Outcomes of Infants Receiving Palivizumab Prophylaxis for Respiratory Syncytial Virus in Canada and Italy

An International, Prospective Cohort Study

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**Background:** Respiratory syncytial virus (RSV) infection frequently results in RSV-related hospitalization (RSVH) in young infants. We examined the outcomes of palivizumab recipients within the Canadian Registry (CARESS) and the Torino-Verona Italian Registry over the 2002–2014 RSV seasons.

**Methods:** RSVHs were captured during the study seasons. Premature infants of ≥32 completed weeks’ gestational age (group 1) were compared with infants given palivizumab for underlying disorders regardless of gestational age (group 2). Variables and between-group incidences were analyzed. Risk factors associated with RSVH were assessed by logistic regression.

**Results:** A total of 14,468 palivizumab-exposed infants were enrolled (group 1, n = 9093; group 2, n = 4856; miscellaneous, n = 519). RSVH was significantly more frequent in group 2 (211/4856, 4.34%) versus group 1 infants (216/9093, 2.37% [relative risk 1.93; 95% confidence interval (CI): 1.60–2.33; P < 0.001]). Infants with neuromuscular disorders (7.88%), airway anomalies (5.95%), bronchopulmonary dysplasia (4.75%) and hemo-dynamically significant congenital heart disease (4.10%) had the highest RSVH incidences. After multivariable logistic regression, only neuromuscular disease [odds ratio [OR] 4.29; 95% CI: 2.30–8.00; P < 0.01], airway anomalies (OR 3.23; 95% CI: 1.92–5.43; P < 0.01), Down syndrome (OR 2.25; 95% CI: 1.31–3.89; P < 0.01), hemodynamically significant congenital heart disease (OR 2.24; 95% CI: 1.52–3.31; P < 0.001), prematurity (≥28th completed weeks’ gestational age (OR 1.82; 95% CI: 1.29–2.58; P < 0.001), and bronchopulmonary dysplasia (OR 1.81; 95% CI: 1.31–2.50; P < 0.001) significantly predicted RSVH. No significant association was detected with the number of doses administered or the time elapsed after the previous dose.

Conclusions: RSVH rates are higher in infants given palivizumab for reasons other than prematurity. It is uncertain whether these findings relate to inadequate current palivizumab dosing protocols or to a specific increased RSVH risk inherent in infants with severe underlying comorbidities.

Key Words: respiratory syncytial virus, neuromuscular disease, Down syndrome, immune deficiency, palivizumab

(Pediatr Infect Dis J 2017;36:2–8)
METHODS

This study was designed as a prospective, multicenter, international cohort project. During 13 consecutive RSV epidemic seasons from 2001 to 2014, infants in Canada and in the Northern Regions of Italy were recruited and received PVZ based on risk factors for severe RSV disease; prematurity (≤35 weeks’ gestational age), bronchopulmonary dysplasia (BPD), hemodynamically significant congenital heart disease (HSCHD), neuromuscular and pulmonary disorders, airway anomalies, cystic fibrosis and Down syndrome. Data were collected and prospectively recorded in 2 registries: the Canadian RSV evaluation study of palivizumab (CARESS),14 and the Torino-Verona Northern Italy Network Registry (Sant’Anna Hospital, Torino, and Orlandi Hospital in Busseto, Verona). For the purpose of the present study, the 2 datasets were merged and harmonized. Data of all included patients who received PVZ from 2001 to 2014 during consecutive RSV seasons were then reviewed and analyzed.

Data Collection and Quality Control

Parental or legal guardian informed consent was obtained before patient enrolment for PVZ and both the registries, and the current study was approved by the respective institutional research ethics boards. Demographic, medical and family history data were collected at the time of patient enrollment and hospitalization, and PVZ administration data were obtained monthly. In the event of a hospitalization, relevant hospital records were reviewed by the site’s research nurse or primary investigator for detailed information on patient diagnosis, reason for hospitalization and length of stay.

