Pediatric Pulmonology 34:181–188 (2002)

Incidence of Respiratory Syncytial Virus-Related Hospitalizations in High-Risk Children: Follow-Up of a National Cohort of Infants Treated With Palivizumab as RSV Prophylaxis

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Summary. The prophylactic administration of Palivizumab, a monoclonal antibody binding the respiratory syncytial virus (RSV) fusion protein, was recently shown to significantly decrease the incidence of RSV-related hospitalizations among high-risk children (IMpact-RSV trial). While awaiting marketing authorization in France and through a cohort of patients' name-based national program temporarily authorized by the French Drug Agency, a prospective register of all Palivizumab-treated patients in France was set up during the epidemic season 1999–2000. Based on this register, this study was carried out to evaluate the incidence of RSV-related hospitalizations and the safety of prophylaxis among a national cohort of children at high-risk of severe RSV disease.

During the study period, guidelines issued by the French Pediatric Society recommended prophylaxis for children either aged less than 6 months at inclusion and born at less than 33 weeks of gestation with a history of bronchopulmonary dysplasia (BPD) at 28 days of life, or aged less than 2 years, born at less than 36 weeks of gestation, and having required treatment for BPD over the previous 6 months. Once included in the program, investigators were to prospectively report the clinical and demographic characteristics of children, all hospitalizations, and reasons for the hospitalizations.

Five hundred and sixteen children were treated with 1–5 monthly doses. The median gestational age was 28 weeks, and children born at less than 33 weeks of gestation accounted for 88% of the cohort. The prevalence of BPD was 81%. Ninety children were hospitalized for respiratory illness. In 39 children, hospitalizations were attributed to RSV (7.6% of the total cohort). Among those 39 children, 10 (1.9% of the total cohort) required admission into an intensive care unit, and 4 required mechanical ventilation. No deaths or serious adverse events attributable to RSV infection or Palivizumab treatment were reported.

We conclude that the RSV-related hospitalization rate in this high-risk cohort was comparable to the rate observed in the subgroup of Palivizumab-prophylaxed children with BPD in the IMpact-RSV trial. **Pediatr Pulmonol. 2002; 34:181–188.** © 2002 Wiley-Liss, Inc.

Key words: bronchiolitis; bronchopulmonary dysplasia; premature birth; Palivizumab; respiratory syncytial virus; chronic lung disease of newborns.

INTRODUCTION

The risk of serious disease caused by respiratory syncytial virus (RSV) depends on both age at the onset of the epidemic season and underlying medical conditions such as prematurity, bronchopulmonary dysplasia (BPD), and cardiac disease.[1–3] According to a recent population-based retrospective cohort study of a large group of

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Received 6 August 2001; Accepted 6 June 2002.

DOI 10.1002/ppul.10175
Published online in Wiley InterScience (www.interscience.wiley.com).

children born prematurely and already home at the start of the season, the risk of RSV-related hospitalization before age 1 year is 3.2%.[4] The risk increases up to 24.6% for the subgroup of children born at less than 33 weeks of gestation, with BPD (defined as the need for supplemental O_2 at 28 days of life), and discharged at home within 3 months before the beginning of the epidemic season.[4] In a retrospective survey performed in Rochester, NY, the risk of rehospitalization during the first year of life was estimated to be 11.2% in a cohort of children born prematurely before 33 weeks of gestation.[5] It increased up to 24.4% in children with BPD (defined as the persistent need for either supplemental O_2 or ventilation at a postconceptional age of 36 weeks) and to 20.6% in children born at less than 27 weeks of gestation. The risk of RSV-related rehospitalization during the first year of life of children born at less than 33 weeks of gestation was recently reported to be similar (13.4%) in a prospective multicenter survey performed in Spain during the 1998–1999 season.[6]

In recent years, several prophylactic agents have been developed and evaluated in high-risk groups by prospective, controlled, randomized trials.[1,7,8] Palivizumab (Synagis®, Abbott Laboratories) is a human-ized monoclonal G-1k (IgG-1k) immunoglobulin to an epitope of antigen site A on the RSV fusion protein.[9–11] The efficacy of Palivizumab has been evaluated in a prospective, randomized, controlled trial of 1,502 preterm children in the USA, Canada, and Great Britain during the 1996–1997 RSV season.[8] The main finding of this study (IMpact-RSV) was the demonstration of a significant fall in hospitalization rates for RSV infection in the Palivizumab-treated group (4.8%) in comparison with the placebo group (10.6%). Based primarily on the results of this trial, the European Agency for Medicinal Products granted a marketing authorization to Palivizumab in 1999. The accepted therapeutic indication (15 mg/kg of Palivizumab at monthly intervals throughout the epidemic season, with a maximum of 5 injections) is for the prevention of serious forms of RSV infection in the two following high-risk subgroups:

