

HOSPITALIZATIONS FOR PEDIATRIC ANAPHYLAXIS

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The aim of the study is to examine the epidemiology of anaphylaxis in hospitalized children in Lazio (Central Italy) and to evaluate the incidence and case fatality rate. We also verified the concordance of diagnosis between the Emergency Department and Ordinary Hospitalizations. In order to obtain these results, we reviewed all ICD-9 codes indicative of anaphylaxis in all primary and secondary diagnoses from 2000 to 2003 in all Emergency Departments, Ordinary Hospitalizations and Day Hospitals in Lazio. We then identified 203 ICD-9 diagnoses of anaphylaxis in children aged between 0 and 17 years. Anaphylactic shock (995.0) accounted for 109 (53.7%) of cases. Food anaphylaxis (995.60 onwards) accounted for 87 (43.0%) of cases. Food anaphylaxis was more frequent in the first years of life. In fact, it decreased from 12.5/100,000 resident children/year in the first year of life to 6.1/100,000 resident children/year in the first two years of life, and less than 3/100,000 resident children/year after the seventh year ($p < 0.001$). Only 12.5% of cases of anaphylaxis diagnosed in Ordinary Hospitalizations were subsequently diagnosed by the Emergency Department as anaphylaxis. Moreover, only 42.3% of the diagnoses of anaphylaxis made in the Emergency Department were later confirmed during Ordinary Hospitalization. In the four years of study, one child died from anaphylaxis. Thus, mortality was 0.038 cases/100,000 resident children/year. In conclusion, the incidence of hospitalization was highest in the first years of life, during which food anaphylaxis accounted for most hospitalizations. The inconsistency of diagnoses between Emergency Departments and Ordinary Hospitalizations suggests the need to increase awareness of anaphylaxis among health workers.

Anaphylaxis is a severe, sometimes life-threatening reaction that can involve the skin, respiratory, cardiovascular and gastrointestinal systems. Although anaphylaxis is the most dangerous allergic disease, it is often under-recognized (1). Data on anaphylaxis epidemiology and number of deaths in children are scarce and are mostly calculated from hospital-based admissions (2-3), emergency department admissions (4), allergy practice (5) or

pediatric practice (6). Only two population-based studies have reported data of anaphylaxis in children, one in the USA (7) and one in Australia (8).

The aim of this study is to describe the epidemiology of anaphylaxis in a hospitalized pediatric population in the Lazio region, and to evaluate the incidence and the case fatality rate. We also recorded the causes of anaphylaxis, the age and sex of the cases, and the percentage of episodes based

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on admission to the emergency department (ED) or day hospital (DH), or ordinary hospitalizations (OH), namely hospitalization overnight. We also verified concordance of diagnosis between the ED and OH.

MATERIALS AND METHODS

Study population

We accessed the two databases managed by the Lazio Region Public Health Agency to determine the incidence of anaphylaxis in Lazio for the last four years available (from 2000 to 2003). The systems are: the *Sistema Informativo Ospedaliero* (SIO) (Hospital Information System) and the *Sistema Informativo Emergenza Sanitaria* (SIES) (Emergency Health Information System). The former contains OH and DH admissions, and the latter ED admissions. Both databases contain data from all (n. 182) hospitals and ED (n. 60) in the Lazio region. They contain some information about the patient, date of admission, date of discharge, type of hospitalization (DH or OH) and ED admissions and diagnosis. We examined the data of children aged between 0 and 17 years who had at least one diagnosis of anaphylaxis.

Identification of cases and data analysis

Anaphylaxis was classified according to the International Classification of Disease 9th revision – Clinical Modification (ICD9-CM) discharge diagnostic codes indicative of anaphylaxis: 995.0 (anaphylactic shock or reaction), 995.4 (anaphylactic shock caused by anesthesia), 995.60 (anaphylactic shock caused by unspecified food), 995.61 (anaphylactic shock caused by peanuts), 995.62 (anaphylactic shock caused by shellfish), 995.63 (anaphylactic shock caused by fruits and vegetables), 995.64 (anaphylactic shock caused by walnuts, hazelnuts and seeds), 995.65 (anaphylactic shock caused by fish), 995.66 (anaphylactic shock caused by nutritious additives), 995.67 (anaphylactic shock caused by milk derivatives), 995.68 (anaphylactic shock caused by eggs), 995.69 (anaphylactic shock caused by other specified foods), 999.4 (anaphylactic shock caused by serum).