Objectives of the Study

The primary objective of this study was to assess and compare the incidence of RSVH in infants who received PVZ for prematurity (gestational age ≤35 completed weeks; group 1) versus those who were prophylaxed for underlying medical disorders other than prematurity, regardless of gestational age (group 2). The latter group included infants with BPD, HSCHD, neuromuscular and pulmonary disorders, airway anomalies, cystic fibrosis, Down syndrome, miscellaneous dysmorphic and genetic disorders, primary immunodeficiency syndromes and other immunocompromised conditions.

The secondary objectives were (1) to assess the timing of RSVH (calculated as the number of days elapsed after the previous PVZ dose) in all infants who received prophylaxis, and individually for the groups of patients with preexisting disorders and (2) to investigate whether an association exists between RSVH and the number of PVZ doses received.

Definitions

Palivizumab [Synagis, MedImmune, Inc. Gaithersburg, MD (in Canada); AbbVie S.r.l., Aprilia, Italy (in Italy)] 15 mg/kg was administered in 5 monthly dose courses over the epidemic seasons (November to March) according to existing protocols and guidelines.15–19 The same timing and dosing schedule was used for all infants regardless of their gestational age and/or underlying condition. None of the infants were evaluated out of season.

Adverse events (AEs) possibly or probably related to PVZ were captured as per local protocols, recorded and submitted to the respective investigators within 24 hours of occurrence.

An AE was defined as any unexpected occurrence in a patient after PVZ was administered, that may or may not have a causal relationship with the drug. The AE qualified as a serious adverse event (SAE) if it involved: death, a life-threatening event, hospitalization or prolongation of existing hospital stay, persistent or significant disability or incapacity of the subject, or required medical or surgical intervention to prevent serious outcome.20 The data related to adverse events have been previously published by our group of investigators.11

BPD was established in both cohorts through medical discharge summaries and conforming to qualifying criteria stipulated by the BPD consensus definitions.14 HSCHD was similarly defined in both groups as uncorrected or palliated cyanotic or acentic CHD with pulmonary hypertension (systolic pulmonary arterial pressure >40 mm Hg) or a need for medication to manage congestive heart failure and confirmed by a pediatric cardiologist.15

RSVH was defined as a symptomatic admission to hospital for deep or wet cough, wheezing, hoarseness, stridor or shortness of breath. RSV positivity was confirmed by enzyme or immunofluorescent assay, polymerase chain reaction or a positive viral culture for RSV from nasopharyngeal secretions.25

For the purpose of this study, only the first episode of RSVH in each infant was considered.

Statistical Analysis

The association between RSVH and the underlying medical disorder (classified as a dichotomous variable: prematurity/other medical conditions) was assessed by a Fisher exact test. We computed RSVH risk ratios and corresponding 95% confidence intervals (CIs) to compare between-group cumulative incidences.

The effects of relevant risk factors possibly associated with RSVH were estimated and assessed using different models of multivariable logistic regression analyses. Covariates included in the models were age at first PVZ dose (weeks), sex and underlying conditions. The latter group comprised infants with HSCHD; BPD; neuromuscular, cardiac or pulmonary problems; airway anomalies; Down syndrome; cystic fibrosis; preterm children (3 categories: ≤28 completed weeks’ gestational age; between 29 and 32 weeks and between 33 and 35 weeks; and miscellaneous problems (including undefined conditions, multiple problems or very rare medical conditions). In the first model, RSVH was controlled for different underlying conditions versus prematurity. A second model was developed to control for different subgroups of prematurity based on gestational age, and a third model was constructed to control RSVH for different underlying conditions and prematurity.

The reference group consisted of children born after 35 completed weeks’ gestational age with no other preexisting medical disorders. These infants in the majority received RSV prophylaxis for intrauterine growth restriction or because they were small for gestational age.

