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PRACA POGLĄDOWA
REVIEW

Fatal outcome of anaphylaxis – triggers, cofactors, management, prevention and forensic aspects

Śmiertelny skutek anafilaksji – czynniki wyzwalające, kofaktory, postępowanie, zapobieganie i aspekty medyczno-sądowe

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ABSTRACT

Anaphylaxis is a life-threatening condition characterized by a rapid onset, requiring immediate intervention. It occurs through immunologic or non-immunologic mechanisms and can be triggered by various factors such as foods, medications or insect venoms. The spectrum of symptoms is broad, with skin, respiratory, and gastrointestinal symptoms being most commonly observed. Diagnosis relies on clinical criteria, with the primary treatment involving the intramuscular administration of adrenaline. Prevention involves avoiding triggers and if avoidance is not possible, desensitization should be considered. Deaths from anaphylactic shock are rare and often result from delayed or improper medical assistance and the absence of witnesses to summon help. It is estimated that around 1% of anaphylactic shock cases result in death. Deaths from intentional attempts to induce anaphylactic reactions through suicide are rare. Postmortem diagnosis presents a challenge due to the lack of specific changes, therefore it is essential to thoroughly assess the circumstances of death, medical history and exclude other potential causes. Identifying factors that may trigger an anaphylactic reaction, such as ingested foods or contact with allergens is crucial. A rapid and accurate diagnosis is key to avoid errors resulting from post-mortem processes. Histopathological examinations and the measurement of biochemical markers, such as tryptase and IgE levels, may be helpful in determining the cause of death.

KEYWORDS

allergy, anaphylaxis, hypersensitivity, forensics

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STRESZCZENIE

Anafilaksja to stan zagrażający życiu, charakteryzujący się szybkim przebiegiem i wymagający natychmiastowej interwencji. Zachodzi zarówno w mechanizmie immunologicznym, jak i nieimmunologicznym. Wywoływana jest przez różnorodne czynniki, takie jak pokarmy, leki czy jady owadów. Spektrum objawów jest bardzo szerokie; najczęściej obserwuje się objawy skórne, ze strony układu oddechowego oraz pokarmowego. Diagnostyka opiera się na kryteriach klinicznych, a głównym elementem leczenia jest domięśniowe podanie adrenaliny. Prewencja polega na unikaniu wyzwalaczy, a gdy nie jest to możliwe, należy rozważyć przeprowadzenie desensytyzacji. Zgony spowodowane wstrząsem anafilaktycznym są rzadkie i często wynikają z opóźnionej lub niewłaściwej pomocy medycznej oraz braku świadków, którzy mogliby wezwać pomoc. Szacuje się, że około 1% przypadków wstrząsu anafilaktycznego kończy się zgonem. Rzadko dochodzi do zgonu w wyniku samobójczych prób poprzez celowe wywołanie reakcji anafilaktycznej. Diagnostyka pośmiertna stanowi wyzwanie ze względu na brak specyficznych zmian, dlatego należy dokładnie ocenić okoliczności zgonu, historię medyczną oraz wykluczyć inne potencjalne przyczyny. Istotne jest zidentyfikowanie czynników mogących wywołać reakcję anafilaktyczną, takich jak spożyte pokarmy czy kontakt z alergenami. Kluczowa jest szybka i dokładna diagnostyka w celu uniknięcia błędów wynikających z procesów rozkładu ciała po śmierci. Badania histopatologiczne oraz oznaczenie markerów biochemicznych, takich jak poziomy tryptazy i IgE, mogą być pomocne w ustaleniu przyczyny zgonu.

SŁOWA KLUCZOWE

alergia, anafilaksja, nadwrażliwość, medycyna sądowa

INTRODUCTION

Numerous definitions of anaphylaxis have been proposed over time. Among the current ones, it is described as a severe or acute, generalized life-threatening reaction [1,2]. Additionally, longer definitions list typical symptoms or affected systems [3,4]. This term originates from ancient Greek and consists of two components: *ana* meaning opposite, and *phyl* meaning protection [5]. The first recorded case of death likely caused by the venom of stinging insects was presented in hieroglyphs found in ancient Egypt. This phenomenon was also recognized in ancient Greece and China, primarily of food origin. In the 18th and 19th centuries, case reports emerged and animal studies began [6]. A breakthrough in understanding the pathomechanism of anaphylaxis came with the research of Richet and Portier, initially conducted on guinea pigs and pigeons, and later on dogs. They observed that the first dose of toxin extracted from jellyfish and sea anemones was well tolerated by animals, while subsequent doses were often fatal. Richet continued his research independently and was awarded the Nobel Prize in 1913 for his work [7].

It is estimated that globally anaphylaxis occurs at a rate of 50–112 episodes per 100,000 people per year with the lifetime risk of experiencing anaphylaxis being 0.3–0.5%. These figures vary depending on the authors, and differences are observed depending on specific regions of the world [8]. In recent years, there has been a global increase in hospital admissions due to anaphylaxis [9].

Anaphylaxis is divided into immunologic and non-immunologic types [10]. The former represents a type 1 hypersensitivity reaction, where IgE antibodies play a crucial role by binding to the antigen. Subsequently, IgE binds to FcεRI receptors located on effector cells such as mast cells, basophils, monocytes, neutrophils, and platelets. This leads to the release of inflammatory mediators and cytokines, primarily histamine but also tryptase, carboxypeptidase A, and proteoglycans. These mediators are responsible for increasing vascular permeability and dilating blood vessels, as well as inducing smooth muscle contraction in the bronchi, uterus, and gastrointestinal tract [11]. Additionally, vasodilation and increased vascular permeability result from the production of nitric oxide by endothelial cells, which occurs due to the activation of endothelial nitric oxide synthase (eNOS) by histamine and the platelet activating factor (PAF) [12]. As a result of the described mechanisms, anaphylactic shock or biphasic anaphylaxis may occur. Anaphylactic shock occurs as result of a decrease in arterial blood pressure caused by the vasodilatory effects of inflammatory mediators. However, in biphasic anaphylaxis, there is a recurrence of symptoms meeting the criteria for anaphylaxis within 1 to 72 hours after the cessation of symptoms from the initial phase [13]. The release of inflammatory mediators by effector cells as a consequence of their direct damage occurs in a non-immunologic mechanism. This mechanism is independent of IgE [14]. Currently, such a reaction is referred to as non-immune anaphylaxis, previously known as an anaphylactoid reaction or pseudoanaphylaxis. Severity grading systems for acute allergic reactions have been introduced, classifying anaphylaxis based on the number of affected systems and the severity of symptoms. Depending on the authors, these systems are usually classified into four or five degrees [15,16].

