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Anaphylaxis in pediatric patients: single-center study in a private hospital

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Abstract
This study aimed to characterize the profile of probable anaphylaxis cases treated at a private pediatric hospital emergency department in São Paulo. It investigated triggering factors, the presence of cofactors, treatments administered, and follow-up for these cases through interviews with the patients' families. A single-center cross-sectional study analyzed medical records of children and adolescents treated between 2016 and 2020. Allergist physicians evaluated cases with symptoms consistent with anaphylaxis to identify probable cases, and the parents or legal guardians of these cases were interviewed to gather detailed information about the episodes. A total of 69 probable cases of anaphylaxis (PCA) were identified among 460,434 visits. Of the 51 PCAs evaluated, most presented with cutaneous and respiratory symptoms, with a male predominance (63%), and 27% were under 2 years old. Foods, particularly nuts and peanuts, were the primary triggers. Nearly one-third of the patients did not undergo investigation following the episode, and intramuscular adrenaline (37%) and auto-injectable adrenaline (4%) were underutilized as treatments. Eight cases exhibited recurrence of symptoms after initial improvement, suggesting a potential biphasic reaction. In conclusion, this study revealed that the majority of PCAs occurred in male children, with nuts and peanuts as the main triggers. The management of PCAs was suboptimal, characterized by the underutilization of intramuscular adrenaline as the first-line treatment and low rates of auto-injectable adrenaline prescriptions during follow-up. Increasing awareness and education about anaphylaxis in children, along with emphasizing the importance of proper treatment, are crucial to reducing the risk of morbidity and mortality in this vulnerable population.

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Introduction

Anaphylaxis is a severe manifestation of systemic allergy and represents the most critical form of allergic reaction. It typically occurs suddenly after exposure to a trigger and can be fatal if not treated promptly.[1,2] The clinical manifestations of anaphylaxis are varied, including skin symptoms (e.g., hives, angioedema), respiratory issues (e.g., dyspnea, wheezing), gastrointestinal symptoms (e.g., vomiting, abdominal pain), and cardiovascular complications (e.g., hypotension, syncope).[1,3] This range of clinical presentations complicates the rapid recognition and treatment of anaphylaxis, increasing the risk of fatal outcomes.[4]

The incidence of anaphylaxis is low; however, the number of related visits to emergency rooms and hospitals has increased in recent years.[1,5] Research on anaphylaxis in children remains limited, especially within the Brazilian population.[6]

We recently published data on anaphylaxis cases from a private pediatric hospital in São Paulo.[7] In this study, the incidence of probable anaphylaxis cases among emergency room visits from 2016 to 2019 was 0.013%.[7] Medical records indicated that skin symptoms, particularly urticaria, were the most common, with food identified as the primary associated trigger.[7] Studies based on medical records, especially in emergency departments, may be subject to biases due to incomplete data and variability among attending physicians.[8] Validating and supplementing findings from medical records can improve our understanding of patient profiles, management strategies, and follow-up care for anaphylaxis cases.

The objectives of this study were to characterize the profile of probable anaphylaxis cases in a private pediatric emergency service in São Paulo (Hospital Infantil Sabará) and to analyze the triggering factors, the presence of cofactors, and the treatments administered. Additionally, the study aimed to assess the follow-up and investigation of these episodes through interviews with the families of the children.

Methods

This was a unicentric, cross-sectional study approved by the Research Ethics Committee (CEP) of the Fundação José Luiz Egydio Setúbal, under CAAE [Certificate of Presentation for Ethical Review] 44861721.9.0000.5567. All participants and/or their guardians provided written informed consent (TCLE) and assent (TALE), in accordance with the participants' ages.

The study began with a review of medical records for children and adolescents treated at the emergency care unit from January 2016 to December 2020, who had a diagnosis potentially related to anaphylaxis (ICD-10). Following the methodology of Nunes et al. (2022), medical records were examined, and those with compatible symptoms were categorized as possible cases. If the records indicated a history and progression suggestive of anaphylaxis, as assessed by at least two allergists, they were classified as probable cases. In this initial phase of the project, informed consent was not required (CAAE 99260818.0.1001.5567). Subsequently, the medical records were reviewed again, reaffirming those with compatible symptoms as possible cases, while probable cases were identified based on the same criteria. Parents or legal guardians of probable cases were contacted by phone and invited to participate in a teleconference with an allergist. After completing the online informed consent forms (TCLE and TALE), teleconferences were conducted, during which the researcher filled out a standardized clinical form and gathered background information, clinical data, and details related to the event. Data were extracted from both the emergency care records and the standardized clinical forms from the interviews to evaluate and describe the information.

