ANAPHYLAXIS IN CHILDREN: A 6-YEAR EXPERIENCE (2014-2019)

Larisa CHIRIAC¹

"Carol Davila" University of Medicine and Pharmacy, Dionisie Lupu Street no. 37, Bucharest, 020022, Romania

*corresponding author: larissa_0107@yahoo.com

<https://doi.org/10.52846/jskm/37.2021.1.4>

Abstract

Allergic reactions are a real problem all over the world and the number increased both for adults and children. Anaphylactic reactions showed a small raise in number as well. Despite the importance of anaphylaxis, little information is available on its clinical features. *Aim:* this study has the purpose to determine anaphylaxis prevalence for children in Grigore Alexandrescu Emergency Hospital for Children in Bucharest, Romania, as well as the therapeutic approach.

Methods: the research consists in collecting data over a 6-year period, 2014- 2019, from hospitalized children with allergic reactions, aged 0-18 years. The patients were selected from Grigore Alexandrescu Emergency Hospital for Children. Anaphylaxis prevalence, etiology and therapeutic approach were analyzed. *Results and conclusions:* during the 6-year study period (January 2014 - December 2019), at Grigore Alexandrescu Emergency's Children Hospital, Bucharest, 829 children were hospitalized having allergic reactions, with an annual average of 138 cases. From the total children with allergic reactions, 6% (50 cases) developed anaphylactic reactions at the beginning or during hospitalization. During this period, we noticed an increase of hospital admissions for children with allergic reactions, and even anaphylaxis. Anaphylaxis was mostly caused by drugs and shortly after by food. Epinephrine has been used in few cases of anaphylaxis, more frequently in severe forms. Almost all patients received, during hospitalization and at home, treatment with steroids and antihistamines. An important issue, in the treatment of anaphylaxis, is parents' education in identifying anaphylaxis and quick treatment with epinephrine. Epinephrine auto-injector should be prescribed at patients discharge, but only one patient from our study group had that prescription. Most patients continued their treatment with steroids and antihistamines at home.

Keywords: epinephrine, anaphylaxis, children, systemic allergic reaction

Introduction

Anaphylaxis is a severe systemic, allergic reaction, life-threatening, that starts quickly, caused by sudden chemicals release into blood stream from mastocytes and basophils through an IgE or non-IgE mediated mechanism. This reaction will cause a lot of signs and symptoms that can mime other diseases, making it hard to put an early and proper diagnostic (Kemp & Lockey, 2002). In our area, foods, particularly seafood and milk, seem to be the most important etiologic factors triggering anaphylaxis (Novembre et al., 1998).

Anaphylaxis is the most severe allergic reaction that can occur in all ages, but most studies reveal that adults are mostly affected. Most children with anaphylaxis have no stated histories of prior reaction to the causative agent (Dibs & Baker, 1997). Children can have different signs and symptoms in anaphylactic reactions, therefore research is needed and special guidelines adapted for this category of age. Anaphylaxis is a medical emergency and quick diagnosis and treatment are extremely important. For over 40 years, epinephrine is the first-line treatment for anaphylaxis but many studies sustain that it is not

used in numerous cases (Kemp, Lockey & Simons, 2008, Bock, Munoz-Furlong & Sampson, 2006, Pumphrey & Gowland, 2007, Greenberger, Rotskoff & Lifschultz, 2007, Gaeta et al., 2007, Simons et al., 1998).

Anaphylactic reactions are known even from ancient times, but in the last years, it can be easily observed that all allergic reactions increase all over the world and become a serious problem for the health system. The Center for Prevention and Control of Diseases (CDC) admits that between 1997 and 2011 the number of children manifesting allergies has grown and it is still growing. Anaphylaxis has a prevalence of 6% in population and the risk of fatal anaphylaxis is 1 % from the total mortality risk. In the last 20 years, hospitalization caused by anaphylaxis has grown in Europe, Australia and North America and the etiology was food and drugs. Mortality due to anaphylaxis has doubled in Australia, while in United Kingdom and North America remained at the same levels (Comberiati, Joseph & Diego, 2019).

In Romania, there are few data of allergic reactions in children and their most severe forms (anaphylaxis). Also, there are not enough

informations about therapeutic management of these reactions in hospital or pre-hospital stage.

