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REVIEW ARTICLE

Anaphylaxis in Public Health

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Abstract

The increasing number of patients with anaphylactic reactions is a modern challenge for healthcare professionals in clinical practice and public health professionals. It remains difficult to determine the prevalence or incidence of anaphylaxis in the population due to the long absence of a consensus definition, the fact that analyses are performed on various population groups and the use of different data collection methodologies. In the United States, anaphylaxis mortality ranges from 0.63 to 0.76 cases per million inhabitants, with 58% of these deaths due to drug anaphylaxis. The risk factors for anaphylaxis are ramipril and metoprolol use, which is common in patients with cardiovascular disease. Also, a higher level of gliadin following excess gluten intake is associated with a higher incidence of anaphylaxis. Drugs, food and insect stings have long been known as anaphylaxis inductors. In diagnosis, determination of serum tryptase concentration is used. In patients with normal tryptase concentration, it is appropriate to screen other inflammatory mediators. The authors of this article present new findings on anaphylaxis in the literature and recommended practices of professional societies in the context of public health.

INTRODUCTION

Knowledge of anaphylaxis management is essential for medical personnel in many clinical fields. The emphasis is on early detection and initiating appropriate therapy. Best practices for anaphylaxis management are currently available, presented by national and international professional societies (Cmorej *et al.* 2017). Nevertheless, deaths from anaphylaxis are still reported in patients who did not receive appropriate therapy, consisting primarily of epinephrine administration. The main public health priority is to monitor the incidence and prevalence of anaphylaxis and to eliminate risk factors in the environment covered by public health authorities. At the same time, public health faces the challenge of confirming the safety of vaccination, which some

see as having a negative impact on the health of the child population, including the development of severe allergic reactions. This paper aims to present the latest findings related to anaphylaxis in clinical and preventive health care.

DEFINITION OF ANAPHYLAXIS

Anaphylaxis is a severe life-threatening generalized hypersensitive allergic reaction mediated by immunoglobulin E (IgE). Anaphylactic reaction can also be initiated by nonimmune path leading to the release of mediators responsible for causing the anaphylactic reaction (Cmorej *et al.* 2017).

Currently there is no uniform exact definition of anaphylaxis (Johansson *et al.* 2004). The European Academy of Allergology and Clinical Immunology Nomenclature Committee adopted a broader definition of anaphylaxis. It is a serious, life-threatening, generalized or systemic hypersensitive reaction which quickly causes life-threatening airway obstruction and/or respiratory failure and/or circulatory instability usually associated with cutaneous and mucosal changes. This definition was presented at the European Resuscitation Council Guidelines for Resuscitation 2015 and replaced the larger, organ-specific characteristic of anaphylaxis published in 2005 in the above-mentioned recommended procedures. In this paper, the authors also stated that anaphylactic reaction is a rare and potentially reversible cause of sudden cardiac arrest. The paper stated that the term anaphylactoid reaction for non-IgE mediated response is no longer recommended (Soar *et al.* 2010; Truhlar *et al.* 2015).

PATHOPHYSIOLOGY OF ANAPHYLAXIS

Initial exposure to an allergen may lead to sensitization of the organism. The result of sensitization is binding of specific IgE antibodies to receptors on the cell membrane of mast cells and basophil granulocytes. Repeated exposure to an allergen leads to the bridging of bounded IgE receptors on mast cells and basophil granulocytes. This is followed by a massive release of inflammatory mediators represented by histamine, leukotrienes, prostaglandins, thromboxanes and bradykinin. Inflammatory mediators increase capillary permeability and mucous secretion while reducing vascular tone. The result of these processes is the development of clinical symptoms presented as oedema of airways, bronchospasm, hypotension and cardiovascular failure. In non-immune-mediated anaphylaxis, the essence of the development of clinical symptoms is liberation of histamines, which is caused by degranulation of cells without the participation of IgE. The degranulation of the cells occurs due to complement activation with development of anaphylatoxins and contact with hyperosmolar substances or histaminoliberators (Soar *et al.* 2010).