At the conclusion of the study, all patients received guidance from an allergist and, when necessary, were referred to the pediatrics department or the institution's specialized allergy service for follow-up care.

Data for the study were collected using Google Forms based on the standardized clinical record and organized into a numerical table. To describe the sample of identified anaphylaxis cases, descriptive statistics and summary measures were utilized. The cases were categorized and compared based on relevant factors such as age, time from exposure to reaction, triggering factors, clinical manifestations, cofactors, treatment, monitoring, investigation, and medical history. The comparison of characteristics between hospitalized and non-hospitalized patients was conducted using Fisher's exact test, with a significance level set at $p < 0.05$. Analyses were performed using IBM SPSS Statistics for Windows, Version 18.0.

Results

Between 2016 and 2020, there were a total of 460,434 emergency room visits. After analyzing the medical records using relevant ICD codes, 69 probable cases of anaphylaxis were identified (see Figure 1). Of these, 51 cases were included in the study, with three patients having experienced two episodes each. Selection details are provided in Figure 1.

The median age of the patients was 3.8 years (IQR: 1.7 to 7.1 years). Among them, 27% (n = 14) were under 2 years old, 31% (n = 16) were between 2 and 5 years old, 37% (n = 19) were between 6 and 11 years old, and 4% (n = 2) were 12 years or older. Males constituted the majority, representing 63% (n = 32) of the cases.

In approximately one-third of cases (31%; n = 16), the exposure-reaction time was unknown. Among the remaining cases (n = 35), 48% (n = 17) reported symptoms within 10 minutes of exposure.

All cases exhibited some form of skin symptoms (see Table 1). There were no instances of heart failure. Eight cases (16%) experienced a recurrence of symptoms after the first hour, suggesting a possible biphasic reaction. Twelve cases (24%) required hospitalization following emergency room care, with two patients admitted to the intensive care unit (ICU).

Among the 51 cases that were interviewed, 75% (n = 38) had a known triggering factor, with 84% (n = 32) identifying a food trigger. Three cases were associated with medications—specifically ibuprofen, dipyrone, and amoxicillin. Additionally, one case was linked to an ant bite and