The following distributions were analyzed: number of days elapsed between the last injection received and the day of RSVH; number of doses received prior to RSVH (eg, 1 dose if the admission occurred between the first and second injection, 2 doses if between the second and third injection etc.). We assessed whether there was an association between RSVH rates and number of doses administered. Six time intervals were identified for possible hospitalizations; before the first dose, after the first and before the second, between second and third, between third and fourth, between fourth and fifth, and after the fifth dose. We calculated the proportions of infants hospitalized in each time interval and compared it with a reference value (ie, the proportion of those hospitalized between the second and the third dose) using large-sample statistics. The period between the second and third dose was chosen as the reference value based on the pharmacokinetic characteristics of PVZ, indicating that full efficacy is reached after the second dose in the majority of treated patients.17–19

RESULTS

Overall, 14,468 infants received prophylaxis with PVZ during 13 consecutive RSV seasons, from 2001 to 2014, in all centers
affiliated with the Canadian–Italian network. Group 1 included 9093 premature infants <35 completed weeks’ gestational age, whereas group 2 comprised 4856 infants with underlying medical disorders other than prematurity. Five hundred nineteen infants (3.5% of the total) were >35 completed weeks’ gestational age and were categorized as the reference group because they received PVZ prophylaxis for reasons other than prematurity or the presence of an underlying condition. These infants were therefore not included in group 1 or 2.

Patients in groups 1 and 2 were significantly different in mean birth weight, gestational age, enrolment age and concomitant underlying risk factors. Nonetheless, they all received the same course of PVZ injections during the respective RSV season. Premature infants ≤35 weeks’ gestational age comprised 62.8% of the cohort (9093/14468), while infants affected by any underlying condition were 33.5% (4856/14468) of the total. Figure, Supplemental Digital Content 1, http://links.lww.com/INF/C534, shows the distribution of the different types of underlying conditions among group 2 infants.

Overall, PVZ was safe because SAEs occurred only in 7 patients (0.04%) who had a total of 15 hypersensitivity reactions that were deemed possibly or probably related to PVZ. The SAEs of 49 patients were assessed as not related to PVZ.

The overall RSVH rate was 2.95% (427/14468). RSVHs occurred with significantly increased frequency in group 2 infants, with the incidence being almost 2-fold higher (211/4856; 4.35%) than in group 1 (216/9093; 2.37%) (relative risk 1.93; 95% CI: 1.60–2.33; P < 0.0001). Among group 2 infants, the incidence rates of RSVH varied widely (Table 1). Of note, most of the analyzed underlying conditions (neuromuscular disorders, airway anomalies, BPD, Down syndrome, HSCHD and pulmonary disorders) yielded a significantly higher risk of RSVH compared with prematurity (incidence range: 3.95–7.88% versus 2.25%, respectively). No RSVHs were recorded in immunocompromised infants, or in patients affected by genetic disorders who received PVZ prophylaxis.

The incidence of hospital admissions due to RSV in patients with BPD and HSCHD was compared with the cumulative incidence in all other neonates. Among neonates with BPD, the RSVH rate was 4.75% (57/1199) versus 2.79% (370/13,269) in all other patients including premature babies and children with the remaining underlying conditions (relative risk 1.70; 95% CI: 1.30–2.24; P = 0.0027). Among HSCHD children, RSV admissions accounted for 4.10% (59/1438) versus 2.82% (368/13,030) in the combined cohort of preterms and those with the rest of the medical disorders (relative risk 1.45; 95% CI: 1.11–1.90; P < 0.0008).

| TABLE 1. Cumulative Incidences of Respiratory Syncytial Virus Hospitalization According to Different Types of Underlying Conditions |
|-----------------|-----------------|-----------------|
| **Total Number of Patients** | **Cumulative Incidence of Hospital Admission for RSV Bronchiolitis (95% CI)** |
| Neur muscular | | |
| 185 | 7.88%  (3.72–12.03) |
| Airway anomalies | 353 | 5.95%  (3.47–8.43) |
| Bronchopulmonary dysplasia | 1199 | 4.75%  (3.55–5.96) |
| Down syndrome | 459 | 4.14%  (2.31–5.97) |
| Hemodynamically significant congenital heart disease | 1438 | 4.10%  (3.08–5.13) |
| Pulmonary disorders | 354 | 3.95%  (1.91–5.99) |
| Cystic fibrosis | 232 | 1.29%  (0.00–2.76) |
| Immunocompromised | 56 | 0 |
| Genetic disorders | 4 | 0 |

