] and AAP[2] recommendations would have required the screening of 3022 and 2733 eligible infants respectively, without additional benefit. If the outlier infant was included in the analysis, the most efficient screening strategy to include all infants treated for ROP is to screen only infants with a 1800 g or lower BW (requires screening of 3980 eligible infants).

Table 4, **Table 5**, and **Table 6** summarize the costs of using different screening criteria in the NICU, arranged by ascending order of persons with improved vision. Screening criteria that produce equivalent (or worse) outcomes at higher cost are considered "dominated" and are excluded from the table or indicated as "dominated" in the table. In cost-effectiveness analysis, the critical consideration is the additional cost of a unit of improved outcome at the margin (MC/APIV). For instance, as presented in Tables 4, 5, and 6, for cryotherapy outcomes in the observed cohort, the MC/APIV in shifting from screening infants born at 700 g or less BW to screening infants born at 26 weeks or earlier is $53 354. Shifting from screening infants born at 26 weeks or earlier to infants born at 27 weeks or earlier results in a lower MC/APIV ($179 476) than shifting to screening infants born with a 1 kg or lower BW (MC/APIV, $314 269). Therefore, screening infants born at 27 weeks or earlier dominates screening infants born with a 1 kg or lower BW.

A clear pattern emerges from Tables 4 through 6. If the outlier infant is excluded, the strategy to screen only infants with a 1200 g or lower BW dominates all other strategies capable of capturing all infants treated for ROP. No additional benefit is derived from screening infants with a greater than 1200 g BW. It is possible to achieve the same outcome using a combined GA of 28 weeks or less and a BW of 1200 g or less as the screening criteria, but this provides no improvement in either detection or cost-effectiveness (the MC/APIV for shifting from screening infants with a ≤28-week GA to a combined GA ≤28 wk/BW ≤1200 g screening criteria is $789 521, compared with $513 081 for shifting to the BW ≤1200 g criterion). The AAP[2] and CPS[1] guidelines provide no additional benefit as compared with the criterion we used (BW ≤1200 g), and cost significantly more (MC/APIV, $1 800 039 for AAP criteria and $2 075 874 for CPS criteria). Finally, moving to a criterion of a BW of 1800 g or less, from a BW of 1200 g or less, captures the outlier infant, but at a MC/APIV of $3 407 425.

The results are similar for laser therapy, but the costs are lower using the assumptions that laser therapy results in a 10% to 50% improvement in visual outcomes compared with cryotherapy. The criterion using a BW of 1200 g or less dominates all other screening strategies. Moving from screening infants with a GA of 28 weeks or less GA to screening infants with a 1200 g or lower BW results in a MC/APIV that ranges from $214 028 (50% improvement in visual outcomes) to $416 166 (10% improvement in visual outcomes). The cost is significantly higher for the AAP criteria (equivalent MC/APIV range, $750 874-$1 460 032) and the CPS criteria (equivalent MC/APIV range, $865 936-$1 683 764), with no increase in benefit. Shifting criteria (from ≤1200 g BW to ≤1800 g BW) captures the outlier infant, but at a significantly higher cost (equivalent MC/APIV range, $1 421 383-$2 763 801).

Given the small numbers of cases in total, it is important not to interpret the differences too broadly, but using a BW limit of 1200 g would achieve the maximum health gain at the lowest cost. Most of the gain is achieved using a much lower threshold, such as 26 weeks GA. Screening very preterm and low-birth-weight infants provides benefits at modest costs. Moving to include all infants who are likely to benefit achieves its gains at a much higher cost. The analysis shows that there was no advantage in using screening criteria that combine both GA and BW, since BW alone is more cost-effective.