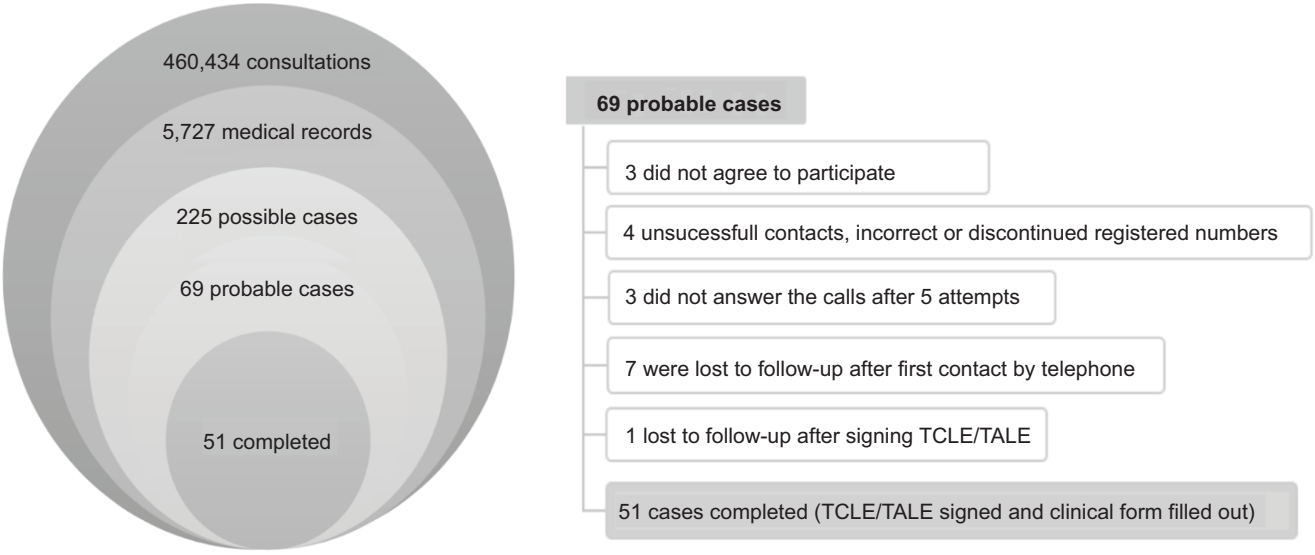

Figure 1 Flowchart for case selection of probable anaphylaxis cases treated in the emergency room.

Table 1 Clinical manifestations of probable cases of anaphylaxis (n = 51).

	N	%
Skin manifestations	51	100
- Urticaria	40	78
- Angioedema	33	65
- Itching	18	35
- Erythema	11	22
Respiratory manifestations	40	78
- Cough	27	53
- Dyspnea	21	41
- Nasal symptoms: runny nose and/or nasal obstruction	14	28
- Wheezing	13	26
- Dysphonia	6	12
- Drop in O_2 saturation < 94%	9	18
Gastrointestinal manifestations	30	59
- Vomit	23	45
- Abdominal pain/colic	11	22
- Nausea	4	8
- Dysphagia	4	8
- Diarrhea	3	6
Cardiovascular manifestations	5	9
- Hypotension	2	4
- Tachycardia[a]	2	4
- Syncope	1	2
Other symptoms	26	51
- Reduced alertness	10	20
- Irritability	7	14
- Conjunctivitis	5	9
- Sweating	1	2
- Tingling	1	2
Recurrence of symptoms	8	16

Tachycardia: Heart rate of 162 bpm in a 2-year-old child and 137 bpm in a 10-year-old child

another to latex exposure. The reported triggers are illustrated in Figure 2.

Cofactors associated with the anaphylaxis episodes were reported in 9 cases, including infections, fever, and medication use (NSAIDs, antibiotics, and immunosuppressants). In 90% (n = 46) of cases, the patients had some comorbidity, as noted by their parents. The most common comorbidities included rhinitis (65%; n = 33), asthma (41%; n = 21), atopic dermatitis, and food allergy (both 39%; n = 20). Among those with asthma, 86% (n = 18) exhibited respiratory symptoms as a manifestation of anaphylaxis. Seven cases (14%) had a history of previous anaphylaxis, including three patients who each experienced two episodes. The most frequently reported location of exposure to anaphylaxis triggers was the home, accounting for 63% of cases.

Half of the patients (51%; n = 26) received pre-hospital treatment, which was administered by a family member in 88% of cases (n = 23); details are presented in Table 2. All patients received treatment in the hospital, with 92% (n = 47) receiving antihistamines and 86% (n = 44) receiving intravenous corticosteroids. Intramuscular (IM) epinephrine was administered in 37% (n = 19) of cases. Only one patient was not kept under hospital observation; 45% were monitored for at least 4 hours, and 82% for at least 2 hours. Upon discharge from the hospital, both from the emergency room and after hospitalization (general ward/ICU), 88% (n = 45) of patients received some form of anaphylaxis management measures, with 59% (n = 30) referred to a specialist for further investigation. The treatments and procedures performed in the emergency room and at discharge are outlined in Table 2.

The clinical presentation varied between hospitalized and non-hospitalized patients, with a higher frequency of epinephrine autoinjector (EAI) use by family members (2 vs. 0; p = 0.02), the provision of hospital oxygen (5 vs. 3; p = 0.02), and a greater frequency of symptom recurrence (6 vs. 2; p = 0.003) among those who were hospitalized.