There were no significant differences in regard to length of stay in hospital, rates of intensive care unit admission or need for mechanical ventilation among the different groups of PVZ-treated patients. Mean (±standard deviation) length of stay was 8.7 ±10.6 days in premature infants, 10.0 ± 10.4 in BPD patients, 7.9 ± 8.2 days in HSCHD infants and 7.7 ± 6.8 in infants affected by other underlying conditions (P values = 0.41, 0.59 and 0.38, respectively). Similarly, intensive care unit admissions occurred in 16.6% of RSV hospitalized premature infants, compared with 7.0% in BPD, 23.7% in HSCHD and 14.0% in infants affected by underlying morbidities (P values = 0.07, 0.20 and 0.55, respectively). Finally, 13.7% of premature infants needed mechanical ventilation, compared with 7.0% of BPD, 22.0% of HSCHD and 12.0% of conditions infants with underlying conditions (P values = 0.17, 0.12 and 0.67, respectively).

When exploring the time interval between the RSV admission and the previous PVZ injection, the data showed that the mean day of RSVH was 12.9 days (median = 13). The distribution of hospital admissions consistently spanned 4 weeks of the month. Approximately 75% of the admissions occurred within the first 21 days and 12% of the hospitalizations occurred on the same day of the injection. The scheme depicting the percentile distribution of the relationship between RSVH and day of the actual RSVH event is reported in Table, Supplemental Digital Content 2, http://links.lww.com/INF/C535.

The time distributions of RSVH in preterm neonates and infants with underlying conditions were assessed separately and compared. The mean day of admission did not differ significantly between the 2 groups (14.8 vs. 15.3). However, the RSVH episodes showed a nonsignificant trend toward a later occurrence in group 2, with a peak in the third week, as identified by the median day of RSVH and the quartile distribution. These differences were not statistically significant after analysis by the Wilcoxon–Mann–Whitney test (P = 0.5754) (Fig. 1 and Table, Supplemental Digital Content 3, http://links.lww.com/INF/C536). Table 2 and Figure, Supplemental Digital Content 4, http://links.lww.com/INF/C537, show the distribution of RSVH episodes according to the number of doses administered. No clustering of RSVH was noted. Interestingly, 1 of 4 admissions occurred after the third dose.

The results of the 3 different models of multivariable logistic regression analyses assessing the effects of relevant risk factors possibly associated with RSVH are shown in Tables 3–5. In the first model (Table 3), where RSVH was controlled for different underlying conditions versus prematurity, children with HSCHD, BPD, neuromuscular problems, airway anomalies and Down syndrome showed a significantly increased risk for hospitalization, whereas near-term children [i.e., gestational age >35 weeks (reference group)] experienced a lower risk of hospitalization when compared with preterm neonates <35 completed weeks’ gestational age.

The second model (Table 4) controlling for different subgroups of prematurity based on gestational age indicated that preterm neonates were at increased risk of hospitalization in comparison to near-term children, with a significant trend toward higher risk with lower gestational age (P < 0.001).

The third model (Table 5) controlling RSVH for different underlying conditions and prematurity showed that children with HSCHD, BPD, neuromuscular problems, airway anomalies, Down syndrome and prematurity ≤3 weeks are at increased risk of hospitalization, when compared with near-term neonates. Again, a trend of higher hospitalization with lower gestational age was found.

No deaths occurred in this cohort that were directly attributed to RSV.

Because our study spans a prolonged period of time (2002–2014), we checked for possible changes in RSVH rates in both
groups throughout the respective years. Additional subanalyses were performed after dividing the total study duration into 3 time periods, 2 periods, and after "trimming out" the first and last years of the overall periods, that is, those epochs when fewer patients were enrolled. The findings were similar across the analyzed time frames and were not significantly different from the results obtained over the original, total 12-year duration (data not shown).