SENSITIVITY ANALYSIS

The data from this study confirm that, at least for some infants, screening and follow-up observation or treatment is likely to be cost-effective, and that the policy issue is whom the program should cover. Since some infants were not screened because of differences in screening criteria among NICUs, it is worth looking at the sensitivity to the assumptions if the costs of screening all eligible infants are included in the analysis. It is also worth looking at the sensitivity to the assumptions if infants having a BW between 1200 g and 1800 g are screened only

Table 2. Implications Using Different Screening Criteria*

Criteria	Eligible	Screened in NICU	Transfer to Community Hospital for Screening	Unscreened	≥Stage 3 Diagnoses in NICU	Treated for ROP in NICU or Other Hospital
GA, wk						
≤26	607	572	34	1	121	78
≤27	939	859	73	7	142	85
≤28	1327	1137	164	26	151	91
≤29	1838	1428	324	86	154	91
≤30	2369	1641	508	220	156	92
≤32	3982	1958	737	1287	158	94†
BW, g						
≤700	235	218	16	1	60	37
≤1000	965	862	98	5	140	82
≤1100	1299	1122	170	7	149	88
≤1200	1631	1369	253	9	155	93
≤1300	1966	1533	364	69	158	93
≤1500	2710	1853	574	283	158	93
≤1600	3086	1910	618	558	159	93
≤1800	3980	1984	713	1283	160	94†
Combined GA-BW, wk/g						
≤28/1200	1824	1487	302	35	158	93
≤28/1500 (AAP)	2733	1861	581	291	158	93
≤30/1500 (CPS)	3022	1939	674	409	158	93
≤32/1800	4730	2077	794	1859	160	94†

*All data are presented as number of infants. GA indicates gestational age; NICU, neonatal intensive care unit; ROP, retinopathy of prematurity; and BW, birth weight.

†Value includes 1 treated infant at 32 weeks' GA and 1785 g BW.

Table 3. Cost Inputs and Cost Calculations*

Cost Analysis	Cost Values
Cost inputs	
Screening fee	117.84 × No. of eyes examined for screening
Consultation fee	64.70 × No. of patients referred for ROP treatment
Treatment fee	464.72 × No. of eyes treated (includes postoperative care)
Anesthesia fee	(64.01 + 212.80) × No. of treatments needing general anesthesia
Laser therapy equipment costs	617.74 × No. of eyes treated
Operating theater costs	400 × No. of treatments in the operating theater
Additional inpatient costs	709.41/d in NICU × No. of readmitted patients
Additional nursing costs	27.86/h × 4 hours per patient
Ambulance transport costs	(3729.48 × No. of air transfers) + (507.46 × No. of land transfers) for eye surgery
Total cost (TC)	Sum of all cost inputs
Persons with improved vision (PIV)	No. of persons treated × 0.14
Additional PIV (APIV)	(PIV strategy 2 – PIV strategy 1) when shifting from strategy 1 to strategy 2
Average cost per PIV	TC ÷ PIV
Marginal cost per APIV	[(TC strategy 2 – TC strategy 1) ÷ APIV] when shifting from strategy 1 to strategy 2

*All numeric values for cost inputs are given in Canadian dollars. ROP indicates retinopathy of prematurity; NICU, neonatal intensive care unit; and strategies 1 and 2, opposing screening criteria.

once at 37 weeks GA. This low-cost strategy minimizes screening of larger infants with low risk of ROP, but permits inclusion of the outlier infant.

ASSUME ALL ELIGIBLE INFANTS HAVE BEEN SCREENED

Additional stage 3 cases and treated cases among unscreened infants occur in the same proportion as for screened infants. Our estimates of costs from the observed study cohort underestimate the actual costs because screening criteria of some hospitals excluded larger infants with low risk of ROP. A more realistic estimate of the relative cost-effectiveness of different screening strategies would assume that all eligible infants are screened, and that additional cases of a stage 3 or greater ROP and treatment for ROP among unscreened infants occurred in the same proportion as for screened infants of equivalent BW and GA. The only exceptions are infants who may have moved out of the study regions within 1 year of birth and thus escaped inclusion in the results. This scenario does not change the relative cost-effectiveness of the different screening strategies, but the MC/APIV of screening infants at 28 weeks GA and with 1200 g BW is $479 895 for cryotherapy (range, $200 185 - $389 248 for laser therapy, corresponding with a 50%-10% improve-

