A randomized trial of aggressive versus conservative phototherapy for hyperbilirubinemia in infants weighing less than 1500 g: Short- and long-term outcomes

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OBJECTIVE: Treatment regimens for hyperbilirubinemia vary for very low birth weight infants. The present study seeks to determine whether the initiation of conservative phototherapy is as effective as aggressive phototherapy in reducing peak bilirubin levels without increasing adverse effects.

STUDY DESIGN: The present randomized, controlled study included infants with birth weights between 500 g and 1500 g, stratified into two birth weight groups. In one group, aggressive phototherapy was commenced by 12 h of age, while in the other group, conservative phototherapy was commenced if serum bilirubin levels exceeded 150 µmol/L. The primary outcome variables were peak serum bilirubin levels and hours of phototherapy. Secondary outcomes were age at peak bilirubin levels, number of infants with rebound hyperbilirubinemia, and number of adverse short- and long-term outcomes.

RESULTS: Of 174 eligible infants, 95 consented to participate – 49 in the conservative arm and 46 in the aggressive arm. Ninety-two infants completed the study. There was no significant difference in peak bilirubin levels except in infants who weighed less than 1000 g – 171.2±26 µmol/L (conservative) versus 139.2±46 µmol/L (aggressive); P<0.02. There was no difference in duration of phototherapy or rebound hyperbilirubinemia. There were no differences in short-term adverse outcomes. Of the 87 infants who survived until hospital discharge, 82 (94%) had some follow-up and 75 (86%) attended follow-up until 18 months corrected age. The incidence of cerebral palsy, abnormal mental developmental index at 18 months corrected age, or combined outcome of cerebral palsy and death did not significantly differ between the two groups.

CONCLUSIONS: In infants weighing less than 1000 g, peak bilirubin levels were significantly higher using conservative phototherapy regimens and there was a tendency for poor neurodevelopmental outcome.

Key words: *Hyperbilirubinemia; Paediatrics; Phototherapy; Population-based; Preterm*

Essai aléatoire d'une photothérapie agressive par rapport à une photothérapie classique dans le traitement de l'hyperbilirubinémie des nourrissons de moins de 1 500 g : Les issues à court et à long terme

OBJECTIF : Les schémas thérapeutiques pour l'hyperbilirubinémie varient chez les nourrissons de très petit poids à la naissance. La présente étude vise à déterminer si l'initiation d'une photothérapie classique est aussi efficace qu'une photothérapie agressive pour réduire les taux de bilirubine de pointe sans accroître les effets indésirables.

MÉTHODOLOGIE : La présente étude aléatoire et contrôlée portait sur des nourrissons dont le poids de naissance variait entre 500 g et 1 500 g, stratifiés en deux groupes de poids à la naissance. La photothérapie agressive était entreprise avant 12 heures de vie, tandis que la photothérapie classique l'était si les taux de bilirubine sérique dépassaient 150 µmol/L. Les taux de bilirubine sérique de pointe et les heures de photothérapie étaient les variables d'issue primaire. Les issues secondaires étaient l'âge au taux de bilirubine de pointe, le nombre de nourrissons atteints d'une hyperbilirubinémie de rebond et le nombre d'issues négatives à court et à long terme.

RÉSULTATS : Des 174 nourrissons admissibles, 95 ont consenti à participer, soit 49 dans le volet classique et 46 dans le volet agressif. Quatre-vingt-douze nourrissons ont terminé l'étude. On n'a observé aucune différence significative des taux de bilirubine de pointe, sauf chez les nourrissons de moins de 1 000 g – 171,2±26 µmol/L (volet classique) par rapport à 139,2±46 µmol/L (volet agressif); P<0,02. De plus, on n'a observé aucune différence dans la durée de la photothérapie, l'hyperbilirubinémie de rebond ou les issues négatives à court terme. Sur les 87 nourrissons qui ont survécu jusqu'au congé de l'hôpital, 82 (94 %) avaient eu un certain suivi et 75 (86 %) ont profité d'un suivi jusqu'à 18 mois d'âge corrigé. L'incidence d'infirmité motrice cérébrale, d'indice de développement mental anormal à 18 mois d'âge corrigé ou d'issue combinée d'infirmité motrice cérébrale et de décès ne différait pas de manière significative entre les deux groupes.

CONCLUSIONS : Chez les nourrissons de moins de 1 000 g, les taux de bilirubine de pointe étaient considérablement plus élevés avec les schémas thérapeutiques classiques et s'associaient à une tendance d'issues neurodéveloppementale négatives.

