

Anaphylaxis admissions to pediatric intensive care units in France

To the Editor,

Hospitalizations for anaphylaxis have been increasing steadily in many countries, whereas the anaphylaxis mortality rate has remained low and stable over the past 20 years.¹⁻³ A small proportion of patients experiencing anaphylactic reactions are hospitalized in an intensive care unit (ICU). In the United States, this proportion was 5% of the patients seen in the emergency department for anaphylaxis.⁴ In the United Kingdom, 81 pediatric anaphylaxis cases were collected between 2005 and 2009, with a steady year-on-year increase.⁵ Data from the anaphylaxis registry show that a higher age and concomitant mastocytosis are the most important predictors for an increased risk of severe anaphylaxis.⁶ We currently lack accurate epidemiological data about children hospitalized for anaphylaxis in a pediatric ICU (PICU). The main objectives of our study were thus to determine the incidence of anaphylaxis cases requiring hospitalization in a PICU in mainland France and to assess the characteristics of these patients.

This retrospective study included all children (<18 years) hospitalized for anaphylaxis (2003-2013) in one of the 32 French PICUs. Patients were selected by querying the database of each medical center with a PICU, with the International Classification of Diseases-10 (ICD-10) anaphylaxis codes as previously described.¹⁻³ All children admitted to a PICU with one of the anaphylaxis codes as a primary or associated diagnosis were included. The medical records for each case were then reviewed by the same two physicians for the whole study to confirm or reject the anaphylaxis diagnosis using the currently accepted consensus criteria for anaphylaxis. Patients with an ICD-10 code for anaphylaxis but medical records that were not indicative of anaphylaxis were excluded. The incidence of anaphylaxis cases requiring hospitalization in a PICU was calculated from data about the pediatric population in France collected in the French National Institute for Statistics and Economic Studies database (www.insee.fr) and was expressed per million children/year. The proportion of children admitted in a PICU for a severe anaphylaxis event was calculated using the total number of PICU admissions per year collected by each center's medical information department and expressed per 100 children/year. The methods and statistical analysis are described (Data S1). The study was approved by the French National Commission for Data Protection (DR-2016-170) and the Advisory Committee on Information Processing in the Field of Health (N°15.493).

From 2003 to 2013, 140 707 children were hospitalized in the 32 French PICUs. In all, 962 admissions were possibly related to

anaphylaxis. Finally, after reviewing of the medical records, 166 (17%, mean number per unit: 5.2 [range: 0-22]) of these patients (90 boys, 54%) had a convincing history of anaphylaxis using the currently accepted consensus criteria for anaphylaxis and were included. The mean ($\pm$ SD) age was 7.9 ± 5.5 years. The incidence was 1.09 (95% CI: 0.93-1.26) per million children/year with the number of cases varying from 2 (2004) to 22 (2008) (mean increase: 11%/year; 95% CI: 5-16; $P < 10^{-4}$; Figure 1). The incidence was the same in boys and girls ($P = .43$). The proportion of children hospitalized for anaphylaxis of all those treated in a PICU was 0.12 (95% CI: 0.10-0.13) per 100 children/year (mean increase: 7%/year; 95% CI: 2-12; $P = .01$) ranging from 0.02 (2004) to 0.18 (2009).

Drugs ($n = 83$, 50%: mainly antibiotics, $n = 23$, 28%), foods ($n = 62$, 37%: mainly cow's milk, $n = 19$, 30%; peanut, $n = 17$, 27%; and nuts, $n = 10$, 16%), hymenoptera venom ($n = 4$, 2%), and latex ($n = 3$, 2%) were the reported triggers. The detailed triggers for drug- and food-related anaphylaxis are shown in Tables S1 and S2. The trigger was not determined for 12 cases. The main characteristics of the patients and the allergic reactions are summarized in Table 1. The 3 deaths recorded were all due to food allergens and occurred during hospitalization (survival rate: 98%): one 11-year-old boy with a peanut allergy died of ventricular tachycardia and fibrillation after receiving intravenous adrenaline injection for an anaphylaxis reaction following an oral peanut challenge in a hospital setting; a 13-year-old girl with a peanut allergy died at home despite late injection of adrenaline; and a 14-year-old boy with a history of asthma and peanut allergy died in a restaurant, despite an early injection of adrenaline (seafood allergy was strongly suspected).

The present study is the first to describe PICU admissions for anaphylaxis based on cases selected by ICD-10 codes and validated by physicians.

