



Incidence, triggering factors, symptoms, and treatment of anaphylaxis in a pediatric hospital

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ABSTRACT

Objective: Assess the incidence of anaphylaxis in the emergency room (ER) of a private pediatric hospital in the city of São Paulo, Brazil, and describe associated factors.

Method: This was a cross-sectional, retrospective, and observational study based on the medical records of patients from 0 to 18 years old seen at the emergency unit during the years of 2016–2019, who had a diagnosis potentially related to anaphylaxis according to ICD-10. All medical records were individually reviewed for the presence of compatible signs and symptoms that identified “possible” cases of anaphylaxis. Cases were considered probable anaphylaxis when medical history was compatible and indicative of anaphylaxis in the opinion of at least 2 allergists.

Results: The incidence of anaphylaxis was 0.013%. Among the 56 patients identified (mean age 4.2 years), food was the most predominant suspected factor (53%), followed by unknown factors (32%), and drugs (12.5%). All patients presented with cutaneous symptoms, 74% with respiratory, and 53% with gastrointestinal. Allergic disease as a comorbidity was found in 39% of the children and 11% had a history of previous anaphylaxis. There were neither cases of syncope or shock, nor deaths. Intramuscular (IM) adrenaline was prescribed in 37.5% of cases.

Conclusions: The incidence of anaphylaxis was low when compared to the worldwide incidence. The severity of most cases was mild, cutaneous symptoms were predominant, and food was the suspected trigger most frequently associated with reactions.

Keywords: Anaphylaxis, Children, Adrenaline, Incidence, Urticaria

INTRODUCTION

Anaphylaxis is a systemic, severe, and potentially fatal hypersensitivity reaction characterized by rapid onset.¹ Symptoms appear after exposure to an allergen or another trigger, with rapid progression in minutes to a few hours.² Anaphylaxis can lead to death due to asphyxia secondary to laryngeal or oropharyngeal edema, circulatory collapse due to hypotensive shock or cardiac arrest, or severe bronchospasm causing respiratory failure.³ Its sudden and heterogeneous

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clinical presentation hinders rapid recognition and treatment, increasing the risk of death.⁴

The incidence of anaphylaxis is relatively low, according to a recent systematic review, ranging from 1 to 761 per 100 000 person-years,⁵ and data indicate that anaphylaxis can relapse in 27%–54% of patients (follow-up from 1.5 to 25 years).⁶ In emergency care, anaphylaxis is diagnosed in about 0.04%–0.96% cases.⁷

Data on the incidence of anaphylaxis are scarce, especially in the pediatric population.⁸ In a recent systematic review, only 44 studies had reported the incidence of anaphylaxis in children up to 2018.⁵ Epidemiological research on anaphylaxis is difficult to carry out for several reasons. The incidence of the disease is relatively low and many physicians are still unaware of the diagnostic criteria and treatment.⁹ Anaphylaxis in infants may be especially difficult to recognize due to the lack of objective symptoms and uncertain history of allergen exposure.¹⁰ Furthermore, the current International Classification of Diseases (ICD-10) does not have a specific code for anaphylaxis, migrating the register of cases to related codes, such as urticaria, angioedema, or laryngeal edema.¹¹

Few studies have evaluated the causal agents and treatment of anaphylaxis involving Brazilian children. In 2012, the pediatric results of an online registry of anaphylaxis in Latin America were published, which compiled 191 cases, 45% from Brazil.¹² However, from our knowledge, there are

no data on the incidence of anaphylaxis among Brazilian children.

The objectives of this study were to assess the incidence of anaphylaxis in a private pediatric emergency room (ER) in the city of São Paulo, Brazil, and describe the triggering agents, symptoms, treatment, and other associated factors.