Table 4. Summary Costs of Progressive Screening and Treatment of Observed Cohort in NICUs and Community Hospitals*

	Screening Criteria										
Cost Derivation	≤700 g	≤26 wk	≤1.0 kg (Dominated)	≤27 wk	≤28 wk	≤1.2 kg†	AAP† (Dominated)	CPS† (Dominated)	≤32 wk‡ (Dominated)	≤1.8 kg‡	≤28 wk/1.8 kg‡ (Dominated)
Total cost	246 657	566 033	749 566	749 457	944 382	1 094 201	1 469 993	1 550 537	1 613 132	1 591 686	1 595 456
No. of PIV (cryotherapy)	5.402	11.388	11.972	12.41	13.286	13.578	13.578	13.578	13.724	13.724	13.724
AC/PIV	45 660	49 704	62 610	60 391	71 081	80 586	108 263	114 195	117 541	115 978	116 253
MC/APIV cryotherapy	45 660	53 354	314 269	179 476	222 517	513 081	1 800 039	2 075 874	3 554 322	3 407 425	3 433 253
MC/APIV laser therapy (10% IVO)	37 036	43 276	254 907	145 575	180 486	416 166	1 460 032	1 683 764	2 882 950	2 763 801	2 784 750
MC/APIV laser therapy (50% IVO)	19 047	22 256	131 095	74 867	92 821	214 028	750 874	865 936	1 482 660	1 421 383	1 432 157

*All values are presented in Canadian dollars unless otherwise indicated. NICU indicates neonatal intensive care unit; AAP, American Academy of Pediatrics; CPS, Canadian Pediatric Society; PIV, persons with improved vision; AC/PIV, average cost per PIV; MC/APIV, marginal cost per additional PIV; and laser (10% IVO) and laser (50% IVO), laser therapy is assumed to improve visual outcomes (IVO) by 10% and 50%, respectively, over cryotherapy.

†MC/APIV are calculated with respect to a ≤28-wk screening criteria.

‡MC/APIV are calculated with respect to ≤1.2-kg screening criteria.

Table 5. Sensitivity Analysis of All Eligible Infants Screened, With Additional Stage 3+ and Treated Patients in Proportion to Screened Cohort*

	Screening Criteria										
Cost Derivation	≤700 g	≤26 wk	≤1.0 kg (Dominated)	≤27 wk	≤28 wk	≤1.2 kg†	AAP† (Dominated)	CPS† (Dominated)	≤32 wk‡ (Dominated)	≤1.8 kg‡	≤28 wk/1.8 kg‡ (Dominated)
Total cost	247 746	567 014	752 513	753 431	958 033	1 098 162	1 599 198	1 735 664	2 235 721	2 132 426	2 137 797
No. of PIV (cryotherapy)	5.402	11.388	11.972	12.41	13.286	13.578	13.578	13.578	13.724	13.724	13.724
AC/PIV	45 862	49 790	62 856	60 712	72 108	80 878	117 779	127 829	162 906	155 379	155 771
MC/APIV cryotherapy	45 862	53 336	317 635	182 404	233 564	479 895	2 195 771	2 663 120	7 791 499	7 083 998	7 120 791
MC/APIV laser therapy (10% IVO)	37 199	43 261	257 638	147 950	189 446	389 248	1 781 015	2 160 086	6 319 771	5 745 909	5 775 752
MC/APIV laser therapy (50% IVO)	19 131	22 249	132 499	76 089	97 429	200 185	915 950	1 110 902	3 250 168	2 955 039	2 970 387

*All values are presented in Canadian dollars unless otherwise indicated. AAP indicates American Academy of Pediatrics; CPS, Canadian Pediatric Society; PIV, persons with improved vision; AC/PIV, average cost per PIV; MC/APIV, marginal cost per additional PIV; and laser (10% IVO) and laser (50% IVO), laser therapy is assumed to improve visual outcomes (IVO) by 10% and 50%, respectively, over cryotherapy.

†MC/APIV are calculated with respect to a ≤28-wk screening criteria.