Among the post-discharge procedures, 65% (n = 33) underwent an investigation of the probable episode of

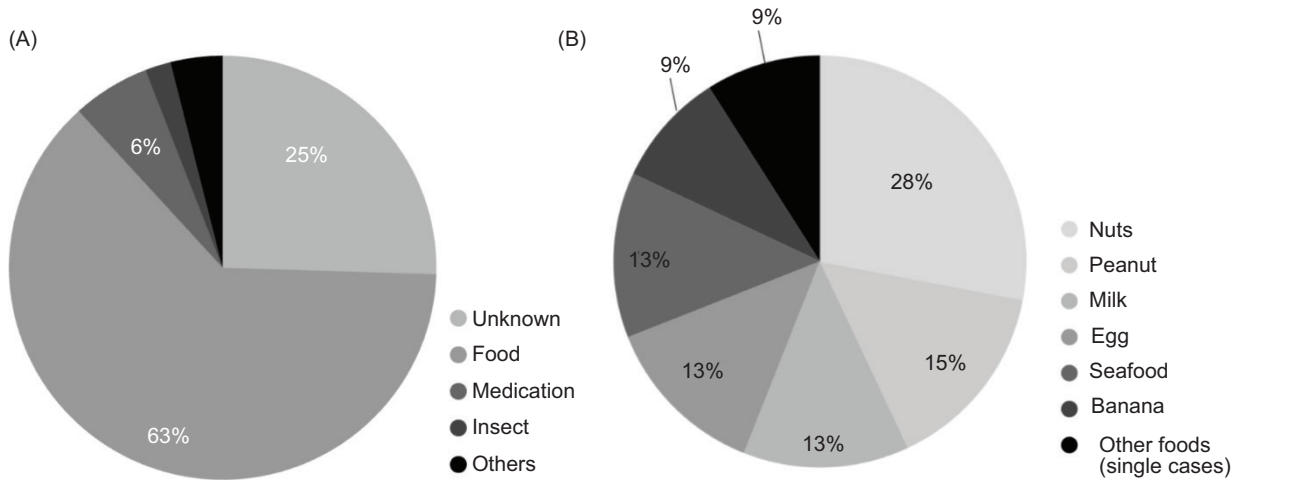

Figure 2 (A) Distribution of triggering factors for probable cases of anaphylaxis (N=51) and (B) reported foods (N=32). Nuts (9): 3 walnuts, 3 cashews, 2 Brazil nuts and 1 hazelnut. Medications (3): amoxicillin, dipyrone, and ibuprofen Others (2): Latex and dust mite. Other foods (with a single case): Fish, peaches, and red dye.

Table 2 Conduct and treatments carried out in probable cases of anaphylaxis (n = 51).

	N	%
Pre-hospital treatment	26	51
Adrenaline autoinjector	2	4
Second dose of adrenaline AI[a]	1	2
Antihistamine PO[b]	18	35
Corticosteroid PO[b]	7	14
Hospital treatment	51	100
Adrenaline IM[c]	19	37
Second dose of IM[c] adrenaline	1	2
IV[d] antihistamine	47	92
IV[d] corticosteroid	44	86
Bronchodilator (inhaled Beta-2 agonist)	11	22
Oxygen	8	16
Volemic expansion	20	39
H2 antihistamine	16	31
Antiemetic	2	4
Hospital observation for at least 4 hours	23	45
Anaphylaxis management measure at discharge	45	88
Emergency medication	40	78
Referral to specialist	30	59
Advice to avoid the trigger	28	55
Written emergency plan	7	14

AI: autoinjector; PO: oral; IM: intramuscular;
IV: intravenous;

anaphylaxis, with 85% (n = 28) consulting an allergist, 12% (n = 4) seeing a pediatrician, and 3% consulting another specialist. Among the cases investigated, 90% (n = 30) had specific immunoglobulin E (IgE) testing, with 80% (n = 24) showing positive results and 77% (n = 23) positive for the suspected trigger at the time of the reaction. Skin prick tests were performed in 27% (n = 9), with positive results for the suspected trigger at the time of the reaction in 67%. Additionally, 12% (n = 4) underwent an oral provocation test (for red dye, nuts, amoxicillin, and paracetamol), with only the test for nuts returning positive.

During follow-up with the attending physician (73%, n = 37), 63% (n = 32) received guidance to avoid the trigger, with 84% (n = 27) identifying food triggers. Antihistamines as needed were prescribed to 51% (n = 26) of patients, and corticosteroids were prescribed to 37% (n = 19). An epinephrine autoinjector (EAI) was prescribed to 37% (n = 19) of patients, all by an allergist. Only 35% (n = 18) received written emergency plans. The sole case of a reaction to an ant bite underwent specific allergen immunotherapy following the described episode.