DISCUSSION

Triggers and cofactors

The triggers can vary significantly depending on factors such as the age group, dietary preferences or the presence of plants and animals in a particular geographical area [17]. The most common triggers are presented in Table 1, divided into groups. Epidemiological data indicate that foods are the most frequent cause of anaphylaxis worldwide. They also account for the majority of cases in the pediatric population. In adults, however, medications and insect venoms are the leading causes. According to data from the European Anaphylaxis Registry and a study conducted in Germany, Austria, and Switzerland, food-induced anaphylaxis (FID) occurs most frequently in children after consuming peanuts, cow's milk, chicken eggs, hazelnuts and fish, while in adults, it occurs after consuming wheat, soy, celery and shellfish [18,19]. There is variation in triggers in the pediatric population depending on the age group, which is attributed to differences in diet according to age [20]. In most countries, the main food factors are the same, but there are exceptions. For example, in Australia, anaphylaxis as a consequence of seafood consumption is more common than in other countries [21].

Table I. Most common triggers of anaphylaxis, divided into groups*

Food	Drugs	Venoms
• Children	antibiotics	wasp
peanuts	monoclonal antibodies	bee
cow's milk	NSAIDs and acetaminophen	hornet
cashews	intraoperative agents	fire ant
chicken eggs	chemotherapy agents	
• Adults		
wheat flour		
shellfish		
hazelnuts		
soy		

*Based on: Dölle-Bierke S., Höfer V., Francuzik W., Näher A.F., Bilo M.B., Cichocka-Jarosz E. et al. *Food-induced anaphylaxis: data from the European Anaphylaxis Registry*. J. Allergy Clin. Immunol. Pract. 2023; 11(7): 2069–2079.e7, doi: 10.1016/j.jaip.2023.03.026; Yu R.J., Krantz M.S., Phillips E.J., Stone C.A. Jr. *Emerging causes of drug-induced anaphylaxis: a review of anaphylaxis-associated reports in the FDA Adverse Event Reporting System (FAERS)*. J. Allergy Clin. Immunol. Pract. 2021; 9(2): 819–829.e2, doi: 10.1016/j.jaip.2020.09.021; Jares E.J., Cardona V., Gómez R.M., Bernstein J.A., Rosario Filho N.A., Cherrez-Ojeda I. et al. *Latin American anaphylaxis registry*. World Allergy Organ. J. 2023; 16(2): 100748, doi: 10.1016/j.waojou.2023.100748; Bilò B.M., Bonifazi F. *Epidemiology of insect-venom anaphylaxis*. Curr. Opin. Allergy Clin. Immunol. 2008; 8(4): 330–337, doi: 10.1097/ACI.0b013e32830638c5.

Medications constitute a broad category of triggers. The frequency of drug-induced anaphylaxis increases with age, possibly owing to polypharmacy in the elderly population [22]. Analysis of cases reported to the FDA from 1999 to 2019 indicates that antibiotics is the most common group of drugs causing anaphylaxis, followed by monoclonal antibodies and non-steroidal anti-inflammatory drugs (NSAIDs) [23]. In children, reactions are most commonly observed after cephalosporins, penicillin, analgesics, and immunotherapy [20]. Depending on the field of medicine, different triggers are present. In gynecology, the main threat to patients is antibiotics used, for example, in the prevention of group B Streptococcus (GBS) infections. On the other hand, fields where monoclonal antibodies are frequently used include oncology, rheumatology, and gastroenterology [24]. Also, anaphylaxis associated with medications may be triggered not only by the active substance itself but by additives such as stabilizers, preservatives, solubilizers, dyes and contaminants found in them [25,26].

Cases of anaphylaxis due to the administration of contrast agents are described in the literature. Such complications most often occur after the administration of radiocontrast agents and less frequently after X-ray and MRI contrast media [27,28]. Vaccines are a controversial factor that can lead to anaphylaxis. The risk of such a complication is 1.31 per 1 million vaccine doses, making it an extremely rare occurrence. Post-vaccination complications usually manifest as self-limiting local changes rather than systemic reactions [29]. Iatrogenic anaphylaxis can also be caused by latex, which is used in items such as gloves worn by healthcare workers [30].

Another factor that can lead to anaphylaxis is insect venoms and bites. The frequency of anaphylaxis due to this cause varies depending on the geographical location, climate, and season. In Europe, the most

common causes from this category are wasps, bees, and hornets [18,20]. Nonetheless, according to data from the Health Insurance Review and Assessment (HIRA) in South Korea, bees are the most common insect responsible for anaphylaxis in that country [31]. Fire ants pose a threat in many countries, including the United States of America (USA), Latin American countries, or China. Their bites are very painful, and in individuals with hypersensitivity, they can lead to anaphylaxis [32,33]. Additionally, frequent exposure to insect venoms has been shown to sensitize individuals to them. Studies conducted on beekeepers have shown that the risk varies depending on the number of stings per year [34]. An increase in the frequency of hypersensitivity to insect venoms has been observed among firefighters and forest workers, possibly because of their exposure to insects during work [35,36].

Nonetheless, it is not always possible to determine the causative factor. Therefore, the concept of idiopathic anaphylaxis has been introduced. This phenomenon may result from the presence of hidden allergens in food, which may be present as a consequence of cross--contamination during production and may not have been included on the label [37,38,39].