Hyperbilirubinemia is a common problem in the clinical course of the very low birth weight infant, and although readily treated with phototherapy, controversy remains as to the most effective way of using phototherapy in these infants (1). Elevated serum bilirubin levels in neonates can be damaging to the developing neural system if not adequately monitored and treated, resulting in abnormal neurological signs known as bilirubin encephalopathy or kernicterus (2,3). Safe bilirubin levels in very low birth weight infants have not been delineated (4-7). Very low

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birth weight infants have not completed brain growth and development, which places them at greater risk than their term counterparts for neurological sequelae at similar or even lower serum bilirubin levels (8). They are relatively deficient in albumin, which limits the amount of bound bilirubin that can be safely carried in the bloodstream. Because of these factors, it has been suggested that phototherapy be used in a prophylactic manner in infants weighing less than 1500 g at birth (9). In a cohort study, Oh et al (7) noted a direct correlation of peak serum bilirubin level and death, neurodevelopmental impairment and hearing impairment in extremely low birth weight infants, and suggested that a randomized, controlled trial of aggressive versus conservative phototherapy was needed. There are adverse effects of phototherapy which may be significant for extremely low birth weight infants including dehydration, temperature instability, electrolyte imbalance, and more limited access to the infant by both caregivers and parents (10-12). In a randomized, controlled study (13) comparing routine prophylactic phototherapy with the institution of phototherapy when the unconjugated serum bilirubin level exceeded 5 mg/dL (85 µmol/L), no difference was found in mean peak bilirubin levels but a decrease of 28% in hours of phototherapy was noted.

The present randomized, controlled trial was conducted to determine whether the initiation of conservative phototherapy when serum bilirubin levels exceeded 150 µmol/L compared with aggressive phototherapy initiated within 12 h of birth in very low birth weight infants would provide an equal reduction in peak bilirubin levels, while decreasing the total number of hours of phototherapy. A secondary objective was to examine the 18-month neurodevelopmental outcome.

METHODS

Study design

The present randomized, unmasked clinical trial was approved by the Research Ethics Board at the IWK Health Centre in Halifax, Nova Scotia. Infants weighing less than 1500 g at birth admitted to the IWK Health Centre Level III neonatal intensive care unit, born between May 9, 1999, and January 6, 2002, without isoimmunization or a major life-threatening anomaly were eligible for the study. Parental consent was obtained, and randomization was completed by 12 h of age. Infants were randomly assigned to receive phototherapy within 12 h of birth (aggressive group) or to receive phototherapy when the serum bilirubin level reached 150 µmol/L (conservative group). Unlike phototherapy guidelines for term and near-term populations, well-established gestational age and postnatal age guidelines were not available for preterm infants; therefore, the decision was to use a serum bilirubin level of 150 µmol/L as the level at which phototherapy was initiated in the conservative group, which was reached by clinical consensus within the local group of neonatologists. Randomization was performed by sealed, opaque envelopes prepared in blocks of six. Randomization was stratified into two birth weight groups – infants weighing less than 1000 g and those weighing between 1000 g and 1499 g. All surviving infants were enrolled, as is standard for the nursery, in a comprehensive neurodevelopmental follow-up program. A full assessment was scheduled in the perinatal follow-up program at four, eight, 12, 18 and 24 months' corrected age and information on growth, hospital readmission, interval health, medication use, development and a complete physical examination was collected. All children had hearing and vision screening within 12 months' corrected age. A Bayley Scales of Infant Development (BSID-II) was performed by the developmental psychologist at the 18- and 36-month visits, if the child was cooperative.

Intervention

Phototherapy was instituted using one standard bank of white phototherapy lights. In both study groups, phototherapy was discontinued when the serum bilirubin level was less than 150 µmol/L for 48 h. Extra banks of phototherapy lights were added at the discretion of the attending neonatologist. After discontinuation of the initial phototherapy, resumption of phototherapy was instituted at the discretion of the attending physician if unconjugated serum bilirubin levels exceeded 185 µmol/L.

Bilirubin measurements

Blood samples for bilirubin levels were collected at the time of study entry and each day at 7:00 for the first seven days of postnatal life and at 48 h, 72 h and 120 h of age. Additional blood samples for bilirubin measurement were sent at the discretion of the attending neonatologist; however, they were not used for purposes of the present study.