We first checked whether patients with a diagnosis of anaphylaxis recorded in the SIO were also recorded in the SIES database. The aims were: 1) to determine if each admission to DH or OH was preceded by an ED admission; and 2) to verify the concordance of the diagnostic code assigned in the two archives. A single episode was considered if, within six months, a child was (a) admitted to DH for anaphylaxis twice; (b) admitted to the ED and subsequently to DH; (c) admitted to OH and

subsequently to DH. If a single episode was recorded in the ED and in OH or DH, it was assigned to OH or DH.

We then checked whether children with ED admissions (SIES) were also recorded in the SIO database to determine how many children were subsequently admitted to DH and OH. We also evaluated whether the diagnosis of anaphylaxis was confirmed in the OH or DH. The children whose diagnosis was not confirmed were excluded from the study, the rationale being that discharge diagnoses from OH or DH were probably more accurate. Finally, we determined the mortality rate for anaphylaxis in the four years of the study in the SIO and SIES archives.

In this context, we also accessed the Mortality Information System (SIM) of the Public Health Agency, which records all deaths in the Lazio Region, including those that occurred outside of hospital. The codes used were: 995.0 (anaphylactic shock or reaction), 995.2 (unspecified adverse effects of drugs and biologic products), 995.3 (unspecified allergy), 708.0 (allergic hives), 999.4 (anaphylactic shock caused by serum), 995.4 (anaphylactic shock caused by anesthesia) and 989.5 (animal poison). We estimated the mortality incidence for the study period based on the population (age: 0-17 years) resident in the Lazio region.

Incidence rate calculations

The incidence rates here reported were calculated as the ratio between the number of the cases and the person time at risk. Person time at risk was estimated as the average children resident for two subsequent years as reported in the official Italian statistics web-site (<http://demo.istat.it>).

RESULTS

Fig. 1 shows a flow-chart of the cases of anaphylaxis identified in the SIO and SIES databases. Discharges from DH accounted for most cases (n. 106). No child discharged from DH had been in the ED, whereas all children discharged from OH had passed through the ED. Discharges from OH and the ED accounted for 80 and 42 diagnoses, respectively (Fig. 1). Of 218 ICD-9 diagnoses of anaphylaxis, 15 were excluded because the ED diagnosis was not confirmed in the OH. Thus, we had 203 ICD-9 diagnoses of anaphylaxis relative to 191 children: eight children had had two and one child had had three OH discharges for anaphylaxis, and one child had had two ED discharges.

As shown in Table I, more than half (58.6%) the

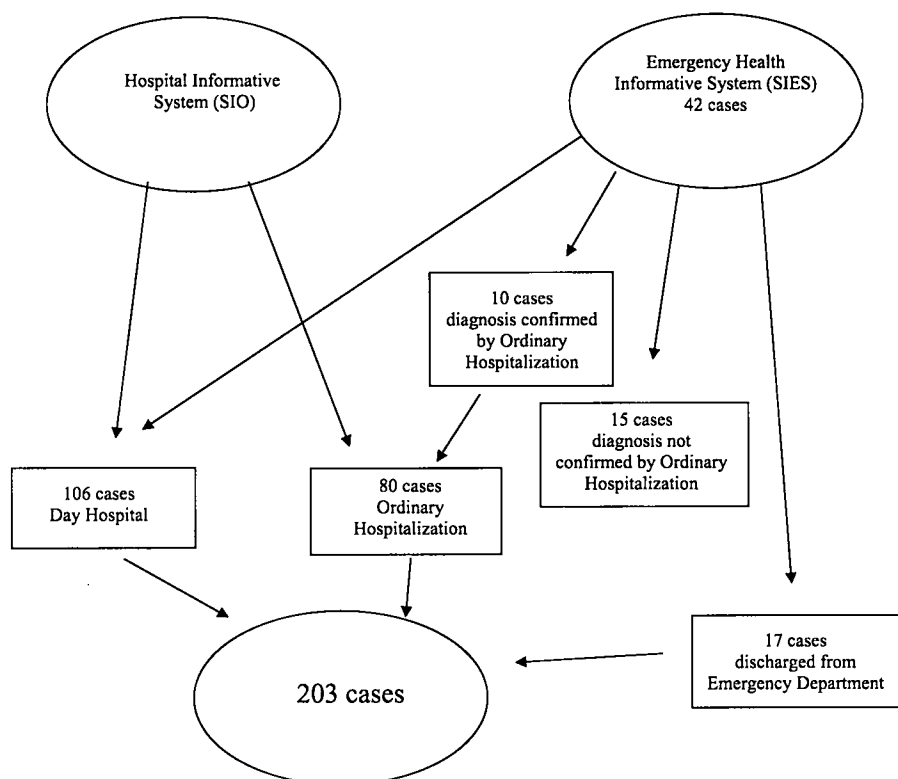


Fig. 1. Identification of cases (ICD-9 codes 995.0, 995.4, 995.60-9, 999.4) from the two databases. Lazio, 2000-2003.

children were boys. The average age of the overall population was 6.6 years. Children discharged from the ED were older than children discharged from OH ($p < 0.01$) or from the DH ($p < 0.01$) (the age range for OH, DH and ED groups was 0-17 years).