‡MC/APIV are calculated with respect to ≤1.2-kg screening criteria.

ment in visual outcomes). Shifting to the AAP[2] criteria (MC/APIV for cryotherapy, $2 195 771; MC/APIV range for laser therapy, $915 950-$1 781 015) or the CPS criteria (MC/APIV for cryotherapy, $2 663 120; MC/APIV range for laser therapy, $1 110 902-$2 160 086) costs significantly more with no additional benefit. Shifting from screening infants born at a BW of 1200 g or lower, to screening infants born at a BW of 1800 g or lower would include the outlier infant, but at a MC/APIV of $7 083 998 for cryotherapy (range, $2 955 039-$5 745 909 for laser therapy). This strategy dominates using a GA criterion of 32 weeks or lower or a combined GA/BW criteria of 28 weeks GA and 1800 g BW (MC/APIV, $7 791 499 and $7 120 791, respectively, for cryotherapy, and slightly less for laser therapy).

COST-SAVING MEASURE

As a cost-saving measure, a regular screening schedule for all infants below cutoff criteria was produced; once-only screening at 37 weeks GA for infants from cutoff criteria, to 1800 g BW. This strategy permits inclusion of the outlier infant, but saves costs by minimizing the frequency of eye examinations for low-risk infants between a cutoff criteria and 1800 g BW. The dominant cutoff criterion is 1200 g BW for regular screening of infants. The MC/APIV for shifting from a cutoff criterion of 28 week or lower GA to 1200 g or less BW is $354 441 for cryotherapy, and this cost ranges from $147 852 to $287 491 for laser therapy. Adopting the AAP and CPS criteria as cutoffs increases costs with no additional benefit. All other strategies are dominated. For comparison, the MC/APIV for shifting from screening only infants with 1200 g or lower BW (ie, no screening for infants >1200 g BW) to this strategy (regular screening schedule for infants ≤1200 g BW, plus once-only screening for infants with a BW of 1201 g to 1800 g) is $1 889 159 for cryotherapy, and ranges from $788 049 to $1 532 318 for laser therapy.

Table 6. Sensitivity Analysis of Infants Below Cutoff Criteria Who Were Screened as per Regular Schedule and Infants Between Cutoff Criteria and 1800 g Who Were Screened Only Once*

	Screening Criteria										
Cost Derivation	≤700 g	≤26 wk	≤1.0 kg (Dominated)	≤27 wk	≤28 wk	≤1.2 kg†	AAP† (Dominated)	CPS† (Dominated)	≤32 wk‡ (Dominated)	≤1.8 kg‡	≤28 wk/1.8 kg‡ (Dominated)
Total cost	495 733	963 984	1 096 590	1 102 394	1 270 483	1 373 979	1 744 233	1 852 410	2 318 951	2 132 426	2 137 797
No. of PIV (cryotherapy)	5.548	11.534	12.118	12.556	13.432	13.724	13.724	13.724	13.724	13.724	13.724
AC/PIV	89 354	83 578	90 493	87 798	94 586	100 115	127 094	134 976	168 970	155 379	155 771
MC/APIV cryotherapy	89 354	78 224	227 064	135 430	191 882	354 441	1 622 431	1 992 901	3 590 645	2 951 860	2 970 256
MC/APIV laser therapy (10% IVO)	72 476	63 449	184 174	109 849	155 638	287 491	1 315 972	1 616 464	2 912 412	2 394 286	2 409 208
MC/APIV laser therapy (50% IVO)	37 273	32 631	94 718	56 494	80 042	147 852	676 786	831 324	1 497 812	1 231 347	1 239 021

*All values are presented in Canadian dollars unless otherwise indicated. AAP indicates American Academy of Pediatrics; CPS, Canadian Pediatric Society; PIV, persons with improved vision; AC/PIV, average cost per PIV; MC/APIV, marginal cost per additional PIV; and laser (10% IVO) and laser (50% IVO), laser therapy is assumed to improve visual outcomes (IVO) by 10% and 50%, respectively, over cryotherapy.

†MC/APIV are calculated with respect to a ≤28-wk screening criteria.