METHODS

In this cross-sectional, retrospective, and observational study, we selected the cases of children and adolescents of both sexes from 0 to 18 years of age attended in the ER of a private pediatric hospital, in São Paulo, Brazil, between January 2016 and December 2019. Cases were initially selected according to a list of ICD-10 diagnoses potentially related to anaphylaxis, including L50 (urticaria), T78 (anaphylactic shock, anaphylactic reaction due to food, other and unspecified allergies), X23 (contact with hornets, wasps, and bees) and others.¹¹ The list of ICD-10 diagnoses potentially related to anaphylaxis is shown in Appendix 1 of the supplementary material.

The electronic medical records of the selected cases were individually reviewed by an allergist to identify possible cases of anaphylaxis, defined by sudden onset of signs or symptoms in at least 2 systems (cutaneous, respiratory, or gastrointestinal) or shock/hypotension.¹³ Subsequently, the selected medical records were thoroughly reviewed by 3 allergists, evaluating the clinical

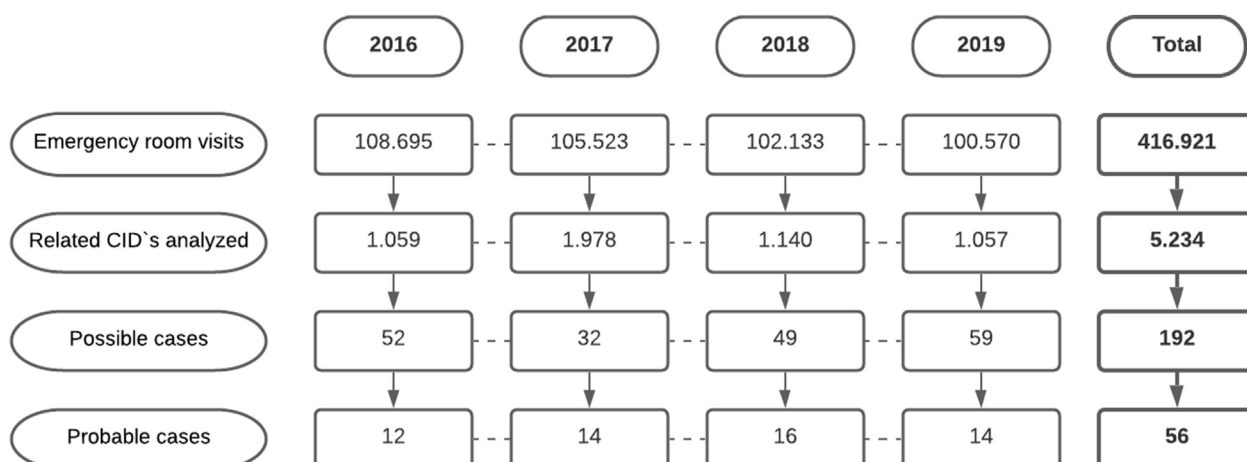


Fig. 1 Emergency room visits, related ICD's analyzed, possible cases and probable cases of anaphylaxis during the four years of the study.

