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Use of Parenteral Lipid Emulsions in French Neonatal ICUs

Alexandre Lapillonne, MD, PhD^{1,2,3,4}; Laure Fellous, MD^{1,2}; and Elsa Kermorvant-Duchemin, MD, PhD^{1,2}; for the French neonatal departments*

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Objective: To determine the types of parenteral lipid emulsions currently used for preterm infants, their mode of delivery, and the main disease conditions that are considered by neonatologists as contraindications. **Design:** National survey using a questionnaire. **Setting:** 155 neonatal departments in France. **Results:** 100 (65%) neonatal departments participated in the survey. The most widely used lipid emulsion was the 20% soybean oil/coconut oil-based emulsion (68% of the units), followed by the soybean oil-based emulsion (28.5%) and the soybean oil/olive oil-based emulsion (3.5%). Peripheral venous access was considered to be a possible route for the infusion of lipid emulsions in only 58 (63.7%) of the units. In 80%–90% of the units, sepsis, hemodynamic failure, thrombocytopenia, disseminated intravascular coagulation, and hyperbilirubinemia were considered to be relative

or absolute contraindications, whereas only hemodynamic failure, disseminated intravascular coagulation, and to a lesser extent sepsis were most often perceived as absolute contraindications. **Conclusions:** Neonatologists are somewhat reluctant to use parenteral lipids when only peripheral venous access is available, despite the low osmolality of the emulsions. This may impair, at least temporarily, the adequate supply of energy and/or essential fatty acids in infants who do not have central venous access. This study also shows a large heterogeneity of responses with regard to the contraindications for parenteral lipids. (*Nutr Clin Pract.* 2011;26:672-680)

Keywords: lipids; fat emulsions; parenteral; parenteral nutrition; infant, premature; infusions, intravenous; fatty acids, essential

As the rates of survival of premature infants, and especially very preterm ones, have increased, provision of better nutrition support for this group has risen in priority.¹ It has become clear that lipids administered at this age can determine various outcomes in later life, including both physical growth and intellectual development.^{2,3} In addition to playing a role in nutrition, lipids can influence numerous pathophysiological processes, including oxidative stress, immune responses, and inflammation.⁴

Low-birth-weight (LBW) infants almost universally exhibit postnatal growth failure, which has been linked to early inadequate nutrition.^{5,6} Furthermore, concerns have been raised about the possible long-chain polyunsaturated

fatty acid (LC-PUFA) deficit that can occur during the early weeks of life of very preterm infants.⁷ Therefore, 2 important aspects need to be considered with respect to parenteral lipids: first, a suitable dose to provide an adequate caloric intake, and second, a fatty acid composition that fulfills essential fatty acid (EFA) and, possibly, LC-PUFA requirements.

At the present time, only 2 emulsions are approved for use in the United States. These are long-chain triglyceride emulsions consisting of either 100% soybean oil or a 50:50 mixture of soybean and safflower oils. In contrast, numerous lipid emulsions of varying oil composition are available in Europe. These lipid emulsions, which contain various amounts of medium-chain triglycerides (MCTs), olive oil, and/or fish oil, have been used to modify the fatty acid composition of the lipid emulsions. They may provide some clinical benefits over the conventional pure soybean oil emulsions,⁸ but it is not known how widely they are used.

If patients receive inadequate nutrition, whether because physicians are not knowledgeable of nutrition support or because of improper implementation, outcomes can be impaired. These concerns require a systematic assessment of nutrition planning and implementation in neonatal intensive care units (NICUs). It has been

From ¹APHP, Department of Neonatology, Necker Hospital, Paris, France; ²Paris Descartes University, Paris, France; ³IPP, Institut de Pédiatrie de Paris, France; and ⁴CNRC, Baylor College of Medicine, Houston, Texas.

*See list of French neonatal departments in the Acknowledgments.

Address correspondence to: Alexandre Lapillonne, Neonatal Department, Necker Hospital, 149 rue de Sèvres, 75015 Paris, France; e-mail: alexandre.lapillonne@nck.aphp.fr.

shown that development and implementation of evidence-based nutrition support practices in neonates led to improved nutrient intake and growth with reduced length of stay and related cost.⁹ Surveys are a useful method for determining the knowledge base and therapeutic intentions of clinicians. Such surveys not only provide a reference standard but can help clinicians assess their practices with respect to published recommendations. Surprisingly, very few studies in the literature provide insight into neonatal parenteral lipid practices, and very little information is available concerning factors that significantly influence the prescription of parenteral lipids for preterm infants.