‡MC/APIV are calculated with respect to ≤1.2-kg screening criteria.

COMMENT

Our findings are highly relevant because they are current, and they are derived from almost 2 years of data from a large cohort of infants in the Canadian Neonatal Network, representing about 60% of the NICU admission, from a population of 30 million in Canada in 1996. We found significant variation in criteria used by different Canadian hospitals for routine screening for ROP (Table 1), even after publication of national guidelines by the CPS[1] in 1998. Reasons given for this variation include limitation of resources, lack of available qualified ophthalmologists, and disagreement with the current CPS recommendations. Differences in screening criteria raise a number of contentious issues, including medicolegal questions arising from noncompliance with nationally accepted guidelines. Disagreement about appropriate criteria for routine screening for ROP is not restricted to Canada. The AAP[2] in the United States and Goble et al[7] in the United Kingdom have advocated different guidelines than those recommended by the CPS in Canada. Clarification of appropriate screening criteria is urgently needed, both for patient management and medicolegal reasons.

GUIDELINES BENEFITS

Guidelines serve to guide physicians in important or contentious issues, and offer reassurance to physicians and to the public that individual physician practices conform to accepted best practice. Guidelines are consensus statements developed by groups of physicians and are based on expert opinion and review of the existing literature. Consequently, the relevance and quality of guidelines depend heavily on the quality of existing literature. The CPS guidelines on routine screening for ROP were developed after an extensive review of the literature.[3] However, most of the studies reviewed were of small sample size (the 7 population-based studies[24-31] ranged from n=117 to n=505), and only 1 study was Canadian in origin.[24] Four of these studies[24-28] were from a much earlier era (1984-1990) and may have limited applicability to current practices and outcomes. Indeed, there is evidence that the incidence of severe ROP has declined in recent years. Kennedy et al[32] reported a 50% decrease in the incidence of severe ROP in the postsurfactant era compared with the presurfactant era. More recently, Hussain et al,[8] Wright et al,[9] and Goble et al[7] have questioned whether we are screening too many preterm infants because of declining incidence and severity of ROP. Consequently, current information derived from large cohorts such as the Canadian NICU Network[11,12] are highly informative.

An important consideration is whether screening criteria should include all infants requiring treatment for ROP or whether outliers with exceptional circumstances should be excluded. In the study cohort, the outlier-treated infant clearly lies outside current screening criteria established by both the CPS[1] and AAP[2] guidelines. Other authors[7,33] have reported similar cases of outlier infants requiring treatment for ROP. Our data show that using a screening criteria that captures the outlier infant (ie, screen all infants with a BW ≤1800 g) would increase the number of eligible infants requiring screening by 144% (from 1631 to 3980 infants), and result in a MC/APIV ranging from $1 421 383 to $7 083 998 for screening all eligible infants with BWs between 1200 g and 1800 g. Total costs of screening and treatment would rise between 45% and 94% each year. Consequently, the most cost-effective strategy is to routinely screen only infants with a 1200 g or lower BW. Infants with a greater than 1200 g BW and with an unstable clinical course should be screened at the discretion of the attending physician.

Examination of the published literature lends support to this approach. The CPS[3] review of the literature found that only 1 study (Fledelius[28]) reported surviving infants with a higher than stage 3 ROP (3/287 infants or a 1% incidence) among infants at 1500 g BW. Six other reports[24-27,29-31] did not find any infants with stage 3 or higher ROP in infants having a 1500 g or higher BW. There were no cases of stage 3 or higher ROP, or blindness among infants with a BW 1200 g or greater in 3 of the 5 studies (Darlow,[27] n=169; Barnekow and Stigmar,[30] n=132; Haugen and Markestad,[31] n=207). Data from the