1. Children born at 35 weeks of gestational age or less, and aged 6 months or less at the beginning of the seasonal epidemic;
2. Children with BPD, under 2 years of age at the start of the seasonal epidemic, having required medical treatment (e.g., oxygen, corticosteroids, diuretics, bronchodilators) during the previous 6 months.

In November 1999, several official bodies of pediatric professionals in France, under the aegis of the Société Française de Pédiatrie (French Pediatrics Society), issued guidelines for the administration of Palivizumab during the season 1999–2000, limiting it to children:

1. Either less than 6 months old at the start of the epidemic season, and born prematurely at 32 weeks of gestational age or less, with a history of BPD, defined as oxygen dependence on day 28 of life;
2. Or under 2 years of age, born prematurely at 35 weeks of gestational age or less, with BPD and on long-term treatment at the start of the epidemic season.

This study reports findings collected in the cohort of children treated with Palivizumab during the 1999–2000 RSV epidemic season.

ABBREVIATIONS

ATU	Autorisation temporaire d'utilisation (temporary authorization of utilization)
BPD	Bronchopulmonary dysplasia
CLD	Chronic lung disease of the newborn
O_2	Oxygen
ICU	Intensive care unit
RSV	Respiratory syncytial virus

PATIENTS AND METHODS

Data Collection

While awaiting approval from the European authorities, Abbott Laboratories made Palivizumab available to French hospital pediatricians in the context of a temporary patient's name-based program (autorisation temporaire d'utilisation, or ATU) before the onset of the 1999–2000 RSV epidemic season. This legal provision enables the use of a drug intended to treat serious or rare illnesses, with presumed high efficacy and safety, when no other appropriate treatment is available. The French Agency for the Safety of Health Products determines what data are to be collected by the pharmaceutical laboratory, along with methods for prescribing and dispensing the drug. In general, data collected concern safety and acceptability. Analysis of these ATU data consists of an observational survey specific to the cohort, and reports the way in which physicians use a drug in realistic pediatric conditions.

After having checked that children met inclusion criteria, pediatricians had to fill out a preinclusion form and transmit it to the pharmacist of the hospital concerned, who sent it to Abbott Laboratories. A file was then created in the database, and medication was sent to the institution concerned. Information in the file included date of birth, gestational age, birth weight, type of birth (singleton or multiple), gender, history of neonatal respiratory failure, history of mechanical ventilation, current weight, and existence of concomitant illnesses at time of inclusion of the child into the ATU program. Prior to study entry and before each injection, the child received a

thorough examination. The pediatrician had to note the weight of the child, the precise amount of Palivizumab injected, the occurrence of any possible adverse events at the time of or since the last injection, and diagnosis at admission in case of hospitalization. If treatment was discontinued, the pediatrician had to inform Abbott Laboratories and state the reason. A final examination was scheduled 30 days after the last injection. When hospitalization possibly related to an RSV infection was reported, Abbott Laboratories contacted the prescriber to obtain information on the hospitalization course (date, duration, admission to an intensive care unit, and mechanical ventilation).

All data concerning medical visits were entered in real time in a database managed by the ATU Unit of Abbott Laboratories. If an adverse event occurred, the pediatrician had to immediately inform Abbott Laboratories and send them a statement documenting the event. In case of missing or inconsistent data, the ATU unit recontacted prescribers in order to obtain missing information.

Statistical Analysis

Data thus collected were examined by descriptive statistical analysis, and probed for relationships between demographics, history, and hospitalization parameters. These relations were quantified using univariate tests: chi-square test for qualitative variables and a *t*-test for quantitative variables. Multivariate analysis consisted of downwards logistic regression in order to select variables significantly linked to hospitalization ($P < 0.1$). Variables selected in the initial model were retained based on their clinical pertinence (gender, gestational age, birth weight, history of BPD, duration of neonatal mechanical ventilation, and age and weight at inclusion in the cohort), independently of the result, and each multivariate regression was tested with the variable of interest (hospitalization). SAS version 6.12 (Statistical Application System, SAS Institute, Inc.) software was used for calculations.