Another crucial aspect is the presence of cofactors. They can exacerbate the reaction to the allergen and cause the dose necessary to trigger anaphylaxis to be much lower than in the absence of a cofactor [40]. The best-known cofactors include NSAIDs, physical exertion, and alcohol [41], but also stress, infections, dehydration, and fatigue [42,43]. In children, physical exertion and infections are predominant cofactors, while in adults, medications and alcohol are more common [44]. Exercise-induced anaphylaxis (EIAn) refers to anaphylaxis triggered by physical exercises with a subcategory known as food-dependent exercise-induced anaphylaxis (FDEIAn). FDEIAn occurs when a patient consumes an allergen and subsequently engages in physical exercise [45,46].

Anaphylaxis occurs in patients of various ages, however, through clinical and population data analysis, researchers have identified certain groups characterized by an increased susceptibility to anaphylaxis. It is undisputed that a history of anaphylaxis is a risk factor for subsequent episodes. Patients with asthma and allergies are also at higher risk [47]. Mastocytosis is a condition characterized by the accumulation of defective mast cells. Depending on the location of the accumulation, it is distinguished as cutaneous mastocytosis or systemic mastocytosis. The risk of anaphylaxis in individuals affected by this condition is higher than in the general population, with a hymenoptera sting being the most common trigger for such patients [48,49].

A group of patients has been identified in whom anaphylaxis may have a significantly worse course and be associated with higher mortality. This group includes older individuals with respiratory and cardiovascular diseases. Some researchers suggest that anaphylaxis tends to have a severe course more often in men, but there are also data indicating that there are no statistically significant differences in this regard. Additionally, anaphylaxis triggered by food or medication may be more dangerous than in the case of other triggers [50,51,52,53,54].

Diagnosis, management and prevention

According to definitions, anaphylaxis is an acute reaction, hence symptoms can appear within minutes. In the case of biphasic anaphylaxis, there is a recurrence of symptoms (2nd phase) within 1––72 hours after the end of the first phase [13]. Also, anaphylaxis is defined as a generalized reaction, thus symptoms should be expected from multiple systems in patients. Most patients experience skin symptoms such as itchiness, hives, flushing, and swelling. There may also be swelling of the tongue or throat [55]. Anaphylaxis leads to airway obstruction, which explains patients reporting a feeling of breathlessness that can cause anxiety. Wheezing and stridor are also observed [56]. Among cardiovascular parameters, indicators characteristic of shock are observed, namely hypotension and tachycardia. Elevated histamine levels not only cause blood vessel dilation but can also cause arrhythmias and atrioventricular conduction blocks [57]. In patients with coronary artery disease, a decrease in coronary blood flow is observed. Low blood pressure leads to reduced oxygen distribution to tissues, resulting in symptoms such as consciousness disorders [58].

Symptoms vary depending on the trigger that caused the anaphylaxis. In the case of food etiology, symptoms appear in most patients within 1–3 hours of exposure. In FIA, symptoms predominantly affect the respiratory, gastrointestinal, and skin systems. Cardiovascular symptoms such as hypotension are less common. Patients report difficulty breathing, wheezing, nausea, vomiting, hives, itching, and swelling [59]. In the differential diagnosis, it is essential to consider diseases whose course may be deceptively similar, including asthma, syncope, panic attacks, acute generalized urticaria, cardiovascular and neurological diseases. Differential diagnosis should also consider non-organic causes such as vocal cord dysfunction or hyperventilation. In the case of shock symptoms, differential diagnosis should be conducted for other types of shock [1].

The definitions of anaphylaxis indicate that it is a life--threatening condition. Its course can be very dynamic and associated with dramatic consequences for the health and life of the patient. Therefore, early recognition and appropriate treatment are crucial.

Diagnosis is made based on clinical criteria. According to the criteria proposed by the National Institute of Allergy and Infectious Diseases (NIAID) in 2006, anaphylaxis is highly likely to occur when one of three criteria is met, including a sudden onset involving skin symptoms, breathing difficulties, and hypotension. Diagnosis can also be made when a patient experiences at least two symptoms such as skin, respiratory, or gastrointestinal symptoms after exposure to a known allergen. A significant arterial blood pressure drop after exposure to a known allergen without other symptoms also indicates anaphylaxis [60,61]. A unique group of patients is newborns and young children, as recognizing the onset of anaphylaxis can be challenging in their case. In this group, respiratory symptoms are more common, while skin symptoms are much rarer. Differential diagnosis is also important as the symptoms of anaphylaxis can resemble other conditions typical in such young patients [24].

Additionally, some guidelines recommend measuring serum tryptase levels. It is important that measuring this parameter does not delay treatment. According to the European Academy of Allergy and Clinical Immunology Anaphylaxis (EAACI), blood should be drawn 0.5–2.5 hours after the onset of symptoms, and then 24 hours after the symptoms have subsided to determine the baseline tryptase level [2,62,63].

If possible, the trigger should be promptly removed, for example by discontinuing the administration of the medication or food allergen. The basis of treatment is the intramuscular administration of adrenaline into the mid anterolateral thigh at a dose of 0.01 mg/kg of body weight. The dose may be repeated every 5––15 minutes if symptoms persist, up to a maximum total dose of 0.5 mg [64]. The medication can be self--administered by patients, ideally using autoinjectors, after appropriate training [65]. Adrenaline is the main drug used in anaphylaxis, and additional medications are added depending on the predominant symptoms presented by the patient. Hypotension, stridor, and wheezing are most commonly observed. Hence, consideration should be given to expanding treatment to include high-flow oxygen therapy, establishing intravenous access for fluid therapy, administering salbutamol via oxygen-driven nebulization at a dose of 2.5–5 mg, and administering methylprednisolone at a dose of 1 mg/kg of body weight [1,2,4,66]. When the patient's condition improves, observation should continue for 12–24 hours as there is a risk of biphasic anaphylaxis [67]. After this time, if there are no indications for further hospitalization, the patient may be discharged from the hospital ward.