Materials and Methods

We made a 6-year retrospective and prospective, observational study in Emergency Clinic Hospital for Children "Grigore Alexandrescu" from the capital of Romania, Bucharest. The group study consisted of patients aged from 0 to 18 years old, hospitalized for allergic reactions. During this time, we selected 50 cases of children with anaphylactic reaction and we obtain data of their etiology, clinic profile, days of hospitalization and therapeutic approach.

The diagnostic criteria for anaphylaxis were initially published by a multidisciplinary team of experts in 2005/2006, that help any clinician to recognize the wide specter of signs and symptoms that are encountered in anaphylaxis. The clinical aspect of anaphylaxis consists of multisystemic signs and symptoms, implying simultaneous harm of at least 2 systems of the body.

This study is an observational, descriptive, retrospective and prospective one, extended within a period of 6 years. The study is retrospective from 01.01.2014 to 31.12.2014 and prospective from 01.01.2015 to 31.12.2019. From all the allergic admissions, we selected children that had on discharge one of the diagnosis: "anaphylaxis", "anaphylactic reaction", "severe allergic reaction" or "anaphylactic shock". Then compare if they have diagnostic criteria of anaphylaxis, found in guidelines of European Academy of Allergy and Clinical Immunology EAACI (Muraro et al., 2014). Moreover, we analysed the total number of

allergic reactions that were hospitalized, having primary or secondary diagnosis at discharge „acute urticaria”, „angioedema” or „Quincke edema”. Patients that didn't had clinic diagnosis of anaphylaxis, another type of shock or another type of allergic reaction, were excluded from this study.

All data was obtained from the "Hippocrate" hospital program and from patients' files, that were introduced in a database. We analyzed especially patients' age, sex, anaphylaxis etiology, clinical presentation and therapeutic approach. For statistics, we used 2 base data programs, Excel and SPSS version 23. The informations was described through percents and medians.

This study was made according to the medical law and ethics.

Results

In Grigore Alexandrescu Emergency Clinic Hospital for Children, during the 6-year period, 2014-2019, were hospitalized 829 patients with allergic reactions, with an annual average of 138 cases per year; increase of hospital admissions due to allergic reactions, during 2014-2019. From the total number of admissions of allergic reactions, 6% (50 cases) were severe forms, anaphylactic reactions, that were included in the study group.

Almost half of admissions caused by allergic reactions were acute urticaria (47%, 391 cases), followed by angioedema (39%, 327 cases), and in a smaller percent Quincke's edema (8%, 74 cases) and anaphylaxis (6%, 50 cases).

Figure 1. Tendency of allergic reactions in the last 6 years

In the chart above (figure 1), we observe a progressive increase of admissions due to allergy in Grigore Alexandrescu Emergency Clinic Hospital for Children. This increase was observed in all types of allergic reactions. In 2014 were 90 admissions with allergic reactions and in 2019 this number was more than double, 219 cases. This increase was seen also for anaphylaxis, 5 cases per year in 2014-2015 to 15 cases in 2019.

We analyzed the study group on terms of gender and noticed that the highest number of

hospitalized patients were boys (62%). The patients were aged from 3 months to 18 years. Based on the age, two incidence picks were seen, around 4 and 17 years old. The average age from the study group was 8.15 ± 5.9 years.

Most patients (62%, n=31) had previous allergic reactions or diseases. Anaphylaxis was the first episode of severe allergic reaction that occurred for 38% of patients (n=18), who had no knowledge of allergy to any substance.

Figure 2. Types of allergens in anaphylactic reactions

In our study group, children were exposed to numerous allergens, like different types of food, drugs, insect venom and others. We noticed that majority of children (46%, n=23) had anaphylaxis after exposure to drugs, followed by food ingestion (34%, n=17) (chart II). A small percent of children had insect bite-anaphylaxis (14%, n=7).

In the study group, food anaphylaxis, occurred because of exposure to proteins from cow milk, kiwi, gluten, but there were some anaphylactic cases without identifying the trigger. Drugs-anaphylaxis was 46% (n=23), the drugs were amoxicillin, cefuroxime, ceftriaxone, penicillin, furazolidone, ciprofloxacin, ibuprofen, paracetamol, methylprednisolone and lidocaine. Insect -bite

anaphylaxis occurred in 14% (n=7) of children, that were older than 6 years. Other triggers were MMR vaccine (measles-mumps-rubella) and rupture of hydatid cyst.

Making a correlation between age and type of trigger, the following results were obtained : in preschool children, food allergies were the main cause of anaphylaxis, followed by drugs. In school children and teenagers, main causes for anaphylaxis were drugs and insect bites.

Clinical aspect of anaphylaxis

Skin was affected in 82% of patients (n=41), respiratory system for half (50%, n=25), circulatory system 30% (n=10) and digestive system 38% (n=19) of the subjects.

Tabele no 01. Grading system of anaphylaxis forms analyzed

Gradation of anaphylaxis severity	Defined by	Number of cases	Number of cases (%)
Mild	Generalized eruption, edema, pruritus, dry cough, mild dyspnea, oxygen saturation > 97% in breathing air	17	34%
Medium	Dyspnea, polypnea, wheezing, oxygen saturation 92-97% in breathing air Vomitus, nausea, abdominal pain, dizziness +/- mild anaphylaxis symptoms	21	42%
Severe	Hypotension, cyanosis, tachycardia/bradycardia, syncope, collapse, urinary incontinence, weak pulse, confusion oxygen saturation < 92% in breathing air +/- medium anaphylaxis symptoms	12	24%

As shown in the table above, the subjects were divided into 3 categories of anaphylaxis: mild, medium and severe. Age-increase growth tendency of severe forms of anaphylaxis was observed in the study group. Teenagers displayed the highest number of severe anaphylaxis cases, from all age categories. Category 0-1 years have the smallest number of cases.

Therapeutic approach

In the study group, we analysed the treatment given to patients, both in the emergency ward, during hospitalization and in ambulance. At home, sporadic antihistaminic treatment was taken orally and no epinephrine was given. Sporadic antihistaminic treatment was taken orally.

Prior to hospitalization (another hospital or ambulance), 5 patients (10%) received epinephrine and steroids 4 patients (8%).

In hospital, epinephrine was used in 34% of anaphylaxis cases (n=17) and was performed subcutaneously in 24% (n=4), intramuscular in 64% (n=11) and intravenous in 12 % of cases (n=2). Medium forms of anaphylaxis were treated with epinephrine in 6 out of 21 cases, from which 4 subcutaneously and 2 intramuscular. Severe anaphylaxis received treatment with epinephrine in 11 out of 12 cases, from which 9 subcutaneously and 2 intravenous. Mild forms of anaphylaxis did not received treatment with epinephrine. All patients from the study group received volume replacement. Oxygen therapy by mask was given in 58% of the patients (n=29), especially to those with respiratory distress. Almost all patients (94%) received intravenous steroids. Most of patients (80%, n=40) received, during hospitalization, antihistamines H1 or H2 or both. Bronchodilators were given to patients with respiratory distress, especially to those with oxygen saturation below 92% in breathing air. In the study group, average inpatient days was $3,62 \pm 2,18$ days, with a minimum of one day and a maximum of 12 days. There were no deaths due to anaphylaxis.

At discharge, patients and their parents or tutors, were informed about anaphylaxis and indication to avoid the suspected allergen that caused the anaphylactic reaction. Most of children received treatment at home with antihistamines (86%, n=46) and steroids (56%, n=28). Epinephrine auto-injector was prescribed only to one patient from the study group (2%).

Conclusions and discussions

Anaphylaxis prevalence in the study group was 6%. The annual number of cases with allergic and anaphylactic reactions has grown in those 6 years (2014-2019). This growth of hospital admissions due to anaphylaxis, but also due to other allergic causes, is similar to other studies from literature. In the last 20 years, worldwide, anaphylaxis hospitalization rate has grown (Muraro et al., 2014, Cho & Kwon, 2019).

Some studies state that women present more often anaphylaxis, while other studies say that the majority consists of men (Lee et al., 2016). More recent studies reveal that in the

pediatric population, boys present more often anaphylactic reactions, fact that emerged as well from the study group (Muraro et al., 2007).

The average age of the patients was 8.15 years, but anaphylactic cases were reported in every age category.

Anaphylaxis was the first episode of severe allergic reaction that occurred in 38% of the patients (n=19). These patients had no knowledge about any allergy, mechanism was probably nonimmunologic.

Analysing the anaphylaxis etiology, we discovered that food was the main cause of anaphylaxis in preschool children, followed by drugs. No case of insect sting-anaphylaxis was reported in this age category. In older children, main causes of anaphylaxis were drugs and insect stings. These results are not according to other studies from literature, that testifies, in the pediatric population, food anaphylaxis represents the biggest percent (Muraro et al., 2007, Vetander et al., 2012). Children from the study group presented more often reactions after receiving drugs, followed by food ingestion. Usually, anaphylaxis caused by drugs or insect sting, is frequently found in adults (Vetander et al., 2012).

Some studies reveal that allergens can vary, depending on age, and the risk of drug anaphylaxis grows with getting older (Simons, 2006). This can be observed in the study group, where drug anaphylaxis becomes major with aging, followed by anaphylaxis caused by insect stings. In the study group, drug anaphylaxis is major, and an explanation could be the presence of more cases of school children and teenagers (n=29), instead of preschool children (n=21).

Clinical aspects of anaphylaxis could vary much. Data from literature reveals that skin involvement are seen in most cases (80-90%), respiratory system is affected in more than half (60-80%), and cardiovascular and digestive systems are affected in 10-40% of the cases (Hompes et al., 2011). Similar data were obtained from our study group as well. In the study group, clinical aspects of anaphylaxis were dominated by skin involvement, but 18% of patients (n=9) had

none. From all age categories, severe anaphylaxis was mostly in teenager group.

The guide of anaphylaxis diagnostic and treatment, developed in 2014, by the European Academy of Allergy and Clinical Immunology (EAACI), reveals that first-line treatment in anaphylaxis consists of immediate intramuscular injection of epinephrine and if possible removal of the inciting cause. Useful second-line intervention may include patients placement in the right position, high-flow oxygen, airway management, nebulized adrenaline or beta-2-agonists, volume resuscitation with intravenous fluids. Steroids and antihistamines can be given as third-line treatment (Vezir et al., 2013).

Data from literature reveals that epinephrine is used rarely in patients with anaphylaxis, usually around 20-40% of cases (Vezir et al., 2013, Dubus et al., 2019). Similar results were obtained also in the study group, epinephrine being used in 34% of the anaphylactic cases (n=17). We have noticed that epinephrine was given according to the severity of the anaphylaxis, these data correspond with studies from the literature (Cheng, 2011). Most of patients received, during hospitalization, therapy with steroids and antihistamines H1 and H2 or both. Bronchodilators were used in patients with respiratory distress.

Analysing the discharge recommendations, the most important aspect is that epinephrine auto-injector was recommended to only one patient (2%) from the study group. Many guides sustain that epinephrine auto-injector should be given especially to patients with food anaphylaxis, anaphylaxis after insect sting, after exposure to aeroallergens or to patients with different comorbidities that can worsen an anaphylactic episode. In the study group we have noticed that, at home, was prescribed treatment with antihistamines (86%, n=46) and steroids (56%, n=28) for almost 5-10 days. In recent guides of therapeutic management of anaphylaxis, after discharge, there is no specificity of the necessity of treatment at home with steroids and antihistamines. However, many physicians recommend a 3-day treatment with

steroids and antihistamines (Dubus et al., 2019).

Limitations of the study

The study was conducted in one Emergency Children Hospital and the study group was quite small, due to the small prevalence of anaphylaxis. Some data were incomplete and the different therapeutic approach was also a problem to draw some conclusions.

The necessity of further research

It would be necessary a multicentric analysis of pediatric anaphylaxis in Romania. It is useful to analyze children's anaphylaxis prevalence, how many of them needed intensive care and also the death rate.

References

- Bock SA, Munoz-Furlong A, Sampson HA: Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol.* 2007, 119: 1016-1018. 10.1016/j.jaci.2006.12.622.
- Cheng, A., Canadian Paediatric Society, & Acute Care Committee. (2011). Emergency treatment of anaphylaxis in infants and children. *Paediatrics & Child Health*, 16(1), 35-40.
- Cho, H., & Kwon, J. W. (2019). Prevalence of anaphylaxis and prescription rates of epinephrine auto-injectors in urban and rural areas of Korea. *The Korean journal of internal medicine*, 34(3), 643.
- Comberiati, P., Spahn, J., & Peroni, D. G. (2019). Anaphylaxis in adolescents. *Current opinion in allergy and clinical immunology*, 19(5), 425-431.
- Dibs SD., Baker MD., (1997), Anaphylaxis in Children: A 5-Year Experience, *Journal of the American Academy Pediatrics*, 99 (1) e7.
- Dubus, J. C., Lê, M. S., Vitte, J., Minodier, P., Boutin, A., Carsin, A., ... & Noel, G. (2019). Use of epinephrine in emergency department depends on anaphylaxis severity in children. *European Journal of Pediatrics*, 178(1), 69-75.
- Gaeta TJ, Clark S, Pelletier AJ, Camargo CA: National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Ann Allergy Asthma Immunol.* 2007, 98: 360-365. 10.1016/S1081-1206(10)60883-6.
- Greenberger PA, Rotskoff BD, Lifschultz B: Fatal anaphylaxis: postmortem findings and associated comorbid diseases. *Ann Allergy*

- Asthma Immunol. 2007, 98: 252-257. 10.1016/S1081-1206(10)60714-4.
- Hompes, S., Köhli, A., Nemat, K., Scherer, K., Lange, L., Rueff, F., ... & Beyer, K. (2011). Provoking allergens and treatment of anaphylaxis in children and adolescents—data from the anaphylaxis registry of German-speaking countries. *Pediatric allergy and immunology*, 22(6), 568-574.
- Kemp, S. F., & Lockey, R. F. (2002). Anaphylaxis: a review of causes and mechanisms. *Journal of allergy and clinical immunology*, 110(3), 341-348.
- Kemp, S. F., Lockey, R. F., & Simons, F. E. (2008). World Allergy Organization ad hoc Committee on Epinephrine in anaphylaxis Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy*, 63(8), 1061-1070.
- Lee, S. Y., Ahn, K., Kim, J., Jang, G. C., Min, T. K., Yang, H. J., ... & Kim, K. E. (2016). A multicenter retrospective case study of anaphylaxis triggers by age in Korean children. *Allergy, asthma & immunology research*, 8(6), 535-540.
- Muraro, A., Roberts, G., Clark, A., Eigenmann, P. A., Halken, S., Lack, G., ... & EAACI Task Force on Anaphylaxis in Children. (2007). The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy*, 62(8), 857-871.
- Muraro, A., Roberts, G., Worm, M., Bilò, M. B., Brockow, K., Fernández Rivas, M., ... & Bindslev-Jensen, C. (2014). Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*, 69(8), 1026-1045.
- Novembre E, Cianferoni A, Bernardini R, Mugnaini L, Caffarelli C, Cavagni G, Giovane A, Vierucci A., (1998), Anaphylaxis in children: clinical and allergologic features. *Pediatrics*, vol. 101(4):E8.
- Pumphrey RSH, Gowland MH: Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *J Allergy Clin Immunol*. 2007, 119: 1018-1019. 10.1016/j.jaci.2007.01.021.
- Simons, F. E. R. (2006). Anaphylaxis, killer allergy: long-term management in the community. *Journal of Allergy and Clinical Immunology*, 117(2), 367-377.
- Simons, F. E. R., Roberts, J. R., Gu, X., & Simons, K. J. (1998). Epinephrine absorption in children with a history of anaphylaxis. *Journal of Allergy and Clinical Immunology*, 101(1), 33-37.
- Vetander, M., Helander, D., Flodström, C., Östblom, E., Alfven, T., Ly, D. H., ... & Wickman, M. (2012). Anaphylaxis and reactions to foods in children—a population-based case study of emergency department visits. *Clinical & Experimental Allergy*, 42(4), 568-577.
- Vezir, E., Erkoçoğlu, M., Kaya, A., Toyran, M., Özcan, C., Akan, A., ... & Kocabaş, C. N. (2013, May). Characteristics of anaphylaxis in children referred to a tertiary care center. In *Allergy & Asthma Proceedings* (Vol. 34, No. 3).