RESULTS

Characteristics of Treated Population

One hundred and six neonatology centers enrolled 547 children. Five hundred and sixteen children were treated with at least one injection of Palivizumab. Inclusions mainly occurred between September 13, 1999 and January 1, 2000. The main demographic characteristics of the cohort are shown in Table 1. There were 440 children (88%) born at less than 33 weeks of gestation. Twenty-eight children (6%) were born at more than 35 weeks of gestation. Most of these near-term or term children had either chronic lung disease associated with cardiac or digestive congenital malformations, interstitial pulmonary disease, or laryngotracheal malformation. Children born at 28 weeks' gestational age or less accounted for 52% of the cohort. Three hundred and nineteen children (65%) were less than 6 months old at inclusion. Table 2 summarizes the number of children treated, month by month, with reasons for early discontinuation.

Ten children died during the 1999–2000 season. None of these deaths was due to an RSV infection. The causes of death were acute respiratory failure in 5 children with severe chronic lung disease of the newborn (CLD), obstruction of the tracheotomy cannula (2 children), intraoperative cardiac arrest, pertussis, and cardiocirculatory failure/pulmonary hypoplasia (one child each).

Adverse Events and Safety

Five hundred and eighty four concomitant illnesses in the neonatal period were reported, with the possibility of any given child having several illnesses during the study period. These illnesses were grouped by system, using the WHO classification. In 457 instances, it was a respiratory tract condition. Four hundred children had BPD, representing 81% of all children treated (23 missing data) in the ATU program. Adverse events reported as potentially related to the administration of Palivizumab are indicated in Table 3.

Respiratory Illness Leading to Hospitalization

One hundred and nine hospitalizations related to a respiratory cause were reported in 90 children. In 9 cases with hospitalization unrelated to a viral infection, RSV testing was not performed. Testing for RSV was positive in 42 cases of hospitalization, and negative in 49. RSV status was unknown or undetermined in 9 cases. The 42 hospitalizations with positive RSV testing occurred in 39 children, and the 49 hospitalizations with negative RSV testing occurred in 46 children. Two successive hospitalizations for RSV infection were reported in 3 children. In 3 other cases, RSV infection occurred in children who had not left hospital since birth. Two other children were hospitalized 6 and 12 weeks, respectively, after interruption of treatment with Palivizumab at the peak of the epidemic.

Children having received at least one injection of Palivizumab and who were hospitalized for one or more RSV infections accounted for 7.6% (39/516) of the cohort. Extrapolating the same ratio of RSV-positive tests found in tested children ($42/91 = 0.46$) to the whole population of children hospitalized for any respiratory illness ($0.46 \times 109 = 43$), the incidence of RSV-related hospitalizations would be 8.1% (43/516).

Seventeen children (3.3% of the total cohort) required admission into an intensive care unit. Seven of them (1.4% of the total cohort) required mechanical ventilation. Among the 17 children hospitalized in an ICU, 10 were positive for RSV testing (1.9% of the total cohort),

TABLE 1— Demographic Characteristics of ATU Cohort

Characteristics (N = 516)	
Male gender, no./total no. (%)	292/504 (58%)
Singleton, no./total no. (%)	362/486 (74%)
Date of birth (median)	June 8, 1999
Range	August 25, 1997–January 4, 2000
Median gestational age (weeks)	28 (total no. = 499)
Range	24–41
Gestational age, no./total no. (%)	
≤ 28 weeks	258/499 (52%)
29–32 weeks	182/499 (36%)
33–35 weeks	31/499 (6%)
> 35 weeks	28/499 (6%)
Median birth weight (g)	985 (total no. = 506)
Range	420–4,300
Median age at inclusion (days)	138 (total no. = 486)
Range	11–821
History of BPD, no./total no. (%)	400/493 (81%)
History of neonatal respiratory failure, no./total no. (%)	437/493 (89%)
History of neonatal assisted ventilation, no./total no. (%)	427/493 (87%)

TABLE 2— Characteristics of Palivizumab-Treated Infants[1]