Anaphylactic shock (995.0) accounted for most diagnoses (n. 109), followed by anaphylaxis caused by food (n. 87). Anaphylactic shock caused by serum (999.4) (which may also include anaphylaxis due to administration of immunoglobulins) and by anesthesia (995.4) accounted for 3 and 4 cases, respectively. Milk (995.67) and egg (995.68) anaphylaxis were the two most common food-specific ICD-9 diagnoses, accounting respectively for 20 (23%) and 4 (4.6%) cases of food-induced anaphylaxis. In two cases, anaphylaxis was due to fish (995.65), and in two, to shellfish (995.62) and to walnut, hazelnut, or seeds (995.64), respectively. No cases of anaphylaxis due to peanut (995.61) or fruit and vegetables (995.63) were recorded.

Sixty-one ICD-9 diagnoses of anaphylaxis were recorded in 2000, 34 in 2001, 55 in 2002 and 53 in 2003. All ICD-9 codes of food anaphylaxis

increased (Chi square for trend: 84.2, $p < 0.001$) and anaphylactic shock (995.0) decreased (Chi square for trend: 13.95, $p < 0.001$).

The cumulative frequency of anaphylaxis episodes (SIO + SIES) was 203 during the entire study (2000-2003). As shown in Table II, the incidence in the period 2000-2003 of all anaphylaxis episodes during the four years was 5.9/100,000 resident children / year: 7.0 in 2000, 3.9 in 2001, 6.4 in 2002 and 6.1 in 2003. The incidence of anaphylactic shock (995.0) and for all food anaphylaxis was 3.1 3.2/100,000 and 2.5/100,000 resident children/year, respectively (Table II).

Anaphylactic shock (995.0) accounted for 53.7% (109) of all diagnoses, and seemed to be more frequent in older children: 3 cases < 1 year, 10 between 1 and 2 years, 29 between 3 and 6 years, 48 between 7 and 14 years, and 19 between 15 and 17 years. The incidence was 1.6 (95% CI 1-5)/100,000 resident children/year in the first year of life and increased to 2.7 (95% CI 1-5)/100,000 and 3.9 (95% CI 3-6)/100,000 resident children/year in the 1-2-year group and in the 3-6-year group, respectively

Table I. Type of hospital and emergency department admissions, and characteristics of patients with anaphylaxis aged from 0 to 17 years in the Lazio Region between 2000 and 2004.

Type of admission	SIO database		SIES database	
	Ordinary hospitalizations n. 80	Day-hospital n. 106	Emergency department n. 17	Total n. 203
	n. 79	n. 99	n. 16	n. 191 ^a
Age (years)				
Average	6.1	5	10.6	6.6
Median	6.3	6	14	6
Gender %				
Male	59.5	56.6	62.5	58.6
Female	40.5	43.4	37.5	41.4
Time of hospitalization (days)				
Average	3.7	3.6	-	-
Median	3	2	-	-

^aThe total does not coincide with the number of patients because some children had multiple admissions.