All serum measurements were performed in one laboratory using the Vitros BuBc slide method, which measures spectral reflectance at 400 nm and 460 nm. This technique uses a slide containing dry, multilayered analytical element coated on a polyester support. A 10 µL drop of blood is deposited and spread on the slide at 37°C. The unconjugated fraction of the bilirubin interacts with the cationic polymeric mordant to form spectrally enhanced complexes with absorptivities at the specified wavelengths. Using reflection densitometry and appropriate mathematical transformation, readings are linearly related to bilirubin concentration. Results obtained by this method correlate well with the Doumas et al modification of the Jendrassik-Grof method (14).

Sample size calculation

A review of the data from the nursery between 1985 and 1993, during which time aggressive phototherapy was routine, showed that the mean peak bilirubin level in infants weighing less than 1500 g at birth was 165 µmol/L, with an SD of 15 µmol/L. It was believed that a clinically significant change in mean peak bilirubin levels would be reached in the conservative group, if the value exceeded two-thirds of the SD of the mean serum bilirubin level found in the aggressive phototherapy group. For a power of 90% (β error=10%) at the 5% significance level assuming a

TABLE 1
Infant characteristics of all patients enrolled in the study (n=95)

	All infants		Infants <1000 g		Infants 1000 g to 1499 g	
Characteristics	**Conservative (n=49)**	**Aggressive (n=46)**	**Conservative (n=21)**	**Aggressive (n=19)**	**Conservative (n=28)**	**Aggressive (n=27)**
Birth weight (g), mean ± SD	1050±290	1082±274	760±136	803±167	1267±148	1485±144
Male:female ratio	29:20	19:27	12:9	5:14	17:11	14:13
Gestational age (weeks), mean ± SD	28.1±2.6	28.7±2.3	26.0±1.9	26.9±1.8	29.8±1.7	30.0±1.6
Death (days 0–7), n	2	1	2	1	0	0
Death (day 7 until discharge), n	3	2	2	2	1	0
Total death	5	3	4	3	1	0

Infants were randomly assigned to receive phototherapy within 12 h of birth (aggressive group) or to receive phototherapy when the serum bilirubin level reached 150 µmol/L (conservative group)

TABLE 2
Bilirubin levels and phototherapy use in infants surviving the study period (days 0–7)

	All infants			Infants <1000 g			Infants 1000 g to 1499 g		
Outcome	**Conservative (n=47)**	**Aggressive (n=45)**	**P**	**Conservative (n=19)**	**Aggressive (n=18)**	**P**	**Conservative (n=28)**	**Aggressive (n=27)**	**P**
Peak unconjugated serum bilirubin (µmol/L), mean ± SD	183.5±28.0	170±49.5	NS	171.2±26.0	139.2±46.0	0.02	191.9±26.5	190.6±40.8	NS
Hours of phototherapy, mean (range)	68.5 (18–84)	85 (35–199)	NS	46.5 (18–167)	60 (35–141)	NS	81 (23–184)	109 (43–199)	NS
Rebound, n	12	18	NS	4	3	NS	8	15	NS
With peak <48 h, n	14	1	<0.001	7	1	0.04	7	0	<0.001

Infants were randomly assigned to receive phototherapy within 12 h of birth (aggressive group) or to receive phototherapy when the serum bilirubin level reached 150 µmol/L (conservative group). NS Nonsignificant

two-tailed test, a sample size of 94 patients, 47 per group, was required to examine the primary outcome.

Outcome measures

The primary outcome was the peak unconjugated serum bilirubin level. Other short-term outcomes included incidence of attaining peak bilirubin levels in the first 48 h, total hours of phototherapy, incidence of rebound hyperbilirubinemia defined as unconjugated serum bilirubin level of 185 µmol/L and per cent weight loss. Other common adverse outcomes that were seen in this population, such as intraventricular hemorrhage, retinopathy of prematurity and periventricular leukomalacia were examined. Long-term adverse outcomes included diagnosis of cerebral palsy, motor development index lower than two SDs below the mean on the BSID-II, visual impairment or hearing loss.

Data analysis

Continuous variables were analyzed using the Student *t* test and discrete variables by χ^2 analysis with and without the Mantel Haenszel procedure to correct for possible confounding due to birth weight. Data were expressed as mean ± SD, and $P \leq 0.05$ was considered significant. All infants were included as intention to treat. Analysis was performed using MedCal for Windows, version 6.16.00 (15).