A patient with a history of anaphylaxis should be appropriately trained to recognize symptoms and self--administer drugs; additionally, further diagnostics and treatment should be carried out under the supervision of an allergist or immunologist. It is recommended that patients carry two epinephrine auto-injectors (EAI). However, this is not always followed, mainly owing to financial reasons [68]. In Korea, the frequency of anaphylaxis is higher in rural areas, yet EAI are more frequently purchased by urban residents [31].

After an episode of anaphylaxis, it is very important to determine the cause. To identify triggers, it is possible to perform skin tests, which involve introducing an allergen into the skin. Nevertheless, this form of diagnosis cannot be conducted on patients who are taking antihistamines and cannot discontinue them before the test, as well as in cases of eczema, dermographism, or urticaria. Additionally, for patients with a history of severe anaphylaxis, it is recommended to start skin testing with diluted extracts, and these tests should be performed no earlier than 4–6 weeks after the anaphylactic event [69]. Generally, a food challenge is not performed in patients who have experienced severe anaphylaxis [70]. To avoid exposing the patient to the allergen during diagnostics, one can conduct tests such as a basophil activation test (BAT test). This is an ex vivo test that assesses the degranulation of basophils after exposure to the allergen [71]. Another tool that allows the identification of triggers is the IgE specific test. This is an in vitro test used, among others, in the diagnosis of drug hypersensitivity [72].

The primary aspect of prevention is avoiding triggers. However, this is not always possible, and in such cases, desensitization should be considered. Desensitization involves gradually administering increasing doses of the allergen to induce tolerance in the body [68]. Administration of the allergen can be done subcutaneously, sublingually, orally, or transdermally. This procedure is particularly useful in the treatment of allergies to drugs, insect venom, and certain food allergens [73,74,75]. Adverse reactions are rare and mostly include mild, local discomfort. Nonetheless, it is worth noting that desensitization itself may rarely trigger anaphylaxis [76].

Forensic aspects and post-mortem diagnosis

Deaths due to severe anaphylactic shock are rare. They typically occur in cases where medical assistance is provided too late or improperly, or when the event happens without witnesses who could call for help. It is estimated that approximately 1% of all cases of anaphylactic shock result in death [77,78,79,80]. The majority of these deaths are accidents. Rare cases have also been described where individuals deliberately induced anaphylactic shock as a suicide attempt by knowingly consuming food products to which they were allergic [81,82]. Death usually occurs resulting from the rapid development

of an inflammatory reaction, resulting in vasodilation, hypotension and shock. Mediators of inflammation also increase vascular permeability, leading to fluid leakage into the third space, predisposing to edema, particularly in the mucous membranes of the airways, causing significant narrowing [83,84]. Additionally, the time and quality of medical assistance provided can determine the time of death, which can range from minutes to up to 3 days after the anaphylactic reaction [85].

Postmortem diagnosis in cases of anaphylactic deaths presents significant diagnostic challenges, mainly owing to the lack of typical and specific changes in such cases. Therefore, the differential diagnosis should be based on a holistic assessment of the entire case and the exclusion of other potential causes of death. Furthermore, it should be conducted as soon as possible after death to avoid the effects of autolysis and decomposition on obscuring the signs of anaphylaxis [83].

An important aspect is the assessment of the body and the location where it was found [86]. It is crucial to search for factors that may trigger anaphylactic reactions. They can include food products (such as fruits, nuts, seafood) and medications. It is important to pay attention to the presence of partially consumed food or medication packaging near the body, which indirectly indicates their ingestion and the potential for triggering anaphylaxis [82]. Additionally, during external body examinations at the discovery site, one should look for skin marks resembling bites or stings, as animal venoms are also common triggers for anaphylactic reactions [82,87].

Valuable information about the incident can also be obtained by interviewing witnesses, if they were present. The interview should focus on the presence of typical symptoms of anaphylactic shock [86]. In cases where the death occurred unwitnessed, establishing the circumstances and cause of death becomes challenging. Analyzing the deceased's past and medical records provides valuable information. Particularly important are details regarding allergies. In cases of suspected suicides, it is also crucial to search for farewell letters [82].

In cases of deaths due to anaphylactic shock, autopsy findings are often inconclusive. Most commonly, changes are observed in the lungs, such as edema and congestion. Additionally, the lungs may show signs of acute distension and the presence of subpleural petechiae. Other changes described in such cases include the presence of mucus in the airways with swelling of their walls, indicators of brain edema, passive congestion of other internal organs, and the presence of liquid blood [84,85,87,88,89,90]. The majority of these findings are nonspecific, meaning they may also occur in cases of deaths from other causes. Furthermore, the mentioned changes may also be absent in cases of anaphylaxis [83]. It should also be noted that some changes in the lungs occurring in cases of anaphylaxis may also result from resuscitative efforts [89].

It is also essential to obtain tissue samples from organs for histopathological examination. Tissue samples should primarily be taken from the lungs, spleen, and respiratory tract. Samples should also be collected from other organs to rule out alternative causes of death [82]. The microscopic evaluation of lung tissue samples typically reveals signs of edema, features of acute distension, and hemorrhages into the alveolar spaces. In the spleen, intensified infiltrations of eosinophils and mast cells are usually observed. Other observed changes include vascular dilation, inflammatory cell infiltration, and signs of edema [88,89,90,91]. However, in most cases, they are non--specific changes that may also occur in other cases [89].

In cases of tissue degradation, histopathological examination of bone marrow can also be performed [92]. Additionally, immunohistochemical examination using antibodies against tryptase is necessary to assess mast cell degranulation [87,93]. The anti-CD117 antibody can also be used to visualize mast cells [81,91,93]. Importantly, such studies can even be conducted in moderately advanced stages of decomposition [88].