BASIC EPIDEMIOLOGICAL DATA FOR ANAPHYLAXIS

It was difficult to quantify the incidence and prevalence in the population mainly due to the lack of consensus in defining anaphylaxis, the fact that different population groups were analysed and the use of different methodologies (Lieberman *et al.* 2006). Epidemiological data presented in the European Resuscitation Council Guidelines for 2015 mention the total number of cases of anaphylaxis between 30 to 950 cases per 100,000 person/years. Lifetime prevalence is presented here between 50 and 2,000 cases per 100,000 people, or 0.05 to 2.0% (Soar *et al.* 2010; Truhlar *et al.* 2015). Decker *et al.* (2008) published a study about the incidence of anaphylaxis in the population over a ten-year period. The study provided the latest data on the epidemiology of anaphylaxis in the United States. The authors estimated the incidence and prevalence in Western countries at 8 to 50 cases per 100,000 person/years, with lifetime prevalence rates from 0.05 to 2.0% (Peng & Jick, 2004). Data on the incidence at the international level are highly variable. Studies from the US report 49.8 per 100,000 person/years, a study from the United Kingdom 8.4 per 100,000 person-years (Mullins, 2003) and a study in Australia 13 per 100,000 person/years (Bohlke *et al.* 2004). To estimate the incidence of anaphylaxis in the UK, databases of practitioners were used (Mullins, 2004). In Australia, the minimum rate of population incidence was estimated on the number of cases of anaphylaxis, which were presented in the outpatient departments of immunologists (Liebermann *et al.* 2006). Bohlke *et al.* (2004) reported incidence in the US of 10.5 per 100,000 person/years in children and adolescents registered in the institution of Health Maintenance Organizations. Differences in incidence are probably the result of differences in population samples, data collection methods and definitions of anaphylaxis (Liebermann *et al.* 2006). Wood *et al.* estimates the risk of anaphylaxis in the general population based on research in 1,000 adult patients admitted to hospital in the United States with life-threatening anaphylactic reactions involving two or more organ systems to more than 1.6% (Wood *et al.* 2014).

EPIDEMIOLOGICAL DATA OF HOSPITALIZED PATIENTS AND FATAL CASES

Recent data presented in the World Allergy Organization Guidelines for Anaphylaxis reported an annually increasing number of hospitalized patients for anaphylaxis (Simons *et al.* 2015). Rudders *et al.* (2014) based on data obtained from the US Healthcare Cost and Utilization Project Kids' In-Patient Database discovered more than a double increase of cases received in children under 18 for food-induced anaphylaxis between 2000 and 2009. A similar trend was seen in the analysis of the

Italian Ministry of Health. The results show an increasing number of hospitalized persons under the age of 18 for food-induced anaphylaxis from 2006 to 2011. A significantly higher increase in the number of hospitalized persons was recorded in the 5–14 age group than in children age four and younger (Nocerino *et al.* 2015). In Australia, Mullins *et al.* (Mullins *et al.* 2015) observed an increased trend in hospital admissions for food-induced anaphylaxis in the period from 1998 to 2012. Even though the largest number of people admitted to hospital was in the 0–4 age group, an increasing trend of anaphylaxis across all age groups was shown. In addition, a significant acceleration of food-induced anaphylaxis in the 5–14 and 15–29 age groups was also seen.

In England and Wales, a 615% increase of hospitalized persons of all ages with anaphylaxis was observed between 1992 and 2012. However, analysis of the data revealed that the number of anaphylaxis fatalities identified stably corresponds to the value of 0.047 cases per one million inhabitants. A higher number of people hospitalized and death due to drug anaphylaxis and anaphylaxis after insect stings were monitored in elderly people. The highest numbers of deaths from food-induced anaphylaxis was observed in young people with a peak between the second and third decade of life (Turner *et al.* 2015). In the United States, there was an increase seen in the number of people hospitalized for anaphylaxis between 1999 and 2009. However, this increase does not correlate with the number of fatalities monitored in the emergency departments and inpatients. Anaphylaxis mortality varies in the US from 0.63 to 0.76% per one million inhabitants (186 to 225 deaths per year). Fatal cases of anaphylaxis were mostly caused by drugs (58.8%), non-specific allergens (19.3%), toxins (15.2%) and food (6.7%). Fatalities were observed more frequently in elderly people (Jerschow *et al.* 2014).