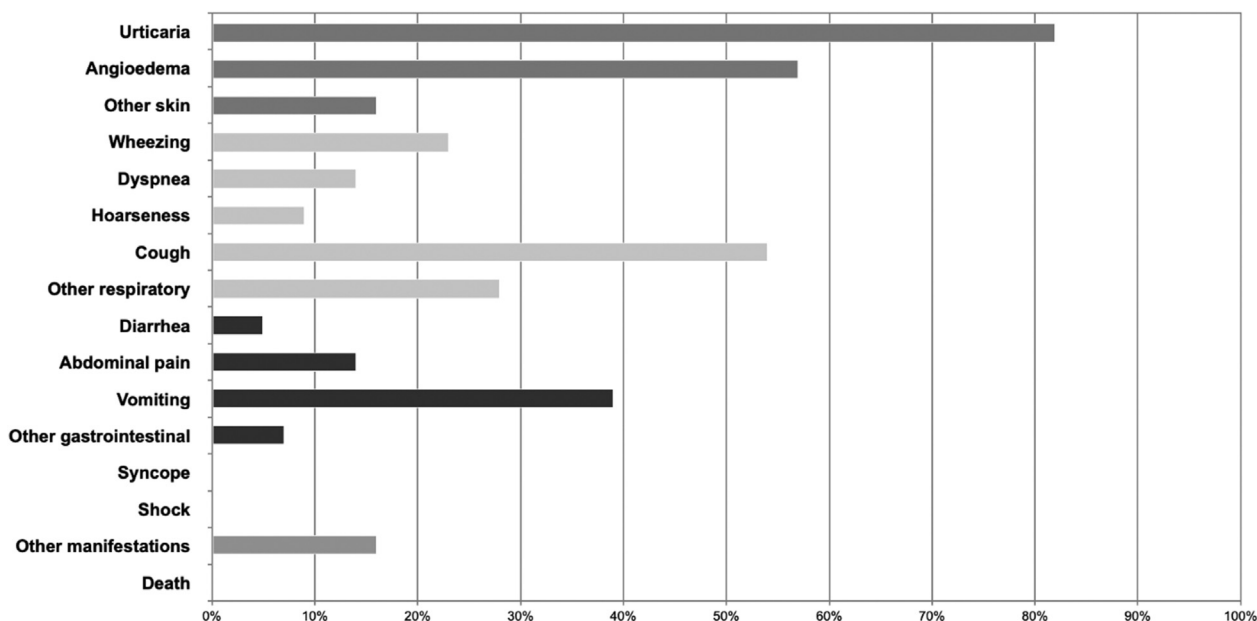


Fig. 2 Clinical manifestation of the 56 probable cases of anaphylaxis. Captions: Other cutaneous: erythema, pruritus, rash, itchy eye and vulval swelling. Other respiratory: runny nose, sneezing, nasal congestion, throat discomfort, choking, tachypnea, decreased pulmonary auscultation, prolonged expiratory time and labral cyanosis. Other gastrointestinal: nausea. Other manifestations: tingling sensation in the arm, sialorrhoea, conjunctival hyperemia, tearing, irritability, hypotonia and decreased general condition

manifestations, the evolution of the patients' condition, the diagnoses reported by the medical team, and the treatments used. Thus, those who had a compatible medical history, in the opinion of at least 2 specialists, were classified as probable cases of anaphylaxis.

The study was submitted to and approved by the local Research Ethics Committee (99260818.0.1001.5567), which waived signing the Free and Informed Consent Form.

RESULTS

The total number of ER visits in the years 2016, 2017, 2018, and 2019 was 108 695; 105 523; 102 133; and 100 570 respectively. The incidence of probable cases in those years was 0.011%, 0.013%, 0.016%, and 0.014%, respectively, and the four-year incidence average was 0.013%. Fig. 1 shows the total ER visits, the number of cases selected by ICD-10, possible and probable cases in each of the 4 years.

In total, 56 probable cases of anaphylaxis were identified, almost half (45%) were female. Mean age was 4.2 ± 3.6 years and 39% were infants (≤ 2 years of age). The ICD most associated with probable cases of anaphylaxis was urticaria (89%).

Cutaneous symptoms were observed in all probable cases, respiratory symptoms in 74% and gastrointestinal symptoms in 53%. Urticaria (82%), cough (54%), and vomiting (39%) were the most reported symptoms in each system. The symptoms/signs of the 56 probable cases are shown in Fig. 2. 16% of probable cases had $<94\%$ oxygen saturation, no cases of syncope, shock, or deaths were found.

Food was the predominant suspected trigger of anaphylaxis (53%), followed by unknown factors (32%) and drugs (12.5%). Nuts, milk, and banana were the most implicated foods. Non-steroidal anti-inflammatory drugs (NSAIDs) were the most related drugs (9% of the probable cases) and there was 1 case associated with amoxicillin plus clavulanate and another with vitamin C. The suspected triggers are shown in Fig. 3. No patient returned to the ER due to the relapse of symptoms after discharge. However, 1 patient was seen twice for probable anaphylaxis with an interval of 5 months, due to different food triggers.