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remaining 2 studies (Ng et al[26] and Holmstrom et al[29]) did not reveal whether there were any cases of stage 3 or higher ROP, or blindness among infants with a BW of 1200 g or higher. It is noteworthy that Fledelius'[28] data were from an earlier period (1981-1988) than those of the other 6 studies (1985-1993), and may reflect clinical practices from a different era. More recently, Keith and Doyle[33] reported 2 cases (BW 1.29 kg/33-wk GA and BW 1.43 kg/32-wk GA) from Australia, and Goble et al[7] reported 1 case (BW 1.37 kg/29-wk GA) from the UK of stage 3 or greater ROP among infants with a 1200 g or lower BW. It was not possible to discern from the reports whether any of these infants required treatment for ROP. Goble et al[7] recommended ROP screening for all infants with a BW 1250 g or lower or a GA 29 weeks or earlier. Our results are in agreement with Goble's findings that it is possible to screen fewer infants without a loss of detection of cases requiring treatment for ROP, but we are at variance with Goble's findings in that we found that the BW criteria dominated both the GA criteria and the combined GA-BW criteria.

As compared with the CPS guidelines, our findings show that a strategy of screening all infants with a 1200 g or lower BW reduces the number of infants requiring screening by 46% annually. This translates into savings on screening costs to the provincial payer of more than $1 million annually in Canada. In addition, 46% fewer infants will be exposed to the risks (including adverse effects of mydiatrics, apnoea, tachycardia, hypoxia, aspiration, and need for reintubation and mechanical ventilation) and discomfort associated with the screening procedure itself.

An alternative strategy of routine screening for all infants with a 1200 g or lower BW, plus once-only screening (at 37 wk GA) for infants having a BW between 1200 g and 1800 g, is a low-cost strategy that attempts to include all potential outlier infants with a BW up to 1800 g. This strategy reduces the cost of screening infants with a BW between 1200 g and 1800 g, but the MC/APIV of shifting from screening only infants with a BW 1200 g or lower to this strategy still ranges from $778 049 to $1 889 159. We did not have data to infer whether this strategy is more or less effective at including high-risk outlier infants in a reliable and timely manner than simply relying on clinician judgement to selectively screen infants with a greater than 1200 g BW who are at high risk because of unstable clinical course.

LIMITATIONS OF STUDY

A limitation of this study is the lack of complete screening information on all infants with a 1800 g or lower BW. Therefore, we assumed (in the sensitivity analysis) that the number of infants with stage 3 or higher ROP and treatment cases among unscreened infants occurred in the same proportion as those among screened cases for the same BW and GA groups. This did not alter the relative cost-effectiveness of the different screening strategies. Another limitation is that we did not include costs of delayed transfer to less costly level I or level II nurseries. Some infants may have slightly fewer than the number of eye examinations assumed because their retinas may mature earlier. However, other infants may have slightly more than the number of eye examinations assumed because they have progressive ROP. A few infants may have relocated away from the study regions and escaped inclusion in our results. However, since our study regions included about 60% of the Canadian population and the incidence of treatment is low, the probability that an infant with threshold ROP escaped inclusion in our data is low. We did not have data on the incidence of severe ROP diagnosed at community hospitals, but this did not affect our analysis since the end point was treatment for ROP and not severe ROP. Another limitation is the lack of cost data from a societal perspective. We did not estimate indirect costs, long-term costs, costs to the family, economic consequences to society, and intangible costs arising from pain and discomfort associated with the screening procedure, or parental anxiety provoked by screening. However, our objective was to determine the most cost-effective strategy for routine screening of ROP, and the perspective of the provincial payor is relevant in this regard. Since the strategy of screening all infants having a 1200 g or lower BW dominates all other strategies; a cost-benefit analysis using a societal perspective is likely to yield the same result. While these limitations may affect our estimates of costs slightly, they neither change

the relative cost-effectiveness of the screening strategies nor alter the central findings of this study.

CONCLUSIONS

It is important to continue to monitor the effects of screening on the cases detected and on treatment provided. Since some diversity is likely to continue, the advantages (if any) of more frequent screening or more inclusive criteria can be monitored. However, on the basis of the best available evidence on the comparative cost-effectiveness of different screening strategies, BW seems to be a better criterion than GA. Routine screening is unlikely to be justified for infants with a BW greater than 1200 g.

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