**DISCUSSION**

Our data provide international, multicenter, prospective evidence that RSVH rates are not negligible in children who receive PVZ and are even higher in those infants who receive prophylaxis for reasons other than prematurity. We analyzed approximately
Infants (Preterms <35 Weeks' GA and Underlying subgroups of patients.17–19 This cohort study provides evidence that the pharmacokinetic and pharmacodynamic features of the drug, in PVZ-treated infants has been attributed to uncertainties about 6 seasons in 2 different countries. To the best of our knowledge, this 15,000 infants who were prophylaxed through 13 consecutive RSV dren hospitalized for RSV after prophylaxis. The pharmacokinetic and pharmacodynamic features of the drug, in PVZ-treated infants has been attributed to uncertainties about

<table>
<thead>
<tr>
<th>RSVH</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Chronologic age at first PVZ dose</td>
<td>1.00 (1.00–1.00)</td>
<td>0.461</td>
</tr>
<tr>
<td>Sex</td>
<td>0.96 (0.79–1.17)</td>
<td>0.679</td>
</tr>
<tr>
<td>HSCHD</td>
<td>2.24 (1.52–3.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD</td>
<td>1.81 (1.31–2.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.60 (0.99–2.59)</td>
<td>0.057</td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>4.29 (2.30–8.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Airway anomaly</td>
<td>3.23 (1.92–5.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2.53 (0.78–8.25)</td>
<td>0.124</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>0.69 (0.21–2.23)</td>
<td>0.529</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>2.25 (1.31–3.89)</td>
<td>0.00</td>
</tr>
<tr>
<td>Pulmonary disorders</td>
<td>1.48 (0.82–2.65)</td>
<td>0.189</td>
</tr>
<tr>
<td>≤28 weeks' GA</td>
<td>1.82 (1.29–2.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>29 to ≤32 weeks' GA</td>
<td>1.17 (0.82–1.66)</td>
<td>0.325</td>
</tr>
<tr>
<td>&gt;33 to ≤35 weeks' GA</td>
<td>0.91 (0.65–1.32)</td>
<td>0.657</td>
</tr>
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Bold text indicates P < 0.05.

GA indicates gestational age.

of PVZ, the same monthly dosing schedules have been applied to all infants eligible for prophylaxis, regardless of their underlying condition or morbidty. Based on our data, it would be interesting to assess whether innovative dosing schedules might overcome the apparent limited efficacy of PVZ in infants with serious disorders other than prematurity.

RSVH rates in preterm infants without BPD in our study (2.2%) were comparable with those found in the IMPact-RSV study (1.8%).21 However, children with BPD had a higher RSVH rate (4.7%) compared with preterms, but nonetheless half of that recorded in the IMPact study (7.9%). The improved efficacy of PVZ in such infants may be due to a putative, overall better respiratory outcome of BPD infants over the last 15 years, as well as the changing pathologic features of BPD over time resulting from tempered and less-invasive ventilation modalities.22

Incorrect or inadequate timing between PVZ doses over the RSV season has been raised as a cause of RSVH despite PVZ prophylaxis.19,23 There is a growing perception that the current dose-interval scheme (PVZ is administered every 30 days, for 5 months during the epidemic season) may not be the most adequate and may not deliver full protection throughout the whole 1-month interval between doses. The concern stems from PVZ pharmacokinetic data, which show that serum levels of PVZ may drop below protective levels (40 μg/mL) in up to 40% of infants well before the end of the month, consistent with the monoclonal antibody’s half-life (16 days). This implies that many treated infants could be unprotected after the third week, especially at the beginning of the RSV season.19 To address this issue, in this study we assessed the time interval between the hospital admission and the previous PVZ injection. Our data showed that hospital admissions in PVZ recipients occurred at a mean of 13 days after the previous PVZ injection. There was no statistically significant association between hospitalization and the number of days elapsed after the previous PVZ injection. RSVH time occurrences followed an apparently normal Gaussian distribution. However, in a subanalysis between group 1 and group 2 infants, a nonsignificant trend was evident in the latter group because the peak of RSVH occurred approximately 21 days after the previous injection. This was consistent with a shift of median and quartiles toward the third–fourth week after the last PVZ dose. Although these differences were statistically insignificant, this finding is in line with some reports23 and may suggest that current schedules are suboptimal in infants who receive PVZ for reasons other than prematurity. Of note, the metabolism of PVZ, which is thought to involve opsonization via the reticuloendothelial system, is not well studied in older infants, and the vast majority of patients with underlying conditions in our study were not premature. Our data support the need for further studies assessing not only the interval between days after the previous injection correlates with increased odds for RSVH in specific categories of patients but also whether the current PVZ schedules may result in similar outcomes in other subpopulations.