Associated comorbidities were reported by 43% of cases of probable anaphylaxis, and allergic diseases (39%) were the most frequently reported. Any cofactor was registered in 23% of probable cases, with a predominance of fever (9%) and

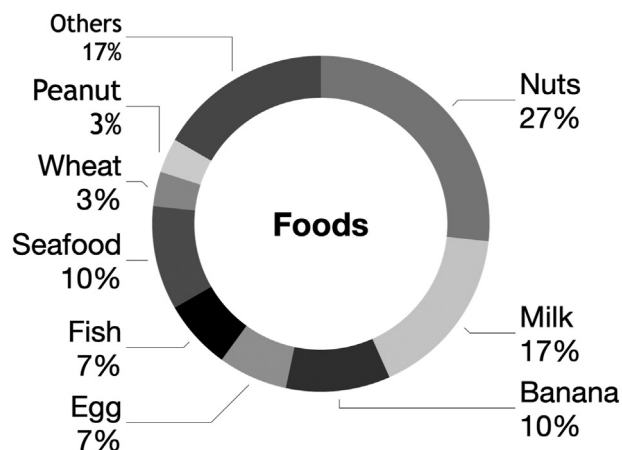


Fig. 3 Foods (N = 30) and drugs (N = 7) reported as triggering factors for anaphylaxis (N = 56). Captions: Other foods: corn, lentils, cake, tomato sauce. Nuts: chestnuts (Brazil Nut, Cashew Nut or unspecified), hazelnuts and walnuts

symptoms of upper respiratory infection (12.5%). Eleven percent (11%) of patients had a history of previous anaphylaxis.

Intramuscular (IM) adrenaline was prescribed in 37.5% of cases, antihistamines in 93%, and systemic corticosteroids in 91%. Almost one-third of the patients (27%) received bronchodilators, 11% oxygen supplementation, and 29% volume replacement. Of the total probable cases, 36% remained under hospital observation for at least 6 h, and 27% were admitted to the hospital. At the

time of hospital discharge, 34% of patients were referred to an allergy specialist and 7% received prescription of self-injected adrenaline. Treatment and outcomes for the 56 probable cases of anaphylaxis are shown in [Table 1](#).

Among all probable cases of anaphylaxis, 22 were infants and 34 were older. Clinical manifestation differed among those groups, with more gastrointestinal symptoms (specially vomiting) among infants and more respiratory symptoms (specially wheezing) among older children. Regarding triggers, drugs were more suspected in older children (0% vs 21%; $p = 0.03$) and foods were more suspected among infants (72.7% vs 41.2; $p = 0.02$). Milk, banana, and nuts were the most frequently reported foods in infants, while nuts and seafood were the most implicated foods in older children. Symptoms, triggers, and other characteristics of probable cases of anaphylaxis in infants and older children are shown in [Table 2](#).

DISCUSSION

According to our data, this is the first study to report the incidence of anaphylaxis in children seen at a pediatric ER in Brazil. Our data were obtained in a pediatric ER in São Paulo, the largest metropolitan region in the country, and we believe

Treatment	Probable cases (N = 56)	
	N	%
Intramuscular adrenaline	21	38
Antihistamine H1	52	93
Systemic corticosteroids	51	91
Short-acting beta2 agonists	15	27
Oxygen supplementation	6	11
Volume replacement	16	29
Antihistamine H2	22	39
Hospital observation for at least 6 h	20	36
Hospitalization	15	27
Referral to specialist	19	34
Prescription for self-injecting adrenaline	4	7

Table 1. Treatment and outcomes for the 56 probable cases of anaphylaxis

	Infants (N = 22)	Older children (N = 34)	p
Male (%)	45.5	58.8	0.58
Respiratory symptoms (%)	59.1	82.4	0.07
Wheezing (%)	9.1	32.4	0.04
Gastrointestinal symptoms (%)	77.3	38.2	0.004
Vomiting (%)	68.2	20.6	<0.001
Food as a trigger (%)	72.7	41.2	0.02
Drug as a trigger (%)	0	20.6	0.03
Unsuspected trigger (%)	13.6	35.3	0.16
Comorbidity (%)	22.7	44.1	0.25
Any cofactor (%)	9	29.4	0.13
History of previous anaphylaxis (%)	0	17.6	0.05
Use of IM adrenaline in the ER (%)	13.6	44.1	0.07
Hospitalization (%)	31.8	23.5	0.6

Table 2. Symptoms, triggers and other characteristics of anaphylaxis in infants and older children

that it encompassed a diverse population of children and teenagers. The hospital where the study was carried out almost exclusively attends patients covered by health insurance; therefore, the sample does not include children from the public health system.