We report a low but increasing incidence of anaphylaxis cases requiring hospitalization similarly to reports of many countries. However, the anaphylaxis mortality rate has decreased in France and remained stable in the United States and the United Kingdom.¹⁻³ The difference in the number of cases recorded between 2003 and 2004 and 2005 may be explained by delayed application of the ICD-10 classification which was implemented in France in 2000. We describe a rate of anaphylaxis PICU admissions of 0.1% and a survival rate of 98%. Similarly, in the United Kingdom (2005-2009), the anaphylaxis PICU hospitalization rate

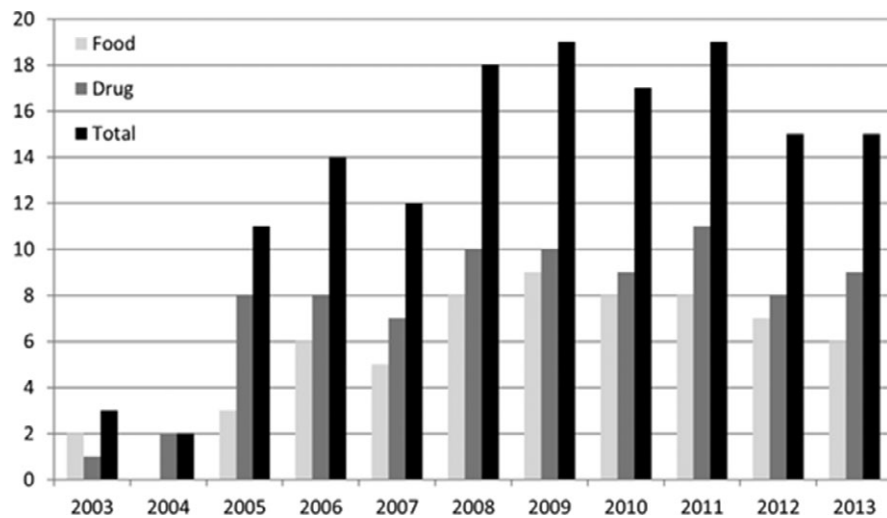


FIGURE 1 Number of children hospitalized for anaphylaxis in the French intensive care units (2003-2013) by trigger (drug or food)

TABLE 1 Main characteristics of children hospitalized in the French intensive care units for anaphylaxis (2003-2013) and comparison with regard to the trigger (drug or food)

	Total N = 166 (%)	Drug N = 83 (%)	Food N = 62 (%)
Sex			
Male	90 (54)	39 (47)	38 (61)
History of atopy or allergy			
Atopy ^a	91 (55)	29 (35)	54 (87)
Asthma	55 (33)	15 (18)	36 (58)
Allergic rhinitis	13 (8)	4 (5)	9 (15)
Atopic dermatitis	14 (8)	2 (2)	11 (18)
Respiratory allergy ^b	28 (17)	6 (7)	18 (29)
Food allergy	33 (20)	4 (5)	47 (76)
Place of occurrence			
Hospital	108 (65)	77 (93)	23 (37)
Home	38 (23)	2 (2)	27 (44)
School/nursery	7 (4)	2 (2)	1 (2)
Hospital setting			
Operating room	45 (27)	39 (47)	0
Oral challenge	19 (11)	0	19 (31)
Organ system involvement			
Cutaneous	131 (79)	60 (72)	56 (90)
Cardiovascular	133 (80)	75 (90)	42 (68)
Cardiorespiratory arrest	13 (8)	9 (11)	4 (6)
Gastrointestinal	46 (28)	10 (12)	33 (53)
Respiratory	101 (61)	43 (52)	45 (73)
Neurological	51 (31)	18 (22)	24 (39)
Severity (according to the Ring and Messmer classification)			
Grade 2	38 (23)	15 (18)	17 (27)
Grade 3	112 (67)	58 (70)	40 (65)
Grade 4	13 (8)	8 (10)	4 (6)

^aAtopy defined as a personal history of either atopic dermatitis, food allergy, allergic asthma, or allergic rhinitis.

^bRespiratory allergy defined as a personal history of either allergic rhinitis or allergic asthma.