Regarding the diagnosis, 45% (n = 23) of patients were diagnosed with anaphylaxis. Of these diagnoses, 56% (n = 13) were made by the emergency room doctor, 30% (n = 7) by an allergist, and 13% (n = 3) by a pediatrician.

Discussion

This study analyzed the medical records of patients treated in the emergency room between 2016 and 2020, encompassing a total of 460,434 visits. A total of 69 probable cases of anaphylaxis were identified, of which 51 were included in the study. The majority of cases presented with skin and respiratory symptoms associated with anaphylaxis. Approximately one-third of patients had an unknown exposure-reaction time; however, among those with a known time, nearly half reported that the onset of the reaction occurred within 10 minutes. Additionally, 24% of patients were hospitalized after emergency room care. The primary reported triggers were food-related, and most patients had at least one comorbidity, with rhinitis being the most common. The most frequent treatments administered were antihistamines and intravenous corticosteroids. Following discharge, most patients were referred for further investigation by allergists, and the exclusion of triggers, particularly food, was widely recommended.

For an accurate diagnosis of anaphylaxis, understanding the exposure and reaction times is crucial.[1,2] Individual

sensitivity and the route of exposure significantly influence the response time to triggers.[10] In our study, symptoms were reported within 10 minutes after exposure to the trigger in 48% of the cases with a known reaction time. Our findings align with those from a recent retrospective analysis of 20 years of pediatric anaphylaxis cases, which found an average time of 23 ± 33 minutes between exposure and the onset of symptoms, with a median of 10 minutes.[11]

In the present study, food was the primary trigger for anaphylaxis episodes, consistent with observations in pediatric cases.[1,2,6,12,13] Among food triggers, nuts (including walnuts, cashews, hazelnuts, and Brazil nuts) and peanuts were the most frequently reported. While milk and eggs are recognized as major triggers in infants and young children, nuts and peanuts may be particularly significant in preschool-aged children and adolescents.[1,13] The largest age group in our study consisted of children over two years old, accounting for 72.5%. Additionally, the higher economic status of these children, predominantly from middle and upper-middle-class backgrounds, may help explain this finding. This suggests a correlation between food allergy, age group, economic status, and access to private health services, a correlation also noted in other contexts.[14]

In our study, we observed a low incidence of anaphylaxis cases related to insect bites, with only one case linked to an ant bite. Although insect bites are the second most common trigger of anaphylaxis in the general population.[1,2] their prevalence in children is estimated at only 0.8%.[15] It is important to note that venom-induced anaphylaxis exhibits specific regional patterns.[1,2] For instance, in South Korea, bee venom is the most common trigger, while in America, Asia, and parts of Australia, ants are the primary trigger.[1]

Cardiovascular manifestations are less common than skin and respiratory symptoms, particularly in children; however, they are associated with more severe anaphylaxis.[1,2,6] In our study, all five cases with cardiovascular manifestations involved female patients, with two requiring hospitalization. The triggers for these episodes were food-related, and the patients also exhibited skin and respiratory symptoms. They were treated with intramuscular (IM) epinephrine and subsequently evaluated by allergists, who confirmed the presence of positive IgE to the relevant allergens. Diagnosing anaphylaxis can be particularly challenging when cardiovascular collapse occurs without other clear signs.[1,2,16] However, severe episodes characterized by rapid cardiovascular collapse and shock can manifest as isolated symptoms of anaphylaxis.[1,2] A survey conducted in the United States indicated an annual incidence of anaphylaxis with cardiovascular manifestations of approximately 8 cases per 100,000 inhabitants.[17] In the United Kingdom, a medical database reported an even lower incidence, with fewer than 1 case per year per 100,000 inhabitants.[18]