Finally, our study suggests that a 5-dose regimen is required to ensure maximum level of protection throughout the entire RSV season. This finding is important since in the US outcomes registry (2000–2001), 75% of all RSVH occurred between the first and second injection intervals24 and the highest RSVH percentage (31%) was also noted in the same time interval in 2000–2004.25 In our study, 25% of RSVH occurred after the third dose. The limited number of RSVHs occurring at the beginning of the prophylactic courses might be partly explained by the dosing schedule in several centers in Canada and Italy that provide the second dose approximately 21 days after the first dose. This practice has been adopted to overcome a possible pharmacokinetic limitation in PVZ efficacy that has been reported.19,22 In contrast,
The Pediatric Infectious Disease Journal • Volume 36, Number 1, January 2017
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it is noteworthy that 1 of 4 PVZ recipients may experience suboptimal prophylaxis effectiveness if the 5-dose regimen is violated. In the past, guidelines issued in British Columbia, Canada, suggested that a maximum of 3-monthly, intramuscular doses of PVZ (15 mg/kg) was adequate to provide protection against severe RSV disease for a 5-month RSV season.26 Those guidelines followed the 2009 recommendations of the American Committee on Infectious diseases,27 where a maximum of 3 doses was endorsed for infants <35 weeks’ gestational age without any additional risk factors. That recommendation was in contrast to the pharmacokinetic data and the population pharmacokinetic model, which showed that a 3-monthly dose regimen cannot protect against severe RSV disease over a typical 5-month RSV season.13,29 The data from our study add to this evidence, and clinically corroborate the hypotheses based on the PVZ pharmacokinetic models. Of note, the recently updated American Academy of Pediatrics guidelines (2014) have amended their previous statement, and now support a complete 5-dose regimen.3

There are several limitations of this study that deserve consideration. First, the groups were recruited in 2 different countries with varying demographic characteristics and environmental risk factors that could predispose to RSV infection and RSVH in the respective populations. However, RSVH rates for preterm infants in the IMpact trial29 were similar to our study but the rates for BPD infants range from 1.64% to 2.4% and may reflect variances in inclusion criteria.23,29 However, combining 2 registries from 2 different countries may be also viewed as a strength because it increases generalizability of the findings. Second, registries are limited by the absence of a control arm which would provide more accurate estimates of the impact of PVZ prophylaxis on RSVH. Registries may also include selection bias because we cannot determine the number of infants that were excluded although they met indications for RSV prophylaxis. However, infants did not get the prophylaxis even when having the indications for it—allocation to PVZ prophylaxis in all Canadian and Italian centers in the majority followed the local guidelines issued by the Canadian Paediatric and Italian Societies of Neonatology, respectively. Third, the effect of PVZ may be underestimated since not all children with the specific conditions in group 2 were enrolled in either the Canadian or Italian registries, and not all were tested for RSV. Fourth, the indications for hospitalization may vary between institutions which could influence the outcomes. However, the use of standardized definitions would likely have minimized ascertainment bias across the enrolled children. Last, RSV detection is influenced by the type of tests conducted, with molecular technology replacing previous assays as the “standard.” This may have reduced the incidence of RSV positive cases in the analysis.

In conclusion, our data shed further light on the outcomes of PVZ recipients, and on the adequacy of the current PVZ dosing protocols. Based on our findings, increased attention should be devoted to infants who are at high risk for severe RSV disease for reasons other than prematurity. New strategies are needed to improve the benefits of PVZ prophylaxis for this group of infants. Further research is warranted to assess whether our findings relate to the current PVZ dosing protocols or on a specific increased risk for RSVH inherent in these “special” populations. The optimal strategy to identify infants eligible for PVZ should be based on demographic characteristics such as gestational age and clinical features, inclusive of serious underlying medical disorders.

They extend our special gratitude to the infants and their families for their dedication and participation in this project.

REFERENCES


ACKNOWLEDGMENTS

The authors thank all the Canadian and Torino-V erona site investigators, the associated research nurses and their support staff for their collaboration and contributions to the respective networks.

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