There are few studies describing the incidence of anaphylaxis in pediatric ERs. The incidence of probable cases of anaphylaxis observed in our study was low (0.013%) when compared to the incidence described by Huang et al in New York City, United States (0.18%)¹⁴ and the one described by Alvarez-Perea et al in Madrid, Spain (0.12%).¹⁵ In a four-year interval, Ghazali et al found 239 cases of anaphylaxis among 260 800 adolescents and adults attended in an ER (incidence of 0.09%) in Tunis, Tunisia.¹⁶ The low incidence of anaphylaxis found in our study may be due to the characteristics of our sample, which did not include children from public health, to the tendency for anaphylaxis to be underrecognized based in part on cases that may recover spontaneously, and also to the lack of a validated diagnostic marker.¹⁷

The only identified Latin American study found that the incidence of children hospitalized for anaphylaxis in Chile varied between 0.6 and 1.0

cases per 100,000 people, depending on the age group.⁴ In a retrospective study of adults cared for in an emergency department in Australia, the incidence of presenting anaphylaxis was 1 in 439 emergency department patients during 1998-1999.¹⁸

Some of our findings are similar to the results of other comparable studies in pediatric population. Cutaneous symptoms were the most frequent and observed in all probable cases, with the predominance of urticaria.¹⁵ Our patients, in general, had mild episodes of anaphylaxis and none presented shock or died, nevertheless 27% of patients were hospitalized reinforcing that anaphylaxis should not be underestimated in children and rapid treatment with IM epinephrine is extremely important.² We did not observe any case of biphasic anaphylaxis, which is in agreement with the low incidence of biphasic reactions among children (around 6%).¹⁹

Food is described as the main triggering factor associated with childhood anaphylaxis, as seen in our study.^{2,19-21} Specifically, cow's milk and eggs are the most commonly reported triggers in several studies.^{2,20,21} In our study, we also found milk as an important trigger, but the main one was nuts (peanuts/chestnuts/hazelnuts), among

the whole group and also among infants. In particular, we highlight the high frequency of banana as a suspected triggering agent, 10% among foods, probably explained by the Brazilian food consumption pattern in which bananas are introduced early in children's diet.¹⁹ Allergic reactions to banana are considered uncommon, with a recent study showing prevalence rates of 0.04%–1.2% in the general population across the world.^{22,24} The frequency of reactions in tropical countries, like Brazil, may be higher, as bananas are also added to processed foods such as flavorings or cosmetic ingredients.²³

In second place among the suspected triggers are unknown factors (32%), which could be associated with the limitation of the study methodology, also demonstrated by other similar studies.¹⁴ Drugs were reported as triggers mainly by older children and NSAIDs (71%) were the most common implicated, similarly to that observed in the general population of Latin America.¹² It is important to point out that NSAIDs are over-the-counter medications in Brazil which could stimulate its overuse.²⁴ It is also worth reporting the absence of anaphylaxis associated with insect stings. It is important to point out that the anaphylaxis trigger identified after an allergology study may differ from those suspected in the emergency department.²⁵

The treatment profile of the identified cases of anaphylaxis was not ideal, as reported by other pediatric studies.^{12,26,27} Further educational measures and training are in need to change the prescription pattern of these patients: high frequency of antihistamine and systemic corticosteroids and sub-use of IM adrenaline. The predominance of cases with mild or moderate conditions found in our study may partially explain the low prescription rate of adrenaline. Adrenaline prescription in the ER has been described to be much less frequent when children have less severe anaphylaxis.²⁷