RISK FACTORS FOR ANAPHYLAXIS

Currently, many risk factors and complicit factors of anaphylaxis are cited in the publications. These risk factors vary with age, but are not yet properly studied in the paediatric population (Simons *et al.* 2015). Data on anaphylaxis in infancy are underestimated, because the clinical picture of anaphylaxis in this age differs from other populations and many anaphylactic events are not diagnosed. That is also why the World Allergy Organization is preparing guidelines for managing child patients with anaphylaxis (Simons & Sampson, 2015).

For adolescents, the risk factors are heterogeneous and include uncontrolled asthma in uncooperative patients, as well as physical stress, starvation, manifestations of disease or denial and delay seeking medical attention. Anaphylactic reaction during pregnancy is infrequent, but dangerous. Anaphylaxis in pregnancy increases the risk of hypoxic-ischemic encephalopathy of the foetus or maternal death (Hox *et al.* 2015).

Elderly patients are a specific risk group, mainly because of the prevalence of cardiovascular diseases or chronic obstructive pulmonary disease. Use of beta-blockers and angiotensin converting enzyme inhibitors (ACE inhibitor) increases the risk of life-threatening anaphylactic reactions (Stoevesandt *et al.* 2014). Nassiri *et al.* (2015) analysed data from more than 5,000 patients with acute allergic reactions and found a higher risk in patients taking concomitant beta-blocker and ACE inhibitor. This finding was confirmed in an experimental model in which administered metoprolol alone led to the aggravation of allergic symptomatology. Isolated administration of ramipril had no significant impact on the development of anaphylactic reactions. However, concomitant administration of metoprolol and ramipril exacerbated anaphylactic release of histamine. The mechanism of action apparently involves priming mast cells and reduction of the threshold of activation.

Systemic mastocytosis may be a predisposing factor for anaphylaxis. In some patients with this disease, severe anaphylactic reactions occurred repeatedly, with some signs of Mast Cell Activation Syndrome (MCAS). Some patients with systemic mastocytosis have IgE-dependent symptoms, although the severity and frequency of MCAS response does not correlate with the level of specific IgE, basal serum levels of tryptase or neoplastically altered mast cells (Gulen *et al.* 2014). Other patients suffer from unexplained recurrent episodes of severe anaphylaxis associated with cardiovascular symptoms such as collapses and elevated baseline serum tryptase levels (> 11.4 ug / l) (Alvarez-Twose *et al.* 2014). Patients with indolent systemic mastocytosis without cutaneous manifestations, in whom anaphylactic reaction occurred exclusively after insect stings, have different clinical and laboratory findings which differ significantly from other patients with indolent systemic mastocytosis. This subpopulation of predominantly male patients shows only a slight increase in basal serum tryptase and mutation of the KIT gene is often limited to mast cells in the bone marrow (Broesby-Olsen *et al.* 2015). Gene mutation of KIT D816V can nowadays be investigated by a screening test from peripheral blood. This test facilitates the diagnosis of systemic mastocytosis for anaphylaxis in patients who showed normal or slightly elevated baseline serum tryptase with absence or minimally expressed skin lesions of urticaria pigmentosa (Fellinger *et al.* 2014).

In the context of the above-mentioned test, many studies were published confirming the determination of basal serum tryptase as a sufficient quality marker of anaphylaxis induced by insect stings. In one controlled study, the low level of acetylhydrolase platelet activating factor (PAF – acetylhydrolase) was associated with serious, toxins induced anaphylaxis (Pravettoni *et al.* 2014). The other factors that may interact in the development of anaphylaxis include physical exertion, alcohol, non-steroidal analgesics, antipyretic and anti-inflammatory drugs (NSAIDs), acute infections, stress and men-

struation. These factors potentially increase the risk of anaphylaxis due to the reduction of the threshold of inflammatory cells activation after allergen exposure. The risk of anaphylaxis is increased in patients with low or borderline sensitization (Ansley *et al.* 2015).

Anaphylactic reactions during menstruation are attributed to various mechanisms, such as hypersensitivity to progesterone and prostaglandins. Oestrogen may also play a role in the synthesis of nitric oxide, which is responsible for the vasodilation of the vascular system, and potentiates the severity of an anaphylactic reaction (Hox *et al.* 2015).

In the prospective study, Brockow *et al.* (2015) identified a relationship between the level of gliadin in plasma and anaphylaxis. Higher levels of gliadin in plasma after intake of higher doses of gluten are associated with a higher incidence of anaphylaxis. The same correlation was found in wheat gluten and related physical exertion or gluten and acetylsalicylic acid in combination with alcohol.