	First dose	Second dose	Third dose	Fourth dose	Fifth dose
Number of children treated	516	500	479	431	302
Early discontinuations before next scheduled injection (no.)	16	21	48	129	NA
Motives for discontinuation					
End of epidemic season	0	5	33	116	NA
Death	2	3	0	2	NA
Respiratory infection	4	10	6	3	NA
Respiratory distress/pneumonia	0	0	1	2	NA
Hospitalization	0	0	2	0	NA
Transfer to another hospital	2	0	1	2	NA
Lost to follow-up	5	2	0	0	NA
Parents' request	0	1	3	2	NA
Miscellaneous	3	0	2	2	NA

[1]NA = not applicable.

TABLE 3— Adverse Events Judged by Physician as Potentially Related to Administration of Palivizumab

	N	%
Apnea	3	0.6
Fever	3	0.6
Pain at injection site	2	0.4
Hyperventilation	2	0.4
Asthenia	1	0.2
Vomiting	1	0.2
Bronchitis	1	0.2
Cough worsening	1	0.2
Urticaria	1	0.2

and 7 were negative. Among those who were mechanically ventilated, 4 were positive for RSV testing (0.8% of the total cohort), and 3 were negative.

Risk Factors for RSV-Related Hospitalization Among the Cohort

The stratified distribution of children hospitalized for RSV infection according to gestational age (GA), presence of BPD, and age at entry is presented in Table 4. The respective incidences of hospitalizations in children with BPD or aged less than 6 months at entry were close to those observed in the whole cohort. The incidence of

TABLE 4— Incidence of RSV-Related Hospitalization According to Gestational Age[1]

	Total ATU cohort (N = 499)	Children with BPD (N = 400)	Children under 6 months at inclusion (N = 319)
Gestational age			
≤26 weeks, n/no. (%)	7/107 (6.5)	7/94 (7.2)	1/50 (2.0)
27–28 weeks, n/no. (%)	8/151 (5.3)	7/126 (5.4)	7/103 (6.8)
29–30 weeks, n/no. (%)	14/113 (12.4)	12/90 (13.3)	10/84 (11.9)
31–32 weeks, n/no. (%)	5/69 (7.3)	5/41 (12.2)	4/44 (9.1)
>32 weeks, n/no. (%)	5/59 (8.5)	5/49 (10.2)	4/38 (10.5)
Total, n/N (%)	39/499 (7.8)	36/400 (9.0)	26/319 (8.3)

[1]No statistical differences ($P < 0.05$) were observed across different categories of gestational age.

hospitalization did not vary significantly across the different categories of gestational age ($P = 0.4$). In near-term or term infants with GA >35 weeks (n = 28), the rate of RSV-related hospitalizations was 7.1%. Among children hospitalized for a respiratory illness, the proportion of children aged less than 6 months at inclusion in the cohort did not differ from that observed among nonhospitalized children (62% and 64%, respectively, $P = 0.9$).

Table 5 shows the characteristics of children hospitalized for respiratory illness (RSV-related or not), as compared with those of nonhospitalized children. Children with BPD were more frequently hospitalized for respiratory illness during the season than those without BPD ($P = 0.035$). In the hospitalized group, more children required mechanical ventilation at birth, compared to the group of nonhospitalized children ($P = 0.015$). Also, the median duration of mechanical ventilation at birth was significantly longer in hospitalized children, compared to nonhospitalized children ($P = 0.045$). The independent relation between the risk of RSV-related hospitalization and several variables including gestational age, birth weight, gender, history of BPD, duration of mechanical ventilation at birth, and age and weight at inclusion was estimated in a multiple logistic-regression model. Each of those covariates was not found to be significantly associated with the risk of RSV-related hospitalization.