The diagnosis of anaphylaxis in infants might be challenging due to the wide range of clinical presentations and differential diagnoses.^{28,29} Although there are criteria for the diagnosis of anaphylaxis, specific criteria for infants have not been developed.³⁰ Infants cannot express their

symptoms and parents often have difficulties in recognizing them, especially cardiovascular.³¹ Although anaphylaxis can be under-diagnosed, it is reported with increasing frequency in infants.^{29,32} Furthermore, behavioral changes such as irritability and inconsolable crying, as well as somnolence and flushing, can be undervalued by parents and may also be confused with normal infant behavior.³³ Data concerning epidemiology, clinical manifestations, and treatment of anaphylaxis in infants and toddlers are even more scarce than in older children.^{29,32} As observed for children in general, food is also the most common trigger for anaphylaxis in infancy, with the predominance of cow milk and eggs as culprits.^{12,15,20,31,34–36} Among the infants in our study, food was the main suspected trigger (72.7%), but the main associated foods were milk and nuts (peanuts/chestnuts/hazelnuts), as observed by others.^{33,37,38} The spectrum of food allergies varies according to geography, lifestyle, and dietary habits.³³ The initial presentation of anaphylaxis in infants typically involves organ systems in the following order of frequency: mucocutaneous, the respiratory system, and the gastrointestinal system.³⁸ Among our infants, 59.1% had respiratory symptoms and 77.3% had gastrointestinal symptoms. Vomiting was the most frequently reported symptom among infants (68.2%) and it was significantly more common in infants than in older children ($p < 0.001$). This observation is in line with other studies that also reported higher presence of gastrointestinal symptoms among infants when compared to older children, especially vomiting.^{34,38} However, this could be explained by foods being the most frequent trigger in this age group.

In general, adrenaline is underutilized in the treatment of anaphylaxis, and it is more evident among infants.^{21,33} In this study 13.6% of infants received IM adrenaline in the ER, compared with 44.1% of older children. This difference may be caused by difficulty in identifying anaphylaxis in infants, fear of more intense adverse events, uncertainty about the real necessity of the medication or even because anaphylaxis tends to be less severe in infants.^{20,36,39} Despite the infrequent use of adrenaline, we found a higher (but not significant) rate of hospitalizations

among infants (31.8%) when compared to older children (23.5%).

The limitations of our study include its retrospective nature, the search of probable cases by ICD-10 that does not address the diagnosis of anaphylaxis adequately, and the lack of information in some medical records. Serum tryptase is a laboratory test which is not yet standardized in most emergency rooms in Brazil and it was not available to confirm our diagnosis of anaphylaxis.

In conclusion, in our study, the incidence of probable cases of anaphylaxis was low when compared to the worldwide incidence. The severity of most cases was mild, and no case of shock or death occurred. Cutaneous symptoms were predominant, mainly urticaria. Food was the suspected trigger most frequently associated with the reactions in infants and older children. Nuts were the most commonly reported food, and we also found a high incidence of banana as a suspected trigger. Intramuscular adrenaline is the first-line therapy for anaphylaxis, but it remains underutilized.

Abbreviations

ICD, International Classification of Diseases; ER, Emergency room; NSAIDs, Non-steroidal anti-inflammatory drugs; IM, Intramuscular.

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Availability of data and materials

Only with the authors.

Author's contribution

Fabiana Oliveira, Fábio Zanini, Camila Braga and Andreza da Silva: participated in data collection, tabulation and analysis of results and preparation of the manuscript. Fátima Fernandes and Dirceu Solé: participated in the design of the study, analysis of the results and the preparation of the manuscript. Gustavo Wandalsen: participated in the design of the study, data collection, analysis of results and preparation of the manuscript. All authors reviewed the final version of the article and approved the submission.

Ethical statement

The study was submitted to and approved by the local Research Ethics Committee (99260818.0.1001.5567), which waived signing the Free and Informed Consent Form.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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