Determining the levels of biochemical markers in the blood can provide key information for establishing anaphylactic shock as the cause of death. Histamine plays a significant role in the mechanism of anaphylaxis, but as a consequence of its short half-life, it is not used in post-mortem diagnosis. Another important marker is tryptase, a protein mainly found in mast cells [94]. It has a longer half-life than histamine, approximately 2 hours, and its level determination is utilized in the forensic diagnosis of anaphylactic shock [95,96,97]. The reference values for the post-mortem determination of tryptase levels remain a subject of discussion in the literature. Nonetheless, the cut-off levels for anaphylaxis are suggested to be approximately in the range of 30––60 μg/L [87,98,99,100,101]. It is crucial to interpret the result correctly, considering the post-mortem interval. This is because of the dynamic balance between the tryptase release from cells due to cell breakdown and the processes of its degradation [83]. Factors triggering anaphylaxis also affect changes in tryptase levels. It is suggested that higher levels occur when the reaction is triggered by venom or drugs compared to when it is triggered by food ingestion [83]. Additionally, the sampling technique influences the result. Blood should be drawn from peripheral vessels. Samples taken from the heart chambers show higher levels owing to the penetration of tryptase released from deteriorating mast cells in surrounding

tissues [77,101,102]. Moreover, the use of opioids leads to increased tryptase levels [103]. Importantly, the result should also be interpreted in the context of the patient's medical history since elevated tryptase levels may occur due to trauma, resuscitation efforts, heart disease or asthma [77]. In cases where blood sampling is not possible, tryptase determination can also be attempted from pericardial fluid [104].

The determination of elevated levels of immunoglobulin E (IgE) also serves as an auxiliary criterion in the post-mortem diagnosis of anaphylactic shock. It is important to remember that elevated IgE levels only indicate immunization and exposure to a specific allergen before death [83]. Studies have shown that the post-mortem assessment of IgE levels can be conducted using blood from peripheral vessels and pericardial fluid [105]. The threshold levels for this parameter remain a subject of discussion and exhibit significant variability, requiring evaluation in the context of all materials collected during the diagnostics and investigation [106].

An important aspect related to anaphylaxis is Kounis syndrome, resulting from a coronary artery spasm mediated by inflammatory mediators released by activated mast cells. Its diagnosis requires the histopathological evaluation of coronary vessels to visualize mast cell infiltration and eosinophilia within the arterial wall and adventitia [107,108,109,110,111, 112,113,114,115,116]. Other factors potentially leading to death should also be excluded. To achieve this, toxicological testing should be performed to investigate the possibility of xenobiotic poisoning.

CONCLUSIONS

Anaphylaxis is a serious condition that requires prompt action and appropriate intervention. There is a wide spectrum of triggers for anaphylaxis including foods, medications and insect venoms, which necessitates the consideration of individual risk factors and diagnostic capabilities. Early recognition and proper management are crucial for patient survival, with emphasis on the immediate administration of epinephrine. Diagnosing and assessing anaphylaxis post-mortem pose challenges because typical and specific changes do not always occur and the approach must consider various factors such as the circumstances of death, medical history, toxicological and biochemical investigations. The main biomarkers used in diagnosing anaphylaxis include tryptase and IgE. Interpretation of the results must be carefully conducted, taking into account the circumstances of death. A comprehensive approach to diagnosing, treating and preventing anaphylaxis is necessary, as well as in investigating fatal cases. The continuous improvement of diagnostic methods and clinical management is important to enhance treatment outcomes and understand the mechanisms and risk factors associated with this serious allergic reaction.

Author's contribution

Study design – M. Kycler
Data collection – M. Kycler, S. Rzepczyk, P. Świderski
Manuscript preparation – M. Kycler, S. Rzepczyk
Literature research – M. Kycler, S. Rzepczyk, P. Świderski
Final approval of the version to be published – M. Kycler, P. Świderski

REFERENCES

1. Cardona V., Ansotegui I.J., Ebisawa M., El-Gamal Y., Fernandez Rivas M., Fineman S. et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ. J. 2020; 13(10): 100472, doi: 10.1016/j.waojou.2020.100472.

2. Muraro A., Worm M., Alviani C., Cardona V., DunnGalvin A., Garvey L.H. et al. EAACI guidelines: Anaphylaxis (2021 update). Allergy 2022; 77(2): 357–377, doi: 10.1111/all.15032.

3. ICD-11 for Mortality and Morbidity Statistics, 4A84 Anaphylaxis [online] https://icd.who.int/browse/2024-01/mms/en#1868068711 [accessed on 15 March 2024].

4. ASCIA Guidelines – Acute Management of Anaphylaxis. Ascia [online], updated July 2024, https://www.allergy.org.au/hp/papers/acute-management-of-anaphylaxis-guidelines [accessed on 15 March 2024].

5. English-Greek Dictionary: A Vocabulary of the Attic Language. S.C. Woodhouse [ed.]. Routledge, 2020, p. 577 (entry *opposite*), p. 653 (entry *protection*).

6. Ring J., Behrendt H., de Weck A. History and classification of anaphylaxis. Chem. Immunol. Allergy. 2010; 95: 1–11, doi: 10.1159/000315934.

7. Cohen S.G., Zelaya-Quesada M. Portier, Richet, and the discovery of anaphylaxis: a centennial. J. Allergy Clin. Immunol. 2002; 110(2): 331–336, doi: 10.1016/S0091-6749(02)70118-8.

8. Tejedor Alonso M.A., Moro Moro M., Múgica García M.V. Epidemiology of anaphylaxis. Clin. Exp. Allergy 2015; 45(6): 1027–1039, doi: 10.1111/cea.12418.

9. Turner P.J., Campbell D.E., Motosue M.S., Campbell R.L. Global trends in anaphylaxis epidemiology and clinical implications. J. Allergy Clin. Immunol. Pract. 2020; 8(4): 1169–1176, doi: 10.1016/j.jaip.2019.11.027.

10. Johansson S.G.O., Bieber T., Dahl R., Friedmann P.S., Lanier B.Q., Lockey R.F. et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J. Allergy Clin. Immunol. 2004; 113(5): 832–836, doi: 10.1016/j.jaci.2003.12.591.

11. Shulpekova Y.O., Nechaev V.M., Popova I.R., Deeva T.A., Kopylov A.T., Malsagova K.A. et al. Food intolerance: the role of histamine. Nutrients 2021; 13(9): 3207, doi: 10.3390/nu13093207.