was 0.1% of all children admitted in a PICU and the survival rate 95%.⁵

Our data confirm that drugs play an important role (50%) in the most severe anaphylactic reactions in children even if the 3 fatal cases we describe here were not drug-related. Food-related severe anaphylaxis reactions occurred in 37% of cases. This distribution differs from that described in pediatric studies conducted in emergency departments or from registries.⁷ In the pediatric European anaphylaxis registry, food was the predominant cause (66%), ahead of hymenoptera venom (19%), and drugs were identified in only 5% of reactions.⁷ These data, based on voluntary declarations and not reflecting all the anaphylactic reactions, provide complementary information from a different angle. In the United Kingdom (1992-2012), food was also the leading cause of anaphylaxis hospitalization and fatalities in children.¹ In contrast, in the United States and France, drugs were the main cause of anaphylaxis deaths.^{2,3} In the present study, antibiotics were the leading elicitor (28%) of drug-related anaphylactic reactions as reported for fatalities in the United States.² In contrast, analgesics were the most frequently involved drugs (41%) in the pediatric European anaphylaxis registry.⁷ The present study highlights that nearly all the drug-related anaphylactic reactions (93%) occurred in a hospital setting and around half of them in the operating room. The 3 fatal anaphylaxis cases recorded in our study were food-related. No drug-related fatalities were recorded. All 3 children had received adrenaline injection before cardiorespiratory arrest, but the injection was late in one case and given intravenously in another case leading to fatal cardiac dysrhythmia.

The main food allergens involved in our study (cow's milk, peanut, and nuts) were those reported in pediatric emergency departments or registries analyzing severe to fatal anaphylaxis cases.^{1,8,9} Surprisingly, a third of food-related reactions occurred in hospital during food oral challenges.

Finally, we determined two distinct patient profiles: a "drug anaphylaxis profile" (cardiovascular manifestations occurring in hospital with a low frequency of history of atopy) and a "food anaphylaxis profile" (high frequency of history of atopy and asthma, multiple organ system involvement, reactions occurring mainly at home or during oral food challenges).

A limitation of studies examining anaphylaxis epidemiology is linked to the ICD coding system, and epidemiological data based purely on the ICD anaphylaxis codes should be interpreted with caution. An important strength of our study is that all medical records were cross-checked to confirm the anaphylaxis diagnosis. Finally, only 17% of the patient files selected by the ICD-10 anaphylaxis codes actually corresponded to anaphylaxis.

Our data reinforce the fact that drugs play a major role in severe allergic reactions in children and that reactions occur mainly in hospital and in the operating room. Physicians should be alerted to the high risk of allergic reaction during an oral food challenge. Although severe anaphylaxis appears to be infrequent, efforts to identify factors related to these reactions are needed to guide future approaches in management and prevention. Improvements in the reporting of anaphylaxis cases along with appropriate coding using

the ICD-11 and its adoption in registries are crucial for an accurate epidemiological data analysis.

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CONFLICT OF INTEREST

GP and SL have been supported by Stallergènes Laboratory for this study. The remaining authors declare that they have no relevant conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Serum lipid levels are associated with allergic rhinitis, nasal symptoms, peripheral olfactory function, and nasal airway patency in children

To the Editor

Extensive studies support the presence of links between dyslipidemia and allergic diseases, and there has been with particular emphasis on allergen sensitization,¹⁻³ asthma,^{2,4} and atopic dermatitis (AD). Although evidence supporting a link of allergic rhinitis (AR) with dyslipidemia is limited and controversial,^{2,3} many researchers have focused on the relationship of obesity and rhinitis, rather than blood lipids.⁵

This study determined the association of different blood lipids with current rhinitis and rhinitis-related parameters, including nasal symptoms, peripheral olfactory function, and nasal volume. Therefore, we investigated the relationship of different components of the blood lipid profile with AR and rhinitis-related parameters in fifth-

APPENDIX 1

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and sixth-grade students enrolled in the Seongnam Atopy Project 2017 (SAP₂₀₁₇) cohort.

This prospective, general population-based, cross-sectional study examined children from 11 randomly selected elementary schools in Seongnam City (Korea) between January 2017 and October 2017. We investigated 620 fifth- and sixth-grade elementary school students (10-12 years old) who participated in the SAP₂₀₁₇ cohort, sponsored by the Seongnam City Government. The study protocol was approved by the appropriate Institutional Review Board of CHA University (2017-04-049), and written informed consent documents were obtained from all parents or guardians of children who participated.

We reviewed the questionnaires to identify demographic factors and investigate prevalence of allergic diseases. The presence of current allergic disease (asthma and rhinitis) was diagnosed using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, based on symptoms in the previous 12 months.⁶ Children who had rhinitis and allergen sensitization to a serum allergen-

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; B, beta coefficients; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein; IgE, immunoglobulin E; IL, interleukin; ISAAC, International Study of Asthma and Allergies in Childhood; LDL-C, low-density lipoprotein; NAR, nonallergic rhinitis; OR, odds ratio; SAP₂₀₁₇, Seongnam Atopy Project 2017; T4SS, Total Four Symptom Score; TG, triglycerides.

1 Table E1. Drugs involved in the 83 anaphylaxis cases in children admitted to a French intensive
2 care unit (2003-2013).