Among patients with food-triggered anaphylaxis, 97% (n = 31) were on an exclusion diet for the suspected food at the time of the interview. However, it is concerning that nearly a third of these patients (28%; n = 9) did not undergo an etiological investigation of the episode. Investigation by a specialist, including detailed anamnesis and, when necessary, diagnostic tests, is crucial for confirming or ruling out a food allergy diagnosis.[1,19] This approach aims to prevent unnecessary exclusion diets, which can have negative nutritional and psychosocial consequences. Additionally, such diets can impose extra costs on the families of these patients.[20]

In our study, one case of anaphylaxis was associated with the ingestion of dyes, with the parents reporting carmine red dye as a trigger and a history of a previous mild reaction. Despite an investigation by an allergist, which revealed no specific IgE and a negative Oral Provocation Test (OPT), the patient remained on an exclusion diet for the product without experiencing any new reactions. Although additives, including food coloring, have been used since ancient times, few studies report allergic reactions to these substances.[21] The prevalence of reactions to food additives is estimated to be 1-2% in unselected healthy children, but is higher in atopic children, ranging from 7% (after provocation tests) to 2% (in double-blind provocation tests).[22,23]

Three patients included in the study experienced two episodes of anaphylaxis. Notably, one patient, despite being referred to a specialist after both episodes, did not undergo further investigation. International data indicate that the recurrence of reactions occurs in 26.5% to 54.0% of anaphylaxis patients during a follow-up period of 1.5 to 25 years.[24] The guidelines from the World Allergy Organization (WAO) and other societies recommend that patients with anaphylaxis be followed up by a doctor, preferably an allergy specialist.[1,19]

There was low use of intramuscular epinephrine (37%) in the emergency room, and the prescription of epinephrine autoinjectors (EAI) during follow-up was also low (37%), with only 20% of cases meeting both mandatory recommendations for anaphylaxis management. Despite international guidelines on the treatment of anaphylaxis, epinephrine remains underused by both caregivers and health professionals.[1,25,26] A French study analyzing 149 pediatric anaphylaxis cases in emergency services identified key reasons for the lack of epinephrine administration. Both caregivers and doctors often failed to recognize the severity of anaphylaxis and noted the rapid spontaneous improvement of symptoms.[25] Another significant issue is access to EAIs in countries like Brazil, where these devices must be imported and are costly for most of the population, limiting accessibility.[27] The number of cases kept under hospital observation for at least four hours fell short of the ideal standard. Epinephrine autoinjectors (EAI) and oxygen supplementation were significantly more utilized in hospitalized patients, likely due to the greater severity of their conditions. Furthermore, we observed eight cases (15.7%) where symptoms recurred after initial improvement, raising suspicion of a biphasic reaction. Notably, symptom recurrence was more prevalent among hospitalized patients (6 cases), while only two non-hospitalized patients experienced this complication (p = 0.003). Although clinically significant biphasic reactions are rare and mortality is very uncommon, all anaphylaxis patients should be kept under hospital observation, as approximately half of biphasic reactions occur within the first six to twelve hours after the initial reaction.[1,2] Two key factors that increase the risk of biphasic reactions are the time between symptom onset and the administration of epinephrine, as well as the number of epinephrine doses needed to resolve the condition.[28,29]

This study has several limitations that should be considered. The sample size was constrained due to the

single-center design and the low incidence of cases. Additionally, the retrospective nature of the study may have introduced recall bias, as parents or guardians might find it challenging to remember precise details about the anaphylaxis episodes, particularly if they occurred several years ago. Furthermore, comorbidities were reported by parents, such as food allergy diagnoses, without data on complementary tests or Oral Food Challenges. Another limitation is that serum tryptase levels were not measured, as this test was not available at the hospital.

Conclusion

In conclusion, anaphylaxis in children is a systemic allergic reaction characterized by varied clinical manifestations, predominantly cutaneous and respiratory symptoms. Our study found that most cases occurred in male children, with foods—especially nuts and peanuts—serving as the primary triggers, which diverges from some national and international trends.[1,2,6,7,12,13] The management of anaphylaxis in these patients was suboptimal, evidenced by the underuse of intramuscular epinephrine in the hospital and low prescription rates of epinephrine autoinjectors (EAI) during follow-up. Increasing awareness and education about anaphylaxis in children, as well as emphasizing the importance of proper management, are essential for reducing the risk of morbidity and mortality in this vulnerable population.

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Author Contributions

All author's contributed equally to the article.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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