12. Nguyen S.M.T., Rupprecht C.P., Haque A., Pattanaik D., Yusin J., Krishnaswamy G. Mechanisms governing anaphylaxis: inflammatory cells, mediators, endothelial gap junctions and beyond. Int. J. Mol. Sci. 2021; 22(15): 7785, doi: 10.3390/ijms22157785.

13. Mack D.P. Biphasic anaphylaxis: a systematic review of the literature. Allergy Asthma Clin. Immunol. 2014; 10(Suppl 1): A5, doi: 10.1186/1710-1492-10-S1-A5.

14. Reber L.L., Hernandez J.D., Galli S.J. The pathophysiology of anaphylaxis. J. Allergy Clin. Immunol. 2017; 140(2): 335–348, doi: 10.1016/j.jaci.2017.06.003.
15. Dribin T.E., Schnadower D., Spergel J.M., Campbell R.L., Shaker M., Neuman M.I. et al. Severity grading system for acute allergic reactions: A multidisciplinary Delphi study. J. Allergy Clin. Immunol. 2021; 148(1): 173––181, doi: 10.1016/j.jaci.2021.01.003.
16. Sánchez-Borges M., Ansotegui I., Cox L. World Allergy Organization grading system for systemic allergic reactions: it is time to speak the same language when it comes to allergic reactions. Curr. Treat. Options Allergy 2019; 6(4): 388–395, doi: 10.1007/s40521-019-00229-8.
17. Cianferoni A., Muraro A. Food-induced anaphylaxis. Immunol. Allergy Clin. North Am. 2012; 32(1): 165–195, doi: 10.1016/j.iac.2011.10.002.
18. Worm M., Eckermann O., Dölle S., Aberer W., Beyer K., Hawranek T. et al. Triggers and treatment of anaphylaxis. Dtsch. Ärztebl. Int. 2014; 111(21): 367–375, doi: 10.3238/arztebl.2014.0367.
19. Dölle-Bierke S., Höfer V., Francuzik W., Näher A.F., Bilo M.B., Cichocka-Jarosz E. et al. Food-induced anaphylaxis: data from the European Anaphylaxis Registry. J. Allergy Clin. Immunol. Pract. 2023; 11(7): 2069––2079.e7, doi: 10.1016/j.jaip.2023.03.026.
20. Grabenhenrich L.B., Dölle S., Moneret-Vautrin A., Köhli A., Lange L., Spindler T. et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. J. Allergy Clin. Immunol. 2016; 137(4): 1128––1137.e1, doi: 10.1016/j.jaci.2015.11.015.
21. Mullins R.J., Wainstein B.K., Barnes E.H., Liew W.K., Campbell D.E. Increases in anaphylaxis fatalities in Australia from 1997 to 2013. Clin. Exp. Allergy 2016; 46(8): 1099–1110, doi: 10.1111/cea.12748.
22. Jerschow E., Lin R.Y., Scaperotti M.M., McGinn A.P. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. J. Allergy Clin. Immunol. 2014; 134(6): 1318–1328.e7, doi: 10.1016/j.jaci.2014.08.018.
23. Yu R.J., Krantz M.S., Phillips E.J., Stone C.A. Jr. Emerging causes of drug-induced anaphylaxis: A review of anaphylaxis-associated reports in the FDA Adverse Event Reporting System (FAERS). J. Allergy Clin. Immunol. Pract. 2021; 9(2): 819–829.e2, doi: 10.1016/j.jaip.2020.09.021.
24. Błażowski Ł., Rogala B., Cichocka-Jarosz E., Kruszewski J., Kuna P., Samoliński B. Anafilaksja: sytuacje szczególne. Alergol. Pol./Pol. J. Allergol. 2014; 1(Suppl 1): S1–10, doi: 10.1016/j.alergo.2014.10.001.
25. Kishimoto T.K., Viswanathan K., Ganguly T., Elankumaran S., Smith S., Pelzer K. et al. Contaminated heparin associated with adverse clinical events and activation of the contact system. N. Engl. J. Med. 2008; 358(23): 2457–2467, doi: 10.1056/NEJMoa0803200.
26. Pfützner W. Anaphylaxis to drug excipients. Allergo J. Int. 2022; 31(5): 137–140, doi: 10.1007/s40629-022-00214-9.
27. Zhao Y., Sun S., Li X., Ma X., Tang H., Sun L. et al. Drug-induced anaphylaxis in China: a 10 year retrospective analysis of the Beijing Pharmacovigilance Database. Int. J. Clin. Pharm. 2018; 40(5): 1349–1358, doi: 10.1007/s11096-017-0535-2.
28. Fukushima Y., Suto T., Hirasawa H., Tsushima Y. Contrast-induced anaphylaxis: does it occur in the medical environment and is it being responded to appropriately? Jpn. J. Radiol. 2023; 41(9): 1022–1028, doi: 10.1007/s11604-023-01427-w.
29. McNeil M.M., DeStefano F. Vaccine-associated hypersensitivity. J. Allergy Clin. Immunol. 2018; 141(2): 463–472, doi: 10.1016/j.jaci.2017.12.971.
30. Parisi C.A.S., Kelly K.J., Ansotegui I.J., Gonzalez-Díaz S.N., Bilò M.B., Cardona V. et al. Update on latex allergy: New insights into an old problem. World Allergy Organ. J. 2021; 14(8): 100569, doi: 10.1016/j.waojou.2021.100569.
31. Cho H., Kwon J.W. Prevalence of anaphylaxis and prescription rates of epinephrine auto-injectors in urban and rural areas of Korea. Korean J. Intern. Med. 2019; 34(3): 643–650, doi: 10.3904/kjim.2018.094.
32. Kruse B., Anderson J., Simon L.V. Fire ant bites. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024, http://www.ncbi.nlm.nih.gov/books/NBK470576/ [accessed on 15 March 2024].
33. Jares E.J., Cardona V., Gómez R.M., Bernstein J.A., Rosario Filho N.A., Cherrez-Ojeda I. et al. Latin American anaphylaxis registry. World Allergy Organ. J. 2023; 16(2): 100748, doi: 10.1016/j.waojou.2023.100748.
34. Hızlı Demirkale Z., Yücel E., Sipahi Çimen S., Süleyman A., Özdemir C., Kara A. et al. Venom allergy and knowledge about anaphylaxis among beekeepers and their families. Allergol. Immunopathol. (Madr.) 2020; 48(6): 640–645, doi: 10.1016/j.aller.2020.01.008.
35. Soriano-Gomis V., Cabrera-Beyrouti R., Serrano-Delgado P., Jimenez-–Rodriguez T.W., Gómez M.B., Fernandez-Sanchez J. Epidemiology of Hymenoptera venom allergy in the Valencia Fire Brigade (Spain). J. Allergy Clin. Immunol. Pract. 2021; 9(2): 1037–1038.e2, doi: 10.1016/j.jaip.2020.09.038.