Drug	N (%)
Antibiotics	23 (28)
Cephalosporin	13 (16)
Aminopenicillin	5 (6)
Glycopeptid	4 (5)
Sulfamid	1 (1)
Radiocontrast agents	7 (8)
Intravenous immunoglobulins	6 (7)
Chemotherapeutics	6 (7)
L-Asparaginase	3 (4)
Etoposide-VP16	2 (2)
Cytarabine	1 (1)
Antipyretics	6 (7)
Nonsteroidal anti-inflammatory drugs	5 (6)
Paracetamol	1 (1)
Neuromuscular blocking agents	4 (5)
Blood products	4 (5)
Platelet transfusion	2 (2)
Fresh frozen plasma, anti-thymocyte globulins	1 (1) for each
Miscellaneous	11 (13)
Iron	2 (2)
Povidone-iodine, povidocanol, hydroxyethyl starch, heparin, interleukin-2, protamine, ethoxysclerol, racecadotril and basiliximab (n=1 for each).	1 (1) for each
Undetermined*	16 (19)

3
4 *Eighty-nine percent of these “undetermined” reactions occurred in the operating room
5 with a combination of drugs including: opioids (n=14), neuromuscular blocking agents
6 (n=14), hypnotics (n=8), and antibiotics (n=3).

7 Supplemental materials

8 Table E2. Foods involved in the 62 food-related anaphylaxis cases in children admitted to a French

9 intensive care unit (2003-2013).

Food allergen	N (%)
Cow's milk	19 (31)
Peanut	17 (27)
Nuts	10 (16)
cashew	7 (12)
walnut	2 (3)
pistachio	1 (1)
Hen's egg	3 (5)
Goat/sheep's milk	2 (3)
Fish	2 (3)
Multiple food allergen	2 (3)
Other food	4 (7)
wheat, potato, apple and amino acid formula	1 (1) for each
Undetermined	3 (5)

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13 Supplemental materials Data S1

14

15 **METHODS**

16 **Design and participants**

17 Patients were selected by querying the database of the medical centers in France for codes

18 corresponding to anaphylaxis according to the International Classification of Diseases, 10th

19 Revision, (ICD-10) recorded during the study period. These ICD-10 codes have been used in other

20 studies of the same topic (ref): R578 ("other shocks") combined with T639 ("toxic effects of contact

21 with a poisonous animal"), R579 ("unaccounted shock") combined with T639 ("toxic effects of

22 contact with poisonous animals"), T780 ("anaphylactic shock due to food intolerance"), T782

23 ("unspecified anaphylactic shock"), T784 ("unspecified allergy"), T805 ("anaphylactic shock due to

24 serum"), T886 ("anaphylactic shock due to adverse effects of an appropriate drug substance and

25 properly administered"), T88.2 ("anesthetic shock"), and J393 ("anaphylactic reaction of the upper

26 airways").

27 All children admitted to a PICU with one of these ICD-10 codes as a primary or associated

28 diagnosis were included. The medical records for each case were reviewed by two physicians (FG

and CT) to confirm or reject the anaphylaxis diagnosis using the currently accepted consensus criteria for anaphylaxis. Patients with an ICD-10 code for anaphylaxis but medical records that were not indicative of anaphylaxis were excluded. The following data were collected anonymously by a single questionnaire: age, sex, medical history of allergy or asthma confirmed, the place in which the reaction occurred, the clinical symptoms at the place at which the reaction occurred and the first medical responder, and the severity of the reaction (according to the Ring and Messmer classification, grades 1 to 4). Five groups were defined according to the triggers of anaphylaxis: food, drug, insect venom, latex, and unspecified.

Statistics

Characteristics of anaphylaxis cases were described using mean and standard deviation (SD) for the continuous variable (age) and proportion for categorical variables. The incidence of anaphylaxis cases requiring hospitalization in a PICU was expressed per million children/year and was calculated from data about the pediatric population in France collected in the French National Institute for Statistics and Economic Studies database (www.insee.fr). Data were extracted by region, year, sex, and age. The admission rate of anaphylaxis cases was expressed per 1000 children/year and was calculated using the total number of PICU admissions per year collected by each center's medical information department. We used a log-linear Poisson regression model to estimate the mean relative increase in incidence rates by year, with number of anaphylaxis cases as a dependent variable, calendar year as a continuous independent variable, and population reference (log-transformed data of French pediatric population or total number of PICU admissions) as an offset variable. The log-linear Poisson regression model was also used to compare the incidence of anaphylaxis between boys and girls adjusted for the calendar year. Statistical testing was performed at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.3 (SAS Institute, Cary, NC).