RESULTS

Of 174 eligible infants, 146 (83.9%) were approached and 95 (65%) consented to participate – 49 in the conservative phototherapy group and 46 in the aggressive phototherapy group. There were no differences between the groups with respect to gestational age, birth weight or male to female ratio (Table 1). There were three deaths during the study period (days 0 to 7) – two in the conservative phototherapy group and one in the aggressive phototherapy group; and five additional deaths before hospital discharge – three in the conservative phototherapy group and two in the aggressive phototherapy group. All infants in the aggressive phototherapy group and all but one infant in the conservative phototherapy group received treatment. There was one protocol violation in the conservative phototherapy group in which an infant received phototherapy with a bilirubin level of 110 µmol/L. This infant was kept in the assigned group for analysis.

Results of the primary outcomes are seen in Table 2. There was no significant difference in peak bilirubin levels in the whole group of those surviving the study period (n=92). In a subgroup analysis, an increase in peak bilirubin levels was seen in patients in the less than 1000 g strata: 171.2±26.0 µmol/L in the conservative phototherapy group versus 139.2±46.0 µmol/L in the aggressive phototherapy group ($P<0.02$). There was no difference in duration of phototherapy or rebound hyperbilirubinemia defined as unconjugated serum bilirubin level of 185 µmol/L requiring phototherapy. There was a significant difference in the number of infants whose peak bilirubin level was reached before 48 h of age – 14 in the conservative phototherapy group versus one in the aggressive phototherapy group ($P<0.001$), which was significant in both weight groups.

TABLE 3
Incidence of short-term adverse neonatal outcomes in all infants surviving to discharge (n=87)

	All infants			Infants <1000 g			Infants 1000 g to 1499 g		
Outcome	Conservative (n=44)	Aggressive (n=43)	P	Conservative (n=18)	Aggressive (n=16)	P	Conservative (n=27)	Aggressive (n=27)	P
Intraventricular hemorrhage, n	13	15	NS	3	5	NS	10	11	NS
Grade I	8	12		2	4		6	9	
Grade II	3	2		0	1		3	1	
Grade III/IV	2	1		1	0		1	1	
Periventricular leukomalacia, n	2	2	NS	1	2	NS	1	0	NS
Retinopathy of prematurity, ≥ stage 2, n	11	7	NS	8	7	NS	3	0	NS
% weight loss, mean ± SD	11±5.0	12.1±4.9	NS	11.2±5.3	12.1±5.8	NS	10.8±4.9	12±4.3	NS
Days to birthweight, mean ± SD	11±4.0	11.8±3.9	NS	11±4.5	11.9±5.0	NS	11±3.6	11.6±3.9	NS
NICU stay, days, mean ± SD	82.7±38.9	82.3±37.9	NS	108±36.3	99.7±35.7	NS	57.4±19.6	63.4±33.0	NS

Infants were randomly assigned to receive phototherapy within 12 h of birth (aggressive group) or to receive phototherapy when the serum bilirubin level reached 150 µmol/L (conservative group). NICU Neonatal intensive care unit; NS Nonsignificant

TABLE 4
Incidence of adverse long-term outcomes in infants who completed 18 months corrected follow-up or died (n=83)

	All infants			Infants <1000 g			Infants 1000 g to 1499 g		
Outcome	Conservative n (%)	Aggressive n (%)	OR (95% CI)	Conservative n (%)	Aggressive n (%)	OR (95% CI)	Conservative n (%)	Aggressive n (%)	OR (95%CI)
Cerebral palsy	5/38 (13)	2/37 (5)	2.43 (0.44–13.34)	4/16 (25)	1/14 (7)	3.50 (0.35–35.11)	1/ 22 (5)	1/23 (4)	1.04 (0.06–17.7)
Cerebral palsy and death	10/43 (23)	5/40 (13)	1.86 (0.58–5.92)	8/20 (40)	4/17 (24)	1.70 (0.44–6.65)	2/23 (9)	1/23 (4)	2.00 (0.17–23.6)
MDI <84 at 18 months	8/38 (21)	9/37 (24)	0.87 (0.30–2.48)	6/16 (38)	4/14 (29)	1.31 (0.31–5.62)	2/22 (9)	5/23 (22)	0.4 (0.07–2.38)

Infants were randomly assigned to receive phototherapy within 12 h of birth (aggressive group) or to receive phototherapy when the serum bilirubin level reached 150 µmol/L (conservative group). MDI Mental developmental index

There were no observed differences in any of the short-term adverse outcomes (Table 3).