36. Ricciardi L., Papia F., Cataldo G., Giorgianni M., Spatari G., Gangemi S. Hymenoptera sting reactions in southern Italy forestry workers: our experience compared to reported data. Clin. Mol. Allergy 2018; 16: 8, doi: 10.1186/s12948-018-0087-6.
37. Skypala I.J. Food-induced anaphylaxis: role of hidden allergens and cofactors. Front. Immunol. 2019; 10: 673, doi: 10.3389/fimmu.2019.00673.
38. Añíbarro B., Seoane F.J., Múgica M.V. Involvement of hidden allergens in food allergic reactions. J. Investig. Allergol. Clin. Immunol. 2007; 17(3): 168–172.
39. Guo C., Greenberger P.A. Idiopathic anaphylaxis. Allergy Asthma Proc. 2019; 40(6): 457–461, doi: 10.2500/aap.2019.40.4271.
40. Wölbing F., Fischer J., Köberle M., Kaesler S., Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. Allergy 2013; 68(9): 1085–1092, doi: 10.1111/all.12193.
41. Cardona V., Luengo O., Garriga T., Labrador-Horrillo M., Sala-Cunill A., Izquierdo A. et al. Co-factor-enhanced food allergy. Allergy 2012; 67(10): 1316–1318, doi: 10.1111/j.1398-9995.2012.02877.x.
42. Versluis A., van Os-Medendorp H., Blom W.M., Michelsen-Huisman A.D., Castenmiller J.J.M., Noteborn H.P.J.M. et al. Potential cofactors in accidental food allergic reactions are frequently present but may not influence severity and occurrence. Clin. Exp. Allergy 2019; 49(2): 207–215, doi: 10.1111/cea.13282.
43. Poziomkowska-Gęsicka I., Kostrzewska M., Kurek M. Comorbidities and cofactors of anaphylaxis in patients with moderate to severe anaphylaxis. Analysis of data from the Anaphylaxis Registry for West Pomerania Province, Poland. Int. J. Environ. Res. Public Health 2021; 18(1): 333, doi: 10.3390/ijerph18010333.
44. Shin M. Food allergies and food-induced anaphylaxis: role of cofactors. Clin. Exp. Pediatr. 2021; 64(8): 393–399, doi: 10.3345/cep.2020.01088.
45. Feldweg A.M. Exercise-induced anaphylaxis. Immunol. Allergy Clin. North Am. 2015; 35(2): 261–275, doi: 10.1016/j.iac.2015.01.005.
46. Minty B. Food-dependent exercise-induced anaphylaxis. Can. Fam. Physician 2017; 63(1): 42–43.
47. Turner P.J., Baumert J.L., Beyer K., Boyle R.J., Chan C.H., Clark A.T. et al. Can we identify patients at risk of life-threatening allergic reactions to food? Allergy 2016; 71(9): 1241–1255, doi: 10.1111/all.12924.
48. Schuch A., Brockow K. Mastocytosis and anaphylaxis. Immunol. Allergy Clin. North Am. 2017; 37(1): 153–164, doi: 10.1016/j.iac.2016.08.017.
49. Alvarez-Twose I., Matito A. Mastocytosis presenting as insect anaphylaxis: gender differences and natural history. Curr. Opin. Allergy Clin. Immunol. 2019; 19(5): 468–474, doi: 10.1097/ACI.0000000000000567.
50. Miller J.M., Forbes-Satter L. Risk factors for severe anaphylaxis in children. Pediatrics 2021; 148(Supplement 3): S9, doi: 10.1542/peds.2021-053843J.
51. Motosue M.S., Bellolio M.F., Van Houten H.K., Shah N.D., Campbell R.L. Risk factors for severe anaphylaxis in the United States. Ann. Allergy Asthma Immunol. 2017; 119(4): 356–361.e2, doi: 10.1016/j.anai.2017.07.014.
52. Kim S.Y., Kim M.H., Cho Y.J. Different clinical features of anaphylaxis according to cause and risk factors for severe reactions. Allergol. Int. 2018; 67(1): 96–102, doi: 10.1016/j.alit.2017.05.005.
53. Turner P.J., Gowland M.H., Sharma V., Ierodiakonou D., Harper N., Garcez T. et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. J. Allergy Clin. Immunol. 2015; 135(4): 956–963.e1, doi: 10.1016/j.jaci.2014.10.021.
54. Brown S.G., Stone S.F., Fatovich D.M., Burrows S.A., Holdgate A., Celenza A. et al. Anaphylaxis: clinical patterns, mediator release, and severity. J. Allergy Clin. Immunol. 2013; 132(5): 1141–1149.e5, doi: 10.1016/j.jaci.2013.06.015.
55. Limsuwan T, Demoly P. Acute symptoms of drug hypersensitivity (urticaria, angioedema, anaphylaxis, anaphylactic shock). Med. Clin. North Am. 2010; 94(4): 691–710, doi: 10.1016/j.mcna.2010.03.007.
56. Pitlick M.M., Volcheck G.W. Perioperative anaphylaxis. Immunol. Allergy Clin. North Am. 2022; 42(1): 145–159, doi: 10.1016/j.iac.2021.09.002.
57. Vigorito C., Poto S., Picotti G.B., Triggiani M., Marone G. Effect of activation of the H1 receptor on coronary hemodynamics in man. Circulation 1986; 73(6): 1175–1182, doi: 10.1161/01.CIR.73.6.1175.
58. Triggiani M., Patella V., Staiano R.I., Granata F., Marone G. Allergy and the cardiovascular system. Clin. Exp. Immunol. 2008; 153(Suppl 1): 7––11, doi: 10.1111/j.1365-2249.2008.03714.x.
59. Rudders S.A., Banerji A., Clark S., Camargo C.A. Jr. Age-related differences in the clinical presentation of food-induced anaphylaxis. J. Pediatr. 2011; 158(2): 326–328, doi: 10.1016/j.jpeds.2010.10.017.
60. Loprinzi Brauer C.E., Motosue M.S., Li J.T., Hagan J.B., Bellolio M.F., Lee S. et al. Prospective validation of the NIAID/FAAN criteria for emergency department diagnosis of anaphylaxis. J. Allergy Clin. Immunol. Pract. 2016; 4(6): 1220–1226, doi: 10.1016/j.jaip.2016.06.003.
61. Sampson H.A., Muñoz-Furlong A., Campbell R.L., Adkinson N.F. Jr., Bock S.A., Branum A. et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J. Allergy Clin. Immunol. 2006; 117(2): 391–397, doi: 10.1016/j.jaci.2005.12.1303.