INDUCTORS OF ANAPHYLAXIS

The most common triggers of anaphylaxis, according to the World Allergy Organization Guidelines for Anaphylaxis, are foods, insect stings and drugs (Cmorej *et al.* 2017).

Induced food allergy is most common in infants, children, adolescents and young adults. The results of a meta-analysis of data derived from 34 studies that reported the incidence of food-induced anaphylaxis as 0.14 cases per 100 person/years across all ages of population and seven cases per 100 person/years in children aged 0–4 years was published. In a retrospective study of 168 people over the age of 18, authors Kamdar *et al.* (2015) observed the highest incidence of newly developed allergies in the second and third decade of life. In 49% of these there were symptoms of an anaphylactic reaction caused by seafood, nuts, fish, soy or peanuts. Due to the increased consumption of cashews over the last two decades, higher incidence of anaphylaxis after ingestion has appeared. Just as with nuts and peanuts, even trace amounts of cashews can cause anaphylaxis. The scientific literature has described cross-reactions between cashews and pistachios (van der Valk *et al.* 2014).

In a prospective controlled study, 10 of 12 patients with a history of urticaria related to the consumption of red meat developed anaphylaxis three to seven hours after eating red meat. Increased expression of CD63 molecules on the surface of basophils correlates with sudden onset of anaphylaxis symptoms due to their degranulation. The likely mechanism for the activation of basophils is related to the presence of galactose-alpha-1,3-galactose (alpha-Gal) in the blood of patients after consumption of red meat. Patients with alpha-gal-induced anaphylaxis had a significantly higher positive cutaneous symptomatology test after consuming pork kidney than after consuming pork muscle. Pork kidneys contain a higher concentration of the oligosaccharide epitope of alpha-gal than muscle. Factors that potentiate the development of anaphylaxis include alcohol, NSAIDs and physical exertion leading to alpha-gal sensitization (Commins *et al.* 2014). In Japan, anaphylactic reactions in patients consuming pancakes contaminated by dust mite (Dermatophagoides) and malignant mite (Tyrophagus) have been reported. In these patients, higher levels of specific IgE antibodies against these mites have been reported (Takahashi *et al.* 2014).

Anaphylaxis has also been observed in paediatric patients with milk allergy and asthma treated with lactose containing methylprednisolone sodium succinate for intravenous administration (Levy *et al.* 2014).

Life-threatening anaphylactic reactions have been reported with topical exposure of casein contained in Everlast boxing gloves (Hamilton *et al.* 2015). The authors conclude this chapter with the case of a patient allergic to seafood, who developed anaphylaxis after having sexual intercourse. When taking a history, it was found that the patient's partner had consumed seafood the previous day (Bulikova & Dobias, 2015).

Stings by Hymenoptera insects are very frequent causes of anaphylaxis. Prior sensitization by sting of these insects is very common in the population. Sturm *et al.* (2014) tested 94 subjects with asymptomatic sensitization to Hymenoptera toxin who had positive skin test, a higher level of specific IgE and positive test for basophil activation. These individuals underwent medically controlled Hymenoptera insect sting. In 43.6% of cases, the sting was followed by extensive skin reactions (9.5 times higher risk vs. asymptomatic unsensitized individuals). Systemic allergic reactions occurred in 5.3% of individuals. From these results, currently available tests clearly are not able to predict the risk of extensive skin reactions or systemic allergic reactions in sensitized asymptomatic individuals. Patients with clinically expressed symptoms of allergies to Hymenoptera insect stings without detectable specific IgE can be identified by detecting serum IgE antibodies using a panel of recombinant bee and hornet allergens. The use of recombinant allergens significantly increases the sensitivity of the test compared to the use of specific IgE antibodies by commercial assays (Cifuentes *et al.* 2014).