Results of the secondary, long-term results are seen in Table 4. Of 95 patients enrolled in the original study, 87 (92%) survived until hospital discharge, of whom 75 (86% of survivors) returned to the perinatal follow-up program for comprehensive neurodevelopmental assessment. The incidence of cerebral palsy was higher in the conservative phototherapy group (five of 38 [13%]) versus the aggressive group (two of 37 [5%]) (OR 2.43, 95% CI 0.44 to 13.34; P=0.44), but did not reach significance. The combined outcome of cerebral palsy and death was also higher in the conservative group (10 of 43 [23%]) versus the aggressive group (five of 40 [13%]) (OR 1.86, 95% CI 0.58 to 5.92; P=0.40), but also did not reach significance. Two-thirds of the infants with cerebral palsy were in the less than 1000 g subgroup. A mental developmental index of less than 84 on an 18-month corrected age BSID-II testing did not differ between the two groups (eight of 38 [21%] in the conservative group and nine of 37 [24%] in the aggressive group) (OR 0.87, 95% CI 0.30 to 2.48; P=0.78). Only six infants had a mental developmental index of less than 70 on an 18-month corrected age BSID-II testing (two of 38 [5%] in the conservative group and four of 37 [11%] in the aggressive group) (OR 0.49, 95% CI 0.09 to 2.49; P=0.43).

DISCUSSION

Hyperbilirubinemia has been extensively studied in full-term infants and there are published guidelines for appropriate treatment regimens using phototherapy and exchange transfusions (16,17); however, it has been less well studied in the very low birth weight population. Treatment practices for low birth weight infants vary from all infants receiving aggressive prophylactic phototherapy to treatment levels close to those recommended for healthy, term infants. In recent years, there has been emerging evidence that bilirubin may have some beneficial antioxidant properties in these infants at risk for oxygen toxicities such as chronic lung disease of prematurity, retinopathy of prematurity and intraventricular hemorrhage or periventricular leukomalacia (18-21). In the present study, we sought to determine whether there was any benefit of using aggressive phototherapy rather than conservative phototherapy at a predetermined bilirubin level in infants weighing less than 1500 g at birth, and to examine the possible short- and long-term outcomes of infants treated using the two treatment protocols. The only previous study (13) published examining this hypothesis found no decrease in peak bilirubin levels, but a decrease in the hours of phototherapy needed; however, phototherapy was started at a very conservative unconjugated serum bilirubin level of 5 mg/dL

(85 µmol/L). Little information has been available about treatment guidelines for very low birth weight infants since this time, despite a resurgence in interest in hyperbilirubinemia and kernicterus in the full-term population.

In our study, infants weighing more than 1000 g at birth did not have any significant change in their peak bilirubin level when treated at the predetermined phototherapy threshold of 150 µmol/L. Infants weighing less than 1000 g in the conservative group had significantly higher peak bilirubin levels than those in the aggressive group, however, this difference may reflect the fact that the mean serum bilirubin level in the aggressive group was low at 139.2 µmol/L, rather than the level being high in the conservative group. Concern is raised in that this subgroup (conservative, weighing less than 1000 g) had the highest incidence of cerebral palsy, although the finding did not reach statistical significance. Potentially even more worrisome in the present study, however, is the finding that in the entire group, peak bilirubin levels were reached earlier in the treatment group: 29% versus only 2% of the prophylactic group reaching peak bilirubin levels by 48 h of age. During the first 48 h, many of these infants are at increased risk for idiopathic respiratory distress syndrome, sepsis, acidosis and metabolic derangements. Because the potential for the neurotoxic effects of bilirubin relate to its ability to cross the blood-brain barrier, the risk should be greatest at a time when the infant has high free bilirubin levels compounded by acidosis, hypocalcemia, hypoalbuminemia or sepsis. Thus, the long-term adverse effects of hyperbilirubinemia may relate not only to the actual peak level, but to the timing of the peak level combined with the illness severity at that time. The present study did not have sufficient sample size to stratify within birth weight groupings by level of illness, to examine the contribution of illness severity.

Examination of the long-term outcomes in the study raises concerns that cannot adequately be answered by the present small trial because it was not powered to examine these outcomes. For infants weighing less than 1000 g at birth, there was a fourfold increase in the rate of cerebral palsy and a 30% increase in the chance of having a significantly abnormal score on standardized testing in the conservative group. The infants weighing less than 1000 g in the conservative group were slightly younger than those in the aggressive group, which may impact the long-term outcome. The suggestion of worrisome trend for poor neurodevelopmental outcome for infants receiving conservative phototherapy in the study requires examination with appropriately powered studies with long-term neurodevelopmental outcome as the primary outcome.