DISCUSSION

All children included in this ATU cohort were at serious risk for RSV-related hospitalization. In most cases, inclusion criteria followed the restrictive criteria recommended by the Société Française de Pédiatrie (French Pediatric Society), which were more restrictive than those of the European marketing authorization. Almost 90% of patients included in the cohort had a gestational age ≤32 weeks of gestation, and more than 50% were children born before 28 weeks of gestation. The rate of BPD among children of the ATU cohort was 81%, whereas the rate of BPD among children enrolled in the IMpact-RSV study was 53%.[8] In the Impact-RSV study, BPD was defined as the need for supplemental O_2 at 28 days of life. While BPD defined as above was a sufficient criterion to include a child in the ATU cohort, many pediatricians only enrolled their most severe cases in this preapproval program, and in particular, those with BPD defined as the need for supplemental O_2 at 36 weeks' corrected gestational age or on home oxygen. Moreover, the median age at inclusion was around 4.5 months in the ATU cohort, compared to 5.7 months in the IMpact trial. In this latter study, the rate of RSV-related hospitalization in the subgroup of children with BPD treated with Palivizumab was 7.9% (vs. 12.8% in the placebo group).[8] While such a comparison is arguable, it is worthwhile to note that Palivizumab treatment resulted in a comparable rate of hospitalization in the ATU program (8.1%).

Overall percentages of RSV-positive children requiring admission to intensive care or assisted ventilation in the ATU program were 1.9% and less than 1%, respectively. Among the 39 children hospitalized for RSV infection, 10 (26%) required admission into an ICU, and 4 (10%) needed mechanical ventilation. According to a secondary analysis of the Pediatric Investigators Collaborative Network on Infection in Canada RSV data base, in patients with BPD hospitalized for RSV infection, the proportion of children requiring admission to an ICU was 35%, and the proportion of children needing respiratory support was 23%.[12] In the treated group of children enrolled in the IMpact-RSV trial and hospitalized for RSV infection, the proportion of children admitted to an ICU was 27%, and the rate of children requiring mechanical ventilation was 15%.[8] Although conclusions from such a comparison should be drawn with caution because of the small number of patients, it must be pointed out that these two variables (ICU admission and mechanical ventilation requirement) are primarily related to degree of severity of RSV infection, while non-ICU hospitalizations depend on more subjective admission criteria, which may vary from one institution to another.

The incidence of hospitalizations did not differ whether children were under or over age 6 months at time of inclusion in the cohort. Also, in a multiple logistic

TABLE 5— Comparison of Hospitalized Children for Respiratory Illness With Nonhospitalized Children[1]

	Children hospitalized for respiratory illness	Children not hospitalized
Number of hospitalizations	109	
Number of children concerned (%)	90 (18%)	416 (82%)
Male gender, no./total no. (%)	57/89 (63)	227/406 (56%)
Median birth weight (g)	1,072	980
Range	540–3,660	420–4,300
Median Gestational age (weeks)	29	28
Range	24–41	24–41
Gestational age, no./total no. (%)		
Less than 32 weeks	79/89 (89%)	354/400 (89%)
More than 32 weeks	10/89 (11%)	46/400 (11%)
BPD, no. (%)	77 (86%)	313 (75%)*
Neonatal assisted ventilation, no. (%)	83 (92%)	340 (82%)*
Median duration (days)	15	23*
Median age at inclusion (days)	145	136
Range	11–656	12–821
Age at inclusion		
< 6 months	57/87 (66)	263/408 (64)
> 6 months	30/87 (34)	145/408 (36)
Median weight at inclusion (g)	4,300	3,860
Range	1,150–10,000	1,000–12,500

[1]Excluding patients who died; BPD, bronchopulmonary dysplasia.
*$P < 0.05$.

regression model, gestational age, birth weight, gender, history of BPD, duration of mechanical ventilation at birth, and age and weight at inclusion were not found to be associated with a higher risk of RSV-related hospitalization. It is nevertheless possible that parameters not recorded in this study, such as socioeconomic or environmental factors, might have influenced the incidence of hospitalizations.

One of the main objectives of this special access program was to evaluate the short-term safety of Palivizumab among very young infants, a majority of them still having symptoms of BPD at initiation of prophylaxis. Despite the abnormal underlying respiratory status of many children in the cohort, as suggested by the high rate of respiratory events as well as the rate of death due to respiratory failure reported during the observation period, the administration of Palivizumab was well-tolerated. The prevalence of adverse effects following the administration of Palivizumab was not found to be higher than that reported in the IMpact trial. Three infants born at less than 28 weeks experienced apneas over a 2-day period after immunoprophylaxis with Palivizumab at around 12 weeks of life, an adverse event which was not reported in the IMpact-RSV trial.[8] These infants were also immunized with DPT and Hib vaccines while receiving Palivizumab, and several studies suggest that infants born very prematurely may develop apneic episodes after early immunization with DTP, with a risk estimated between 8–12%.[13,14]

The results of other postmarketing evaluations of the effectiveness of Palivizumab were recently reported.[15,16] Calculated rates of RSV-related hospitalization ''in real life'' of these cohorts were lower than those estimated in the ATU cohort. This discrepancy may reflect the very high proportion of extremely premature infants with BPD in the ATU cohort. The hospitalization rate for RSV infection in this cohort composed of very high-risk children was comparable to the rate of RSV-related hospitalizations observed in children with BPD enrolled in the IMpact trial. It was also lower than the hospitalization rate for RSV infection reported in the recent observational retrospective or prospective studies focused on risk factors for RSV-related hospitalization among very preterm infants.

ACKNOWLEDGMENTS

Abbott France carried out the logistics of this study. The authors thank, in particular, F. Boer, M.D., for database analysis, J. Groothuis, M.D., and G. Goldfarb, M.D., for helpful discussions, F. Bruno, E. Guillevic, and R. Terrier for their technical assistance in database management, and the pediatricians of the following hospitals: Centre Hospitalier Arnaud de Villeneuve, 34295 Montpellier; Centre Hospitalier arrondissement de Montreuil, 62180 Rang du Fliers; Centre Hospitalier d'Agen, 47000 Agen; Centre Hospitalier d'Albi, 81013 Albi; Centre Hospitalier d'Arras, 62022 Arras Cedex; Centre Hospi-

talier de Bastia, 20604 Bastia Furiani; Centre Hospitalier de Beaumont sur Oise, 95260 Beaumont sur Oise; Centre Hospitalier de Beauvais, 60021 Beauvais; Centre Hospitalier de Briançon, 05505 Briançon; Centre Hospitalier de Brive, 19312 Brive; Centre Hospitalier de Calais, 62107 Calais; Centre Hospitalier de Cornouaille, 29107 Quimper; Centre Hospitalier de Dax, 40107 Dax; Centre Hospitalier de la Cote Basque, 64109 Bayonne; Centre Hospitalier de Libourne, 33505 Libourne; Centre Hospitalier de Lorient, 56322 Lorient; Centre Hospitalier de Meaux, 77108 Meaux; Centre Hospitalier de Montélimar, 26216 Montélimar; Centre Hospitalier de Montereau, 77130 Montereau; Centre Hospitalier de Périgueux, 24019 Périgueux; Centre Hospitalier de Pierre Bénite-Lyon Sud, 69495 Pierre Bénite; Centre Hospitalier de Roubaix, 59100 Roubaix; Centre Hospitalier de Saintes, 17108 Saintes; Centre Hospitalier de Sens, 89108 Sens; Centre Hospitalier de Soissons, 02209 Soissons; Centre Hospitalier de Tarbes, 65013 Tarbes; 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Centre Hospitalier Général de Longjumeau, 91160 Longjumeau; Centre Hospitalier Général de Montauban, 82013 Montauban; Centre Hospitalier Général de Perpignan, 66046 Perpignan; Centre Hospitalier Général de Reims, 51100 Reims; Centre Hospitalier Général de Saint Dizier, 52115 Saint Dizier; Centre Hospitalier Général de Salon de Provence, 13657 Salon de Provence; Centre Hospitalier Général de Dieppe, 76200 Dieppe; Centre Hospitalier Général d'Orsay, 91400 Orsay; Centre Hospitalier Interdépartemental de Fréjus-Saint Raphaël, 83608 Fréjus; Centre Hospitalier Interdépartemental de Créteil, 94010 Créteil; Centre Hospitalier Interdépartemental les Hôpitaux du Léman, 74203 Thonon-les-Bains; Centre Hospitalier Régional Caremeau, 30900 Nimes; Centre Hospitalier Régional de Toulon, 83056 Toulon; Centre Hospitalier Régional d'Orléans, Hôpital de la Source, 45067 Orléans; Centre Hospitalier Régional Universitaire de Lille, Jeanne de Flandre, 59037 Lille; Centre Hospitalo-Universitaire de Grenoble, 38043 Grenoble; 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Hôpital Sainte Croix, 57045 Metz; Hôpital Sud, 35056 Rennes; Hôpital Trousseau, 75571 Paris; Institut de Puériculture, 75014 Paris; and Maternité Régionale, 54042 Nancy.

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