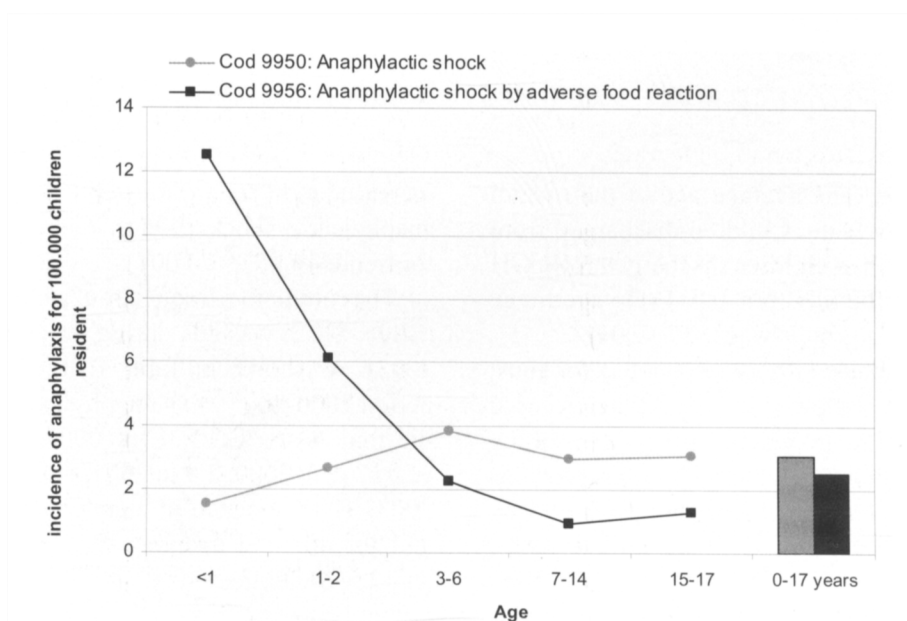


Fig. 2. Incidence of hospitalizations for anaphylaxis in children aged 0-17 years in the Lazio Region between the years 2000-2003.

($p = 0.65$, ns).

Food anaphylaxis hospitalizations were more frequent in the first years of life and decreased thereafter: 24 < 1 year, 23 between 1 and 2 years, 17 between 3 and 6 years, 15 between 7 and 14 years, and 8 between 15 and 17 years (Fig. 2). The incidence of all food anaphylaxis was 12.5

(95% CI 8-19)/100,000 resident children/year in the first year of life; it decreased to 6.1 (95% CI 4-9)/100,000 children in the first two years of life and was approximately 1/100,000 (95% CI 1-2)/100,000 resident children/year thereafter ($p < 0.001$).

We have checked the correspondence between the anaphylaxis diagnoses recorded in SIES (OH

Table II. Incidence rates of anaphylaxis per 100,000 residents 0-17 years in the Lazio Region between 2000-2003.

Codes	2000		2001		2002		2003		Total	
	n.	IR	n.	IR	n.	IR	n.	IR	n.	IR
995.0 (anaphylactic shock. or reaction)	48	5.3	22	2.4	22	2.6	17	2.0	109	3.2
995.6 (anaphylactic shock caused by adverse food reactions)	12	1.3	12	1.3	32	3.7	31	3.6	87	2.5
995.4 (anaphylaxis caused by anesthesia)	0	0.0	0	0.0	0	0.0	4	0.5	4	0.1
999.4 (anaphylaxis caused by serum)	1	0.1	0	0.0	1	0.1	1	0.1	3	0.1
Total	61	7.0	34	3.9	55	6.4	53	6.1	203	5.9
Middle Population resident in the Lazio Region	866,989		861,062		860,046		866,111		3,454,208	

IR: Incidence rate (cases/100,000 resident children 0-17 years)

and DH) and in SIO (ED). Only 42.3% (11/26) of the diagnoses made in the ED were subsequently confirmed in OH. We then searched for the main codes assigned in the ED to the 80 children discharged from OH with a diagnosis of anaphylaxis. Only 12.5% (10/80) were discharged from the ED with a diagnosis of anaphylaxis. The other 70 were assigned 43 different ICD-9 codes, the most frequent being unspecified allergy (code 995.3), followed by diagnostic codes related to diverse disorders: respiratory, mainly extrinsic asthma (code 493.0), gastrointestinal disorders such as persistent vomiting (code 536.2), skin disorders such as allergic urticaria (708.0), and neurologic impairment, such as shock without trauma (785.5). This suggests that only a minority of cases of anaphylaxis are correctly codified in the ED.

During the study, one child died of anaphylaxis. This was a 12-year-old girl who died in the year 2000 from anaphylactic shock caused by an adverse food reaction (ICD-9-CM 99560). Thus, the fatality rate due to anaphylaxis in the study period was 1/203 (0.49% episodes) and the mortality rate was 0.038 cases/100,000 resident children aged 0-17/year. Anaphylaxis accounted for 1/921 child deaths (excluding neonatal death).

DISCUSSION

Here we report the epidemiology of anaphylaxis in a hospitalized pediatric population of an entire geographic region in a four-year period. The analysis includes all the main codes of anaphylaxis and the

three main types of hospital admission (ED, OH, and DH). Data on the epidemiology of pediatric anaphylaxis in a definite population are scarce. Boros et al. (8) found that the rate of parent-reported anaphylaxis in 4,173 South Australian children aged 3-17 years was 0.59/100. In a population-based study using automated hospital, ED and outpatient clinic records, and the same ICD-9 codes we used, Bohlke and colleagues (7) reported an incidence of anaphylaxis of 10.5 cases/100,000 children/year. That rate is higher than our estimate, equal to 5.9 cases/100,000 resident children/year. However, both studies may have underestimated the prevalence of anaphylaxis in the population. In fact, up to one-third of children with anaphylaxis reported in a pediatric Italian study had not been treated in an ED or in a hospital (5). Accordingly, in our population most of the anaphylaxis codes appeared in DH records, where they may have been evaluated for a previous episode of out-of-hospital suspected anaphylaxis, without a previous ED or OH admission. Consequently, it appears that the great majority of cases of anaphylaxis occur outside of hospital.