The potential risks of phototherapy are fairly benign in full-term infants but may be significant for extremely low birth weight infants and include dehydration, temperature instability, electrolyte imbalance, and more limited access to the infant by both caregivers and parents (10-12). In the present study, we did not find any difference between the groups with respect to weight loss, dehydration or electrolyte imbalances. We did not investigate the effect of phototherapy on parent-child interaction, but would expect the impact of phototherapy to be less in these very low birth weight infants than in otherwise healthy full-term infants, who had no other reason to be separated from their parents. Other important short-term outcomes relating to the possibility of a beneficial antioxidant effect of bilirubin on chronic lung disease, retinopathy of prematurity and intraventricular hemorrhage or periventricular leukomalacia were not found to be different between the two groups, but the study was inadequately powered to examine these outcomes and a larger study is necessary to address these very important outcomes.

CONCLUSIONS

The present study showed that conservative phototherapy given for established hyperbilirubinemia defined as serum bilirubin level of 150 µmol/L is as effective as aggressive phototherapy in reducing peak bilirubin levels in infants 1000 g to 1499 g at birth, but not in infants weighing less than 1000 g at birth. Conservative phototherapy for established hyperbilirubinemia defined as unconjugated serum bilirubin level of 150 µmol/L did not reduce the duration of phototherapy compared with aggressive phototherapy for infants less than 1500 g at birth. Infants receiving conservative phototherapy for established hyperbilirubinemia had earlier peak bilirubin levels compared with infants receiving aggressive phototherapy. There were no adverse short-term effects of phototherapy for established hyperbilirubinemia compared with prophylactic phototherapy seen in the present study; however, the study was not powered to investigate these outcomes. Worrisome trends in the over-representation of adverse long-term outcomes were seen. Furthermore, larger randomized trials adequately powered to look at the long-term neurodevelopmental outcomes should be undertaken to examine the use of more conservative bilirubin levels for the institution of phototherapy in infants weighing less than 1000 g to determine whether this is safe.

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ERRATUM

Canadian Paediatric Society position statement – Vitamin D supplementation: Recommendations for Canadian mothers and infants. Paediatr Child Health 2007;12(7): 583-589.

On page 585, the second sentence of the second paragraph should read:

A double blind study by Backström et al (43) (evidence level 1) suggested that **200 IU/kg/day** (to a maximum of 400 IU/day) of vitamin D is sufficient to maintain vitamin D status and normal bone density in premature infants.

On page 587, the first bullet should read:

Total vitamin D intake from all sources for the premature infant should be **200 IU/kg/day** to a maximum of 400 IU/day (recommendation grade A). Subsequent vitamin D dosage should be 400 IU/day for all infants during the first year, with an increase to 800 IU/day from all sources between October and April north of the 55th parallel (approximate latitude of Edmonton) and between the 40th and 55th parallel in individuals with risk factors for vitamin D deficiency other than latitude alone (recommendation grade B).

To access this statement, visit <http://www.cps.ca/english/statements/II/FNIM07-01.htm>

The Canadian Paediatric Society regrets this error.

Document de principes de la Société canadienne de pédiatrie – Les suppléments de vitamine D : Recommandations pour les mères et leur nourrisson au Canada. Paediatr Child Health 2007;12(7): 591-598.

À la page 593, la deuxième phrase du deuxième paragraphe devrait se lire comme suit :

D'après une étude à double insu de Backström et coll. (43) (qualité des preuves 1), **200 UI/kg/jour** (jusqu'à un maximum de 400 UI/ jour) de vitamine D suffisent pour maintenir le statut en vitamine D et une densité osseuse normale chez les prématurés.

À la page 596, la première puce devrait se lire comme suit :

Chez le prématuré, l'apport total de vitamine D, toutes sources confondues, devrait s'élever à **200 UI/kg/jour**, jusqu'à un maximum de 400 UI/jour (catégorie de recommandation A). La dose subséquente de vitamine D devrait correspondre à 400 UI/jour pour tous les nourrissons pendant leur première année de vie, avec une augmentation à 800 UI/jour, toutes sources confondues, entre octobre et avril au nord du 55^{e} parallèle (latitude approximative d'Edmonton), et entre le 40^{e} et le 55^{e} parallèle chez les personnes présentant d'autres facteurs de risque de carence en vitamine D que la latitude seule (catégorie de recommandation B).

Pour accéder à ce document de principes, rendez-vous à < www.cps.ca/francais/enonces/II/FNIM07-01.htm >.

La Société canadienne de pédiatrie est désolée pour cette erreur.