In view of the recognized clinical importance of parenteral lipids for preterm infants and the paucity of data available on the use of parenteral lipids in NICUs, we conducted a nationwide survey in France to determine (1) compliance with the recent European guidelines¹⁰ with regard to the type of lipid emulsions used in NICUs and the timing and dose of parenteral lipids infused to very preterm infants and (2) the main conditions that can preclude or limit the use of parenteral lipids in preterm infants.

Methods

The survey used a questionnaire that was designed by the authors and then validated internally by the physicians of the Department of Neonatology and externally by the chairman of the Groupe d'Etudes en Néonatalogie d'Ile de France (GEN-IF) (Ile-de-France Neonatology Study Group, Pr. Y. Aujard, Paris) and the executive committee of the Fédération Nationale des Pédiatres Néonatalogistes (French Neonatal Society).¹¹ The main aim of the questionnaire was to determine the conditions under which lipid emulsions are prescribed for parenteral nutrition for premature infants. The first series of questions focused on the types of lipid emulsions currently used and their mode of delivery. The second series collected data on the date of initiation, initial dosage, rate of increment, and target parenteral lipid intake for premature infants with a birth weight ≤ 1500 g. The last series of questions related to the clinical conditions considered to be contraindications for the use of parenteral lipids.

An extensive list of neonatal departments in France and the French overseas territories was established by combining the lists of the French scientific societies involved in newborn care and those of the regional healthcare services. In France, the definition of the levels of care differs slightly from that used in the United States.¹² Level I units provide a basic level of newborn care for infants at low risk. Level II special care nurseries can look after infants who are moderately ill with problems that are expected to resolve rapidly and do not require mechanical ventilation. Unlike in the United States, there is no restriction on the basis of birth weight

or gestational age. Some of these level II units (ie, level IIB) are able to provide continuous positive airway pressure and parenteral nutrition. Finally, level III NICUs are defined by their capacity to provide mechanical ventilation. These units are able to care for extremely LBW infants and have the facilities for high-frequency ventilation, inhaled nitric oxide, and surgery on site or at a nearby institution.

The questionnaire, accompanied by a cover letter and a reply envelope, was sent by post to the medical superintendents of all the French level III ($n = 66$) and level IIB ($n = 89$) neonatal units. Units not admitting premature infants were not asked to fill out the questionnaire. Reminders were sent twice to nonrespondents.

Statistical Analyses

The data were analyzed using Minitab 13.3 software (Minitab Inc, State College, PA). General frequency responses to all survey items were determined and used to test for associations among the categorical variables. Results from level II and III units were compared by Pearson χ^2 tests of independence. A P value of ≤ 0.05 was considered to be statistically significant. The study was approved by the GEN-IF and the Fédération Nationale des Pédiatres Néonatalogistes.

Results

Response Rate

Among the 155 level IIB and level III neonatal departments, 100 (65%) responses were obtained, with a higher rate from level III ($n = 56/66$; 85%) than from level IIB units ($n = 44/89$; 50%) ($P < .036$). Nine level IIB units were excluded from the study because they did not prescribe parenteral lipids. The statistical analysis was performed on the remaining questionnaires from 91 units with a total of 2471 beds. Nine departments did not report their annual number of admissions, whereas the 82 others reported a total of 41,861 admissions per year (level III = 31,197; IIB = 10,667). The mean $\pm$ standard deviation number of admissions per unit per year of infants born before 32 weeks of gestation was significantly higher in the level III than level IIB units (133 ± 64 vs 34 ± 29 ; $P < .0001$).

Compliance With Guidelines

Type of lipid emulsion. Two different soybean oil emulsions (Intralipid 20% [French name: Intralipide 20%, Fresenius Kabi, Sèvres, France]; and Lipofundin N 20% [French name: Endolipide 20%, B-Braun Medical, Boulogne, France]), 1 soybean oil/coconut oil emulsion (Lipofundin MCT/LCT 20% [French name: Médialipide

Table 1. Type and Composition of Parenteral Lipid Emulsions Used in French Neonatal Units

	ClinOleic 20%	Intralipid 20%	Lipofundin MCT/ LCT 20%	Lipofundin N 20%
TG, g/L	200	200	200	200
Composition	80% olive oil, 20% soybean oil	100% soybean oil	50% soybean oil, 50% coconut oil	100% soybean oil
Manufacturer	Baxter (Maurepas, France)	Fresenius Kabi (Sèvres, France)	B. Braun (Boulogne, France)	B. Braun
% total fatty acids				
C8:0			27.0	
C10:0			21.0	
C12:0			1.5	
C16:0	13.5	11.0	5.0	12.0
C18:0	2.9	4.0	2.0	4.5
C18:1 (n-9)	59.5	24.0	12.0	24.0
C18:2 (n-6)	18.5	53.0	27.0	50.0
C18:3 (n-3)	2.0	8.0	4.0	7.0

LCT, long-chain triglyceride; MCT, medium-chain triglyceride; TG, total triglyceride.