We found a large discrepancy between the diagnoses made in the ED and OH: only 57.6% of the ED diagnoses were subsequently confirmed in OH and, on the contrary, only 12.5% of the diagnoses made in OH were formerly done in the ED. Anaphylaxis seemed to be more frequently mistaken for non-specific allergy (code 995.3) than for other disorders. Similarly, Klein and Yocum (9), in a retrospective analysis of the ED records of all patients' visits found

that only 23.5% (4/17) of cases was diagnosed by the ED physicians as anaphylaxis, whereas most of the others were diagnosed as having an "allergic reaction" (code 995.3). These findings support our assumption that the hospital discharge diagnostic coding is more accurate than coding in ED.

Bohlke et al. (7) found 222 codes of anaphylaxis, whereas a review of charts showed that only 67 (30.1%) had probable or possible anaphylaxis. However, when they looked at codes that were not specific for anaphylaxis (995.3, unspecific allergy, 995.1, angioneurotic edema etc.), they found that between 1.3% and 7.4% of cases were classified as anaphylaxis after chart review, thus increasing the estimated incidence rate from 10.5 to 68.4/100,000 persons/year. These findings could reflect scant knowledge of anaphylaxis.

Our study shows that food is the main cause of hospitalization for anaphylaxis in the first years of life, during which the impact seems to be ten times more frequent than in the following years. To the best of our knowledge, this is a novel finding, and could be attributed to the high incidence of food allergy in the first years of life, as well as to a tendency to admit younger children more often than older ones. This tendency is reflected in the higher average age of children discharged from ED without further hospitalizations.

In our study, milk and egg were the two most common diagnoses of food anaphylaxis. Reactions to peanut and other nuts and seeds were seldom diagnosed. This is in line with the finding that only one of 95 food anaphylaxis reactions diagnosed in 76 Italian children was caused by peanut (5). Differently, nuts and peanut account for the majority of food reactions in such other countries as the USA and Australia (7-8, 10).

We found that anaphylactic shock (995.0) was less frequent in the first years of life. This coincides with the findings of Sheick and Alves (11), who looked for the ICD-9 codes 995.0 (other anaphylactic shock) and 999.4 (anaphylactic shock by serum) among all admissions for anaphylaxis to the English National Health Service. They found that these codes were higher in the 15-64 age groups. They also found that admissions increased almost twofold over four years, going from 5.6 episodes/100,000 discharges in 1991-2 to 10.2 in 1994-5. The increase involved

all causes, but was particularly significant for food-related anaphylaxis, which accounted for 15% of admissions, was more frequent in the first years of life and became relatively less frequent in the higher age group (12). In our study, hospitalizations for all causes of anaphylaxis did not increase during a four-year period. Hospitalizations for food anaphylaxis increased; however it is unclear if this finding is due to a real increase of food allergy or whether it merely reflects a better diagnosis or better use of the ICD-9 codes, because of the decrease in hospitalizations for anaphylactic shock (code 995.0).

Our fatality rate of anaphylaxis episodes was 1/176 (0.56% children), which is similar to that reported by Yokum et al. (13) (1/154; 0.65%), and the incidence of fatal events in our children was almost twenty times greater than that reported by MacDougall et al. (0.038 vs. 0.006) (14). However, the widespread problem of misdiagnosis of anaphylaxis could have affected the mortality data (15). We advise caution in analyzing our data, since the diagnosis of anaphylaxis was based on ICD-9 codes; we did not review medical records. Moreover, children with anaphylaxis occurring in the community often recover spontaneously and might never be seen by a pediatrician or referred to the hospital. These aspects may have limited the accuracy of the estimated prevalence of anaphylaxis.

In summary, we report data of hospitalizations for anaphylaxis in a definite geographic area. We found that the incidence of hospitalizations was greatest in the first years of life, during which food anaphylaxis accounted for the vast majority of these hospitalizations. The discordance between diagnostic codes assigned by the ED and OR suggests that anaphylaxis may go unrecognized even in a hospital setting. Consequently, efforts should be made to improve awareness of anaphylaxis even for pediatricians who work in a hospital setting.

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