The most common inducers of drug anaphylaxis are antibiotics, NSAIDs and muscle relaxants. Drug-induced anaphylaxis includes reactions which often go unrecognized in clinical practice. An immediate reaction occurs within one hour of application of the drug and is mediated by IgE antibodies. The skin test is valid for beta-lactam antibiotics, while other antibiotics and drugs have lower relevance. Provocative tests are useful in selected patients (Banerji *et al.* 2014). The results of one cohort study of 51,582 hospitalized patients in the United States suggest that patients with a history of penicillin allergy were hospitalized significantly

longer, received a higher number of broad-spectrum antibiotics (mainly fluoroquinolones, clindamycin and vancomycin) and had a higher prevalence of serious infections caused by clostridium difficile, methicillin-resistant staphylococcus aureus and vancomycin-resistant enterococcal infections (Macy & Contreras, 2014). Anaphylaxis due to cephalosporins is very rare. Data from the US Health Care System include only five cases of anaphylaxis after oral administration from 901,908 issued drugs and eight cases of anaphylaxis after parenteral cephalosporins from 487,630 patients treated (Macy & Contreras, 2015). Although many patients allergic to penicillin tolerate aztreonam or carbapenems, rare cross-reactivity in these patients after treatment with the above-mentioned antibiotics were published. Currently, there is still a recommendation to perform a skin test prior to treatment with aztreonam and carbapenems (imipenem-cilastatin, meropenem and ertapenem) in patients allergic to penicillin. Negative skin test indicates tolerance to the antibiotics listed above (Gaeta *et al.* 2015). The use of skin tests to demonstrate hypersensitivity to quinolones is limited to the uncertainty of the outcome. Especially moxifloxacin exhibits a false positive skin test in healthy subjects who were exposed to moxifloxacin. To this day, a few cases of anaphylaxis to macrolide antibiotics (erythromycin and clarithromycin) were reported. In three children, azithromycin-induced anaphylaxis was demonstrated by skin tests (Mori *et al.* 2014). The largest number of drug-induced anaphylaxis is caused by NSAIDs. This information is confirmed by data from the Portuguese Pharmacovigilance system, according to which NSAIDs were responsible for 47.9% of all drug-induced anaphylaxis and 25.6% of anaphylaxis recurrences within four years. Preferentially it is COX-1 inhibitors represented by acetylsalicylic acid, diclofenac, ibuprofen, naproxen and exceptionally paracetamol (Faria *et al.* 2014). The authors of this article complement the experience with anaphylaxis after administration of metamizole, which is the typical NSAID drug in the Czech Republic and Slovakia. In France, several cases of anaphylaxis associated with the use of diclofenac have been recorded. From the data available, it is obvious that tests need to be developed for the detection of IgE antibodies for the most frequently used NSAIDs, such as diclofenac and ibuprofen (Picaud *et al.* 2014). Essentially, any drug received by any route may initiate anaphylaxis. The specialist literature describes cases of hypersensitivity with cutaneous manifestations of moderate to life-threatening anaphylaxis following administration of monoclonal antibodies (rituximab, trastuzumab, cetuximab, ofatumumab, tocilizumab). Desensitization permits continuation of treatment with the above drugs without development of anaphylaxis (Galvao & Castells, 2015). Severe hypersensitivity reactions leading to the development of anaphylaxis have been reported in 3.5% of 230 patients that were subcutaneously administered a reversible inhibitor of kallikrein-ecallantide due to the treatment of hereditary angioneurotic oedema. These reactions have been associated with the detection of specific IgE antibodies against ecallantide or yeast Pichia pastoris, which is used in recombinant DNA technology to produce ecallantide (Craig *et al.* 2015).

Anaphylaxis is a severe complication of anaesthesia and perioperative care. In several published works it is estimated that the development of anaphylaxis associated with anaesthesia is about 1/3500 to 1/20000 cases (44). In a published multicentre trial, Savic *et al.* (2015) state the incidence of severe anaphylaxis at about 1/13000 anaesthesia. The most frequent initiators of anaphylaxis are peripheral muscle relaxants such as atracurium, suxamethonium, rocuronium or vecuronium. Other drugs responsible for the development of anaphylaxis are the previously stated antibiotics, blood derivatives, chlorhexidine and latex. Published data from the French National Pharmacovigilance Network reported 2,022 anaphylaxis cases caused by peripheral muscle relaxants in 2000–2011, 84 of which were fatal (4.1%). Independent risk factors for death were male gender, emergency conditions, hypertension and cardiovascular comorbidity, use of beta-blockers and obesity. The increased use of sugammadex-modified g-cyclodextrin, which leads to the formation of solid complexes with steroid muscle relaxants used to antagonize the effects occurred in 14 of 15 anaphylaxis patients within a few minutes of administration (Reitter *et al.* 2014).