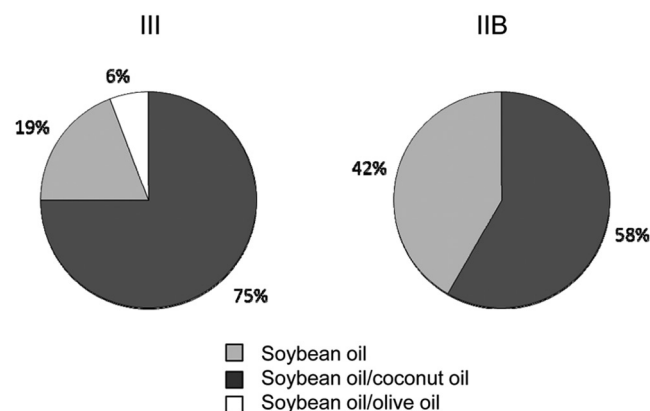


Figure 1. Percentage of neonatal units using a soybean oil-based emulsion, a soybean oil/coconut oil-based emulsion, or a soybean oil/olive oil-based emulsion according to the type of units. The type of lipid emulsion used differed significantly according to the level of the unit ($P = .035$).

20%, B-Braun Medical, Boulogne, France]], and 1 soybean oil/olive oil emulsion (ClinOleic 20%, Baxter, Maurepas, France) were used in the neonatal units for parenteral nutrition.

The composition and frequency of use of each type of lipid emulsion are reported in Table 1 and Figure 1, respectively. Use of a standard 10% emulsion was not reported in any of the units; only 20% emulsions were used (Table 2). The most widely used 20% lipid emulsion was the soybean oil/coconut oil-based emulsion, which was used in 68% of the units; the soybean oil/olive oil-based emulsions and the soybean oil-based emulsions were used in 3.5% and 28.5% of the units, respectively. The type of lipid emulsion used differed significantly according to the level of the unit ($P = .035$) (Figure 1).

Table 2. Number (%) of Units With a Nutrition Protocol for Parenteral Lipids for Preterm Infants That Is Compliant With the European Guidelines¹²

European Guidelines	Units Compliant With Guidelines
Lipid emulsions are an integral part of pediatric parenteral nutrition	88/88 (100%)
Use of 20% lipid solutions	88/88 (100%)
Day of start (ie, day 3 at the latest)	40/82 (49%)
Parenteral lipid intake should usually be limited to a maximum of 3–4 g/kg/d	70/87 (79%)

Timing and dose of lipids infused to very preterm infants. All units use parenteral lipids as part of parenteral nutrition for preterm infants. Compliance with European guidelines with regard to the day of starting nutrition and the maximum intake of lipids infused to infants with a birth weight of ≤ 1500 g is reported in Table 2. The maximum intake was below the recommendations in 15% of the units and above the recommendations in 6% of the units. The initial dosage of lipids infused to infants with a birth weight ≤ 1500 g was 0.5 g/kg/d in 78% of the units and 1 g/kg/d in 22% of the units. The day of start, the maximum intake, and the initial dosage of lipids infused were similar in level IIB and III units.

Main Conditions That Can Preclude or Limit the Use of Parenteral Lipids for Preterm Infants

Venous access. Peripheral venous access, defined as the insertion of a needle or short catheter in a subcutaneous vein, was not considered to be a possible route for the

Table 3. Ranges of Maximum Osmolarity Accepted by Neonatologists According to the Type of Venous Access

	≥1200 mOsm/L	1000 mOsm/L	≤800 mOsm/L	Do Not Know
Peripherally inserted central catheters	35.2%	35.2%	4.4%	25.3%
Umbilical catheters	41.8%	34.1%	0%	24.2%
Peripheral venous access	0%	23.1%	50.6%	26.4%

Data are reported as the percentage of responding units.

Table 4. Relative and Absolute Contraindications for the Use of Parenteral Lipid Emulsions in Preterm Infants as Reported by Neonatal Units

	Not a Contraindication	Relative Contraindication	Absolute Contraindication
Suspected or proven sepsis	7%	47%	46%
Hemodynamic failure	6%	19%	75%
Thrombocytopenia	17%	53%	30%
Disseminated intravascular coagulation	4%	23%	73%
Hyperbilirubinemia unrelated to acute infection	17%	72%	11%

Data are expressed as the percentage of responding units.

infusion of lipid emulsions in 33 (36%) of the neonatal units, with a higher rate in level IIB than in level III units (56% vs 24%, respectively; $P = .002$).