62. Bonadonna P., Scaffidi L., Boni E. Tryptase values in anaphylaxis and insect allergy. Curr. Opin. Allergy Clin. Immunol. 2019; 19(5): 462–467, doi: 10.1097/ACI.0000000000000569.
63. Sala-Cunill A., Cardona V., Labrador-Horrillo M., Luengo O., Esteso O., Garriga T. et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int. Arch. Allergy Immunol. 2013; 160(2): 192–199, doi: 10.1159/000339749.
64. Pflipsen M.C., Vega Colon K.M. Anaphylaxis: recognition and management. Am. Fam. Physician 2020; 102(6): 355–362.
65. Dribin T.E., Waserman S., Turner P.J. Who needs epinephrine? Anaphylaxis, autoinjectors, and parachutes. J. Allergy Clin. Immunol. Pract. 2023; 11(4): 1036–1046, doi: 10.1016/j.jaip.2023.02.002.
66. Simons F.E., Ardusso L.R., Bilò M.B., El-Gamal Y.M., Ledford D.K., Ring J. et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ. J. 2011; 4(2): 13–37, doi: 10.1097/WOX.0b013e318211496c.
67. Lee S., Bellolio M.F., Hess E.P., Erwin P., Murad M.H., Campbell R.L. Time of onset and predictors of biphasic anaphylactic reactions: a systematic review and meta-analysis. J. Allergy Clin. Immunol. Pract. 2015; 3(3): 408–416.e1-2, doi: 10.1016/j.jaip.2014.12.010.
68. Fromer L. Prevention of anaphylaxis: the role of the epinephrine auto-injector. Am. J. Med. 2016; 129(12): 1244–1250, doi: 10.1016/j.amjmed.2016.07.018.
69. Heinzerling L., Mari A., Bergmann K.C., Bresciani M., Burbach G., Darsow U. et al. The skin prick test – European standards. Clin. Transl. Allergy 2013; 3(1): 3, doi: 10.1186/2045-7022-3-3.
70. Barbaud A., Garvey L.H., Torres M., Laguna J.J., Arcolaci A., Bonadonna P. et al. EAACI/ENDA position paper on drug provocation testing. Allergy 2024; 79(3): 565–579, doi: 10.1111/all.15996.
71. Briceno Noriega D., Teodorowicz M., Savelkoul H., Ruinemans-Koerts J. The basophil activation test for clinical management of food allergies: recent advances and future directions. J. Asthma Allergy 2021; 14: 1335–1348, doi: 10.2147/JAA.S237759.
72. National Clinical Guideline Centre (UK). Drug allergy: diagnosis and management of drug allergy in adults, children and young people. London: National Institute for Health and Care Excellence (NICE); 2014 Sep.
73. Hong D.I.C. Desensitization for allergic reactions to chemotherapy. Yonsei Med. J. 2019; 60(2): 119–125, doi: 10.3349/ymj.2019.60.2.119.
74. Kang S.Y., Seo J., Kang H.R. Desensitization for the prevention of drug hypersensitivity reactions. Korean J. Intern. Med. 2022; 37(2): 261–270, doi: 10.3904/kjim.2021.438.
75. Banini M., Salvestrini V., Vultaggio A., Perlato M., Mecheri V., Cerbai C. et al. Desensitization protocol for Cemiplimab-related infusion reaction in cutaneous squamous cell carcinoma: a case report and literature review. Curr. Oncol. 2023; 30(7): 6699–6707, doi: 10.3390/curroncol30070491.
76. Caminati M., Dama A.R., Djuric I., Montagni M., Schiappoli M., Ridolo E. et al. Incidence and risk factors for subcutaneous immunotherapy anaphylaxis: the optimization of safety. Expert Rev. Clin. Immunol. 2015; 11(2): 233–245, doi: 10.1586/1744666X.2015.988143.
77. Garland J., Ondruschka B., Da Broi U., Palmiere C., Tse R. Post mortem tryptase: A review of literature on its use, sampling and interpretation in the investigation of fatal anaphylaxis. Forensic Sci. Int. 2020; 314: 110415, doi: 10.1016/j.forsciint.2020.110415.
78. Turner P.J., Jerschow E., Umasunthar T., Lin R., Campbell D.E., Boyle R.J. Fatal anaphylaxis: mortality rate and risk factors. J. Allergy Clin. Immunol. Pract. 2017; 5(5): 1169–1178, doi: 10.1016/j.jaip.2017.06.031.
79. Liu F.C., Chiou H.J., Kuo C.F., Chung T.T., Yu H.P. Epidemiology of anaphylactic shock and its related mortality in hospital patients in Taiwan: A nationwide population-based study. Shock 2017; 48(5): 