Chlorhexidine, a widely used disinfectant and antiseptic agent, was responsible for sensitization in 9.6% of 228 patients with the emergence of perioperative anaphylaxis. Sensitization was verified by determining specific IgE, basophil activation test, skin test and intradermal test (Opstrup *et al.* 2014). Latex remains an important trigger of anaphylaxis in health care facilities in many countries (Péer *et al.* 2014). The issue of anaphylaxis and the development of anaphylactic shock after administration of iodinated contrast material had been published by Kim *et al.* (Kim *et al.* 2014), who describe the emergence of anaphylaxis induced by iodinated contrast agent in 104 patients. In 34.6% of cases anaphylaxis occurred without prior exposure to an iodine contrast agent. Anaphylactic shock was present more frequently in elderly patients who had already taken an iodine contrast agent. A positive skin test was verified in 64.7% of patients from 51 tested. In the group altered with anaphylactic shock, a positive skin test was expressed in 81.8% (Kim *et al.* 2014). The US Food and Drug Administration's Adverse Event Reporting System 614 registered cases of anaphylaxis after administration of gadolinium contrast agents. Gadolinium contrast agents are recommended in patients with a history of allergy to iodine contrast agents. Of the above number of anaphylaxis, 43% were a reaction to gadopentetate dimeglubine, 29% gadobenate dimeglubine and 17% gadoteridol (Raisch *et al.* 2014). Anaphylaxis after intravenous administration of fluorescein showed hypotension caused immediately

within three minutes of drug administration in many cases (Ha SO *et al.* 2014).

VACCINATION AND ANAPHYLAXIS

Vaccination is one of the main public health tools for preventing many infectious diseases. There is currently broad discussion on the issue of compulsory vaccination in the paediatric population, not only in the Czech Republic. In relation to anaphylaxis after vaccination in childhood, the incidence of severe allergic reactions after vaccination clearly is very low, approximately 0.5–1 anaphylaxis per 100,000 doses administered. Many anaphylactic reactions following vaccination are not caused by the vaccine itself, but contaminants in the vaccine, such as gelatine, egg protein and latex (Echeverria-Zudaire *et al.* 2015). Gruber *et al.* (2016) in their Communication publish available data on immunization of infants with a higher risk of allergy. The text suggests that routine vaccination does not increase the risk of developing atopic dermatitis, asthma or hay fever. The document further states that delaying the standard routine vaccination in children with increased risk of allergic reaction is not justified. Children having an allergic reaction to chicken eggs presented only by cutaneous symptoms should receive vaccination against measles, mumps and rubella according to standard protocol. In children with systemic allergic reaction to chicken eggs, vaccination is recommended with observation by a doctor capable of providing adequate therapy in case of a severe allergic reaction. The skin test cannot be used as a predictive for anaphylaxis, but can be used to identify the most likely components of past anaphylaxis. Bohlke *et al.* (2003) also examined the risk of anaphylaxis after vaccination of children and adolescents. In the reporting period 1991 – 1997, a total of more than 7 million doses of vaccine were applied. The authors identified five cases of anaphylaxis, which make the risk of anaphylaxis 0.65 cases / million doses. None of the episodes resulted in death. Vaccines that were administered before the anaphylactic episodes were generally given in combination and included measles-mumps-rubella, hepatitis B, diphtheria-tetanus, diphtheria-tetanus-pertussis, Haemophilus influenzae type B, and oral polio vaccine. One case of anaphylaxis followed the measles-mumps-rubella vaccine alone. At the site at which we reviewed additional allergy codes, we identified one case after 653,990 vaccine doses, for a risk of 1.53 cases / million doses.