A large proportion of neonatologists did not know the maximum osmolarity of parenteral nutrition that can be tolerated whatever the type of venous access (peripherally inserted central catheters, 23%; umbilical catheters, 26%; peripheral venous access, 26%) (Table 3). None of the units and 4.4% of the units considered that the osmolarity of the parenteral nutrition solution should be ≤800 mOsm/L when an umbilical catheter and a peripherally inserted central catheter are used, respectively, whereas 24% of the units declared that an osmolarity >800 mOsm/L can be used with peripheral venous access (Table 3).

Disease conditions. The percentages of neonatal units considering suspected or proven sepsis, hemodynamic failure, thrombocytopenia, disseminated intravascular coagulation, or hyperbilirubinemia unrelated to acute infection as an absolute or relative contraindication for the use of parenteral lipid emulsions are reported in Table 4. There were no significant differences between level IIB and level III units except in the case of hyperbilirubinemia unrelated to acute infection, which was more frequently rated as an absolute contraindication by level IIB units (13% vs 4%, $P = .004$).

In reply to an open question asking which other special disease conditions respondents considered to be a relative or an absolute contraindication, respiratory failure/hypoxemia/pulmonary hypertension and hepatic dysfunction/cholestasis were each cited 3 times, hypertriglyceridemia and use of ibuprofen were each cited twice, and acidosis and exchange transfusion were each cited once.

Discussion

This study is the first of its type to assess the use of parenteral lipids as part of the nutrition therapy and strategies used in NICUs. This study provides new insights into the type of lipid emulsion used in a European country, the routes of delivery considered to be suitable for parenteral lipids, and the particular disease conditions perceived as contraindications by neonatologists.

Our study reveals that practices in the United States and Europe differ significantly with regard to the choice of the lipid emulsion for parenteral nutrition of newborns. Indeed, our survey shows that whereas only the 100% soybean oil and the 50:50 mixture of soybean and safflower oils are available in the United States, the most widely used type of lipid emulsion in France is the MCT/soybean oil-based emulsion, the soybean oil emulsion being, in contrast, used in only one-quarter of the French neonatal units. Interestingly, both American and European guidelines are fairly imprecise with regard to the choice of the type of lipid emulsion,^{10,13} the only recommendation being the use of 20% emulsions with no mention of the fatty acid composition. The 20% emulsions contain a lower ratio of phospholipid emulsifier/triglycerides than 10% lipid emulsions and allow more efficient triglyceride clearance, even at a higher triglyceride intake.¹⁴ Our study shows that neonatologists are aware of the better tolerance of standard 20% emulsions because only these are currently prescribed.

With regard to fatty acid composition, there are some theoretical benefits to using MCT since their oxidation is rapid¹⁵ and much less dependent on carnitine than that of long-chain triglycerides (LCTs) and since MCT/LCT

emulsions lead to higher net fat oxidation, reduced liver derangement, improved white blood cell function, and fewer effects on pulmonary hemodynamics and gas exchange than LCT emulsions.¹⁰ The use of the new olive oil/soybean oil-based lipid emulsion was recently studied in premature infants with encouraging results,¹⁶ but our study shows that it is seldom used in French NICUs.

Although an intake of polyunsaturated fatty acids (PUFAs) is required to prevent any essential fatty acid deficiency, the adequacy of soybean lipid emulsions has been questioned because of its high linoleic acid content and its ω -6/ ω -3 imbalance. There are some concerns that preterm infants, and especially the very preterm ones, may develop a severe docosahexaenoic acid (DHA) deficit during the first weeks of life.^{7,17} Interestingly, lowering the intake of PUFA precursors appears to enhance LC-PUFA status.^{16,18} The newly developed lipid emulsions containing fish oil may provide benefits over the other emulsions since they may increase DHA status,¹⁹ reduce the severity of retinopathy of prematurity,²⁰ and decrease oxidative stress,²¹ circulating phospholipid and cholesterol levels,¹⁹ pulmonary hypertension,²² and parenteral nutrition-induced cholestasis.²³ The use of these fish oil emulsions is currently under investigation in both the United States and Europe, and their safety should be assessed by adequately designed studies before their routine use.

Lipid emulsions were introduced into clinical practice not only to provide essential fatty acids but also to increase energy intake.^{10,24} Conversely, few data support the early initiation of parenteral administration of lipids as a means to improve growth or decrease long-term morbidity.^{3,25} One study investigated the efficacy of the early introduction of a high dose of parenteral lipids (ie, 3 g/kg/d) and demonstrated good tolerance.²⁶ Our study shows that French neonatologists are somewhat reluctant to start parenteral lipids early, as about half of them do not start lipids during the first 3 days of life as recommended. A survey performed in the United States suggests that lipid emulsions are likely to be started earlier than in France since the mean amount of parenteral lipids on day 1 was 0.67–0.69 g/kg/d (range, 0–3), but it remains unclear when lipids are really started since some units did not start at day 1 of life and since no data after day 1 were reported in this article.²⁷

Although the use of central venous catheters (ie, peripherally inserted central catheters or umbilical catheters) is common and often required for the administration of intravenous nutrition, peripheral venous access can also be used in some cases. Concerns about the osmolarity of peripheral parenteral nutrition formulas usually relate to the risks of thrombophlebitis and extravascular suffusion. Our study shows that one-quarter of the neonatologists do not know what osmolarity of the parenteral nutrition solution can be tolerated according to the type of venous access. There is in fact no strong evidence in the literature indicating a clear cutoff osmolarity for central

versus peripheral parenteral nutrition, and the experimental data obtained in animal models are not completely transferable to humans.²⁸ Parenteral nutrition with an osmolarity exceeding 800–900 mOsm/L has been widely thought to warrant use of a central line.^{29,30} However, it is possible to infuse parenteral nutrition with an osmolarity of around 1100 mOsm/L,³¹ or even up to 1700 mOsm/L, through a peripheral venous line, at least as a short-term strategy,³² without increasing the risk of thrombophlebitis. The guidelines for pediatric parenteral nutrition do not provide any recommendation for osmolarity when peripheral venous access is used.¹⁰ This is probably due to the fact that, to our knowledge, no study has been performed on this topic in a pediatric population. In the absence of any data, it would be advisable to recommend an osmolarity similar to that recommended for adults (ie, peripheral parenteral nutrition should be administered for a limited period of time using solutions whose osmolarity does not exceed 850 mOsm/L).²⁹ Although lipid emulsions have a low osmolarity (~340 mOsm/L) and may have a protective effect on the endothelium,³³ one-third of the neonatal units did not consider peripheral venous access to be a possible route for the infusion of lipid emulsions.

Concerns have been expressed about the early administration of lipid emulsions because of potential adverse effects, including chronic lung disease, increases in pulmonary vascular resistance, impaired pulmonary gas exchange, bilirubin toxicity, sepsis, and free radical stress. The guidelines with regard to side effects or use in special disease conditions are therefore prudent, and it is recommended to avoid supplying lipid emulsions in high dosages or adjusting the delivery of intravenous lipids to plasma triglyceride concentrations.¹⁰ In a recent study in the United States, a majority of neonatologists stated that lung disease, jaundice, pulmonary hypertension, and hyperglycemia were not contraindications to the initiation of parenteral lipids,²⁷ but the low response rate (23%) in this survey did not allow one to draw firm conclusions as to the special disease conditions that most neonatologists considered to be contraindications.³⁴ Contrary to the study of Hans et al,²⁷ we investigated the perceived contraindications of lipid emulsions not only for the initiation of lipids but also for their use throughout the time spent in the NICU. The results showed that in 80%–90% of the units, sepsis, hemodynamic failure, thrombocytopenia, disseminated intravascular coagulation, and hyperbilirubinemia were considered to be contraindications. However, hemodynamic failures, disseminated intravascular coagulation, and to a lesser extent sepsis were most often perceived as absolute contraindications.

There are concerns that lipid emulsions might support microbial growth, affect platelet numbers or function, and be involved in the development of cholestasis.¹⁰ With regard to critically ill or infected patients, the European guidelines do not recommend stopping the lipid infusion but advise clinicians to monitor more

closely the plasma triglyceride concentration and to adjust the dose in case of hyperlipidemia.¹⁰ In case of severe unexplained thrombocytopenia, serum triglyceride concentrations should be monitored and parenteral lipid dosage could be reduced but not stopped in order to supply at least the minimal essential fatty acids requirements to maintain normal platelet function. With regard to severe acute respiratory failure with or without pulmonary hypertension and hyperbilirubinemia, the European guidelines acknowledge the lack of data in preterm infants. Studies aiming at assessing the complications and side effects of the available lipid emulsions for preterm infants are therefore warranted.

Finally, this study confirms the large heterogeneity among centers with regard to the nutrition management of neonates.^{5,9,35} The level IIB centers, for example, were more prone to continue to use the traditional soybean oil-based emulsions and were less likely to use peripheral venous access as an alternative route for the infusion of lipid emulsions. However, the lower response rate of these units precludes drawing firm conclusion about their practice. In contrast, the 85% response rate of the level III units, where most of the very preterm infants are admitted, gives strength to our study and highlights the fact that it is difficult to implement new guidelines, recommendations, and products nationwide.³⁴

In conclusion, our survey shows that the type of lipid emulsion most widely used in French NICUs is the 20% soybean oil/coconut oil-based emulsion and not the traditional soybean oil emulsions. By providing data collected in a European country, our study also highlights the differences between the United States and Europe with regard to the choice of parenteral lipid in neonates, which raise numerous questions with regard to compliance with guidelines, interest of newly designed lipid emulsion, safety of use, and research needed in this field.

Furthermore, our study shows that neonatologists are somewhat reluctant to use parenteral lipids when only peripheral venous access is available, despite the low osmolality of the emulsions. This may impair, at least temporarily, the adequate supply of energy or essential fatty acids in neonates who do not have central venous access. Finally, our study reveals a large heterogeneity of responses with regard to the contraindications for parenteral lipids, highlighting the fact that among the 3 macronutrients, parenterally administered fats are the least studied and least understood, especially in preterm infants.

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French neonatal departments: Hamid Ait Tahar, Centre Hospitalier de Semur en Auxois; Christine Allisy, Centre Hospitalier Victor Dupouy, Argenteuil; Isabelle Arnault, Centre Hospitalier de Troyes; Dominique Astruc, Hôpital de Haute-pierre, Strasbourg; Brigitte Auburtin, Centre Hospitalier Général Jean Monet, Epinal; Yannick Aujard, Hôpital Robert Debré, Paris; Philippe Barré, Hôpital de Fleyriat, Bourg en Bresse; Véronique Barre, Centre Hospitalier du Belvédère, Mont Saint-Aignan; Patrick Bazin, Centre Hospitalier Général René Pleven, Dinan; Nadir Benbrik, Centre Hospitalier Bretagne Atlantique, Vannes; Catherine Benezech, Centre Hospitalier Général Louis Pasteur, Dole; Mabrouk Bengrina, Centre Hospitalier de Remiremont; Jean-Louis Bessis, Hôpital Louis Pasteur, Cherbourg; Pierre Betremieux et Armelle de La Pintièrre, Centre Hospitalier Régional et Universitaire de Pontchaillou, Rennes; Valérie Biran-Mucignat, Hôpital Armand Trousseau, Paris; Jean Francois Blanc, Centre Hospitalier Lucien Hussel, Vienne; Isabelle Blanchot, Clinique de la Sagesse, Rennes; Pascal Bolot, Hôpital Intercommunal Robert Ballanger, Aulnay sous Bois; Jean Jacques Bonnemaïson, Clinique Du Nohain, Cosne sur Loire; Geneviève Bossard, Centre Hospitalier de Cahors; Jacques Bouillié, Hôpital Saint-Antoine, Paris; Isabelle Bréant, Centre Hospitalier Marc Jacquet, Melun; Jean-Pierre Brossier, Centre Hospitalier Départemental Les Oudairies, La Roche sur Yon; Pierre Callamand, Centre Hospitalier de Béziers; François Cambier, Clinique Sainte Claire, Amiens; Carole Carlus, Centre Hospitalier Intercommunal Jean Rostand, Sèvres; Florence Casagrande, Hôpital Archet, Nice; François Cazassus, Centre Hospitalier Louis Constant Fleming, Saint-Martin; William Cécile, Hôpital Victor Fourche, Fort-de-France; Valérie Champion, Centre Hospitalier Intercommunal, Créteil; Jacques Chevalier, Centre Hospitalier de Moulins-Yzeure; Laurent Chevret, CHU de Bicêtre, Le Kremlin-Bicêtre; Didier Chognot, Centre médico-chirurgical Le Parc, Colmar; Francis Chomienne, Centre Hospitalier de Cholet; Olivier Claris, Hôpital Edouard Herriot, Lyon; Yves Coatantiec, Hôpital Foch, Suresnes; Roxanna Condor, Hôpital Saint Camille, Bry sur marne; Gilles Cottacin, Hôpital du Pays du Mont-Blanc, Sallanches; Caroline Coudy-Angelvy, Hopital André Mignot, Le Chesnay; Michel Couronne, Hôpital Clinique Claude Bernard, Metz; Jacky Cuzzi, Hôpital de Girac, Saint-Michel; Thierry Debillon, Hôpital de la Tronche, Grenoble; Edurne de Gamarra, Hôpital Simone Veil, Montmorency; Christiane de Gennes, Centre Hospitalier Général, Orsay; Benoît Delaporte, Groupe Hospitalier du Havre; Reine de la Ville Marque, Brigitte Zamba, Jocelyne Renouard-Pazat, Centre Hospitalier

Privé de Saint Grégoire; Florence Delepoulle et Emmanuelle Robin, Centre Hospitalier de Dunkerque; Martin Delgado, Centre Hospitalier de Mâcon; Rémi Deliege, Clinique de la Châtaigneraie, Beaumont; Inès de Montgolfier, Hôpital Pitié-Salpêtrière, Paris; Emmanuelle Descombes-Barroso, CHU de Poitiers; André Deslypper, Polyclinique de Courlancy, Reims; Laure Desnoullez, Centre Hospitalier de Calais; Clothilde Des Robert, CHU de Nantes; Christine Devulder, Polyclinique Saint André, Reims; Katherine Dieckmann, Centre Hospitalier de Blois; Murielle Dobrzynski, CHU de Brest; Pascal Doeuvre, Centre Hospitalier d'Auch; Philippe Douard, Centre Hospitalier Général, Senlis; Yvonne Dupic, Centre Hospitalier Intercommunal de Castres; Renée-Pierre Dupuy, Centre Hospitalier de Saint-Brieuc; Jean-François Duret, Hôpital Jean Bouveri, Montceau Les Mines; Bernard Faverge, Centre Hospitalier de Martigues; Amelie Favreau et Yasmine Lakhdari, Hôpital Gatiens de Clocheville, Tours; Marc Feldmann, Centre Hospitalier Régional, Thionville; Jean-Paul Ferracci, Centre Hospitalier de Cannes; Jean-Baptiste Fieschi, Centre Hospitalier Notre Dame de la Miséricorde, Ajaccio; Jean Flori, SIHCUS-CMCO, Schiltigheim; Vincent Flurin, Centre Hospitalier du Mans; Martine Franc, Centre Hospitalier d'Agen; Michel Françoise, Centre Hospitalier William Morey, Chalon sur Saône; Hubert Freysz, Centre Hospitalier de Selestat; Marie-Françoise Froute, Maternité Bel Air, Bordeaux; Hélène Fury, Hôpital d'Enfants, Saint-Denis, La Réunion; Chantal Gagliardone, Hôpital Franco-Britannique, Levallois Perret; Henri Giudicelli, Centre Hospitalier d'Antibes Juan-les-Pins; Isabelle Glorieux, Hôpital des Enfants, Toulouse; Isabelle Gothié, Clinique Belledonne, Saint-Martin d'Hères; Hervé Gouedard, Centre Hospitalier des Pays de Morlaix, Morlaix; Pierre Goumy, Centre Hospitalier de Vichy; François Guillot, Centre Hospitalier Intercommunal de Villeneuve Saint-Georges; Olivier Guilluy, Centre Hospitalier de Saint-Omer; Alain Guinchard, Centre Hospitalier de Châtillon-sur-Seine; Albert Hamza, Centre Hospitalier de Coulommiers; Béatrice Harvey, Centre Hospitalier de Saint-Cloud; Frédérique Hayfendler, Centre Hospitalier de Niort; François Hervé, Hôpital Tenon, Paris; Serge Hubert, Centre Hospitalier de Saintes; Alain Hureaux, Centre hospitalier de Sedan; Emmanuel Jeannot, Centre Hospitalier de Dieppe; Philippe Jouvencel, Hôpital de la Côte Basque, Bayonne; Michel Juchereau, Centre Hospitalier de Fontenay Le Comte; Laurence Keller, Centre Hospitalier de Mulhouse; Sophie Ketterer-Martinon, Centre Hospitalier Dupuytren, Limoges; François Kieffer, Institut de Puériculture et de Périnatalogie, Paris; Serge Klosowski, Centre Hospitalier Dr Schaffner, Lens; Eric Lachassinne, Hôpital Jean Verdier, Bondy; Norbert Laisney, Centre Hospitalier Mémorial France-Etats-Unis, Saint-Lô; Delphine

Lamireau, Hôpital Pellegrin, Bordeaux; Fabrice Lapeyre, Centre Hospitalier de Valenciennes; Stéphane Le Bouedec, CHU d'Angers; Bénédicte Lecomte, Hôpital Hôtel-Dieu, Clermont-Ferrand; Marie Anne Le Gall, Centre Hospitalier de Bretagne Sud, Lorient; Agnès Lehnert, Centre Hospitalier de Montargis; André Léké et Sabrina Goudjil, CHU Amiens Nord; Richard Lenclen, Centre hospitalier de Poissy-Saint-Germain-en-Laye; Jacques Lerailliez, Centre Hospitalier René Dubos, Pontoise; Dominique Leyronnas, Hôpital Privé, Antony; Catherine Lhermitte-Cahuzac, Centre Hospitalier Général, Arpajon; Catherine Maingueneau, Clinique Jules Vernes, Nantes; Gwenaëlle Malgorn, Polyclinique de l'Atlantique, Saint Herblain; Jean-Philippe Manchart, Centre Hospitalier de Valence; Romain Mandel, Centre hospitalier de Lagny sur Marne; Thierry Mansir, Centre Hospitalier Général de Pau; Jean-Baptiste Mariette, Groupe Hospitalier Caremeau, Nîmes; Laurent Marquet, Hôpital Hôtel-Dieu, Le Creusot; Jacques Marie Dit Dinard, Centre Hospitalier de Centre Bretagne, Pontivy; Philippe Masson, Centre Hospitalier Henri Duffaut, Avignon; Gérard Menaud, Clinique du Fief du Grimoire, Poitiers; Stephan Menu-Guillemain, Centre Hospitalier Général, Chalons en Champagne; René Mettey, Centre Hospitalier Intercommunal Fréjus Saint-Raphaël; Marc Meunier, Centre Hospitalier Intercommunal du Pays des Hautes Falaises, Fecamp; Daniel Miguët, Centre Hospitalier Privé de la Loire, Saint-Etienne; Véronique Millet et Umberto Simeoni, Hôpital de la Conception, Marseille; Delphine Mitanchez, Hôpital Necker Enfants Malades, Paris; Pascale Monfort et Blaise Mpeti, Maternité Sainte Croix, Metz; Chrystelle Morice, Centre Hospitalier de Laval; Nadine Moulie, Centre Hospitalier de Bigorre, Tarbes; Stéphanie Muller, Centre Hospitalier de Rambouillet; Philippe Mussat, Hôpital Privé de la Seine Saint Denis, Le Blanc Mesnil; Claire Nicaise, CHU Nord, Marseille; Charles Obegi, Polyclinique Pasteur, Saint Priest; Mourad Ouchtati, CHU de Pointe à Pitre; Laurence Pailhé, Centre Hospitalier d'Albi; Micheline Papouin Rauzy et Françoise Pawlotsky, Centre Hospitalier de Papeete, Tahiti; Juliana Patkaï, Hôpital de Port Royal, Paris; Hélène Pecheur, Centre Hospitalier Sainte Catherine, Saverne; Jean-Charles Picaud, Hôpital Arnaud de Villeneuve, Montpellier; Gilles Pierre, Hôpitaux Drôme Nord, Romans sur Isère; Marie-Laure Pignol, Centre Hospitalier de Mont de Marsan; Olivier Pincemaille, Centre Hospitalier Général de Bastia; Didier Pinquier, Centre Hospitalier de Rouen; Laurent Pradeaux, Centre Hospitalier de Périgueux; Emmanuelle Provot, Clinique Sainte Anne, Strasbourg; Jean-René Puech, Centre Hospitalier de Paray Le Monial; Guy Putet, Hôpital de la Croix Rousse, Lyon; Sylvie Racoussot, Centre Hospitalier de Douai; Thameur Rakza, Hôpital Jeanne de Flandres, Lille; Hasinirina Razafimahefa, Hôpital Antoine Béchère,

Clamart; Philippe Rebaud, Centre Hospitalier de Villefranche sur Saône; Sylvain Renolleau, Hôpital Armand Trousseau, Paris; Yves Rimet, Centre Hospitalier du Pays d'Aix, Aix en Provence; Marie-Françoise Rivière, Centre Hospitalier Jacques Cœur, Bourges; Pierre-Yves Robillard, Groupe Hospitalier Sud-Réunion, Saint-Pierre, La Réunion; Jean-Claude Ropert, Hôpital de Courbevoie-Neuilly sur Seine; Sylvaine Rousseau, Centre Hospitalier de Roubaix; Jean Rudler, Centre Hospitalier de Châteauroux; Deo Rugemintwaza, Clinique du Tertre Rouge, Le Mans; Brigitte Santerne, Hôpital Alix de Champagne, Reims; Paul Sanyas, Centre Hospitalier de La Rochelle; Pascal Saunier, Hôpital de Fontainebleau; Hervé Seau, Centre Hospitalier Général de Longjumeau; Denis Semama, CHU de Dijon; David Somerville, Polyclinique de Keraudren, Brest; Jean-Louis Soulier, Centre Hospitalier de Tulle; Christian Spitz, Maternité Sainte Félicité, Paris; Abdelilah Taïma, Centre Hospitalier de Roanne; Agnès Tamboura, Centre Hospitalier de Maubeuge; Régis Tessier, Centre Hospitalier Henri Mondor, Aurillac; Hervé Testard, Centre Hospitalier Intercommunal Annemasse Bonneville, Ambilly; Bernard Theret, Centre Hospitalier d'Arras; Pierre Thevenot, Hôpital Saint-Jean, Perpignan; Gérard Thiriez, CHU Saint-Jacques, Besançon; Frédéric Tronc, Centre Hospitalier Antoine Gayraud, Carcassonne; Jean-Marc Vaillant, Centre Hospitalier Robert Bisson, Lisieux; Catherine Vermeulin, Centre Hospitalier Général, Etampes; Marie Walther, Centre Hospitalier de Chambéry.

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