A similar analysis was performed by McNeil *et al.* (2016), who analysed data from the Vaccine Safety Datalink in 2009–2011. They determined rates of anaphylaxis after vaccination in children and adults, identifying 33 confirmed vaccine-triggered anaphylaxis cases that occurred after 25,173,965 vaccine doses. The rate of anaphylaxis was 1.31 (95% CI, 0.90–1.84) per million vaccine doses. The incidence did not vary significantly by age, and there was a nonsignificant female predominance. Vaccine-specific rates included 1.35 (95% CI, 0.65–2.47) per million doses for inactivated trivalent influenza vaccine (ten cases, 7,434,628 doses given alone) and 1.83 (95% CI, 0.22-6.63) per million doses for inactivated monovalent influenza vaccine (two cases, 1,090,279 doses given alone). The onset of symptoms among cases was within 30 minutes (eight cases), 30 to less than 120 minutes (eight cases), two to less than four hours (ten cases), four to eight hours (two cases), the next day (one case), and not documented (four cases).

Anaphylaxis after vaccination against human papillomavirus was reported within the National Human Papillomavirus Vaccination Program in New South Wales in Australia, in which girls aged 12–26 were vaccinated with quadrivalent HPV vaccine. In total, 269,680 doses were administered under this program. Of the total number of doses, the authors observed seven patients with symptoms of anaphylaxis. This number corresponds to an anaphylaxis incidence of 2.6 cases per 100,000 doses (Brotherton *et al.* 2008).

From the above it is clear that vaccinations are very safe in relation to anaphylaxis and anaphylactic reactions are reported only in isolated cases. Deaths due to anaphylaxis initiated by vaccination are extremely rare.

LABORATORY DIAGNOSIS

Anaphylaxis is primarily diagnosed clinically. From the laboratory tests, determining tryptase level is available. Tryptase is an enzyme that is released together with other mediators from mast cells upon their activation and is barely affected by tryptase from basophils. In anaphylaxis, mast cells are degranulated, causing their significant increase. Tryptase may not be detectable within 30 minutes from the development of anaphylaxis and peaks in one to two hours. The halftime of tryptase is short – about two hours – and returns to baseline within six to eight hours. European Resuscitation Guidelines recommend collecting a sample one to two hours after the development of anaphylaxis. Ideally, three blood samples should be taken: at the beginning of anaphylaxis, one to two hours after occurrence, and 24 hours later to detect basal levels of tryptase (Soar *et al.* 2010). Simons *et al.* (2015) state that blood sampling for the determination of tryptase in the range of 15 to 180 minutes from the onset of symptoms can promote determination of anaphylaxis, but not in all patients. Determination of tryptase in food-induced anaphylaxis may be preferable to determine the ratio (peak tryptase level divided by basal level), which has higher specificity and sensitivity (Wongkaewpothong *et al.* 2014). Patients with clinically expressed symptoms of anaphylaxis and normal serum tryptase levels may have other elevated inflammatory mediators, such as histamine, platelet activating factor (PAF), prostaglandin D2 (PGD2) and leucotriens E4 (LTE4). The pathophysiological processes of anaphylaxis also include activation of the kinin-kallikrein system with the subsequent

release of bradykinin and the activation of factor VII. Elevated levels of these factors correlate with the severity of anaphylaxis (Sala-Cunill *et al.* 2015).

CONCLUSION

Based on the published works, the incidence and prevalence of anaphylaxis is clearly increasing. The highest increase according to epidemiological studies was recorded in children under the age of five and the elderly population. The main risk factors include food, insect stings and medications. Regarding food-induced anaphylaxis, the association between the presence of galactose alpha 1,3-galactose in the blood of patients after consumption of red meat and anaphylaxis is noteworthy. Significant risk factors include concomitant use of ACE inhibitors and beta-blockers. Taking these two drug classes is one of the leading causes of the statistically significant increase in anaphylaxis in the elderly population. Conversely, anaphylaxis in children under five is associated with allergy to casein. A positive finding is the fact that vaccination is only rarely associated with the emergence of anaphylaxis. From this point of view, vaccination by all kind of vaccines remains very safe (Babela *et al.* 2017).

Anaphylaxis remains an interesting topic of research for many renowned experts, despite the well-mapped pathophysiological processes. This article has shown that there is still room for new studies that focus on new risk factors and laboratory diagnosis. Epinephrine has been the recommended first choice drug for three decades. In accordance with evidence-based medicine, there are indisputable data on its impact in averting pathophysiological processes directly threatening the patient's life. Yet today we are confronted with a situation where a patient with anaphylaxis was not administered epinephrine in a medical facility and consequently died. The task of public health is primarily to study the risk factors for anaphylaxis and to prepare and implement prevention programs targeted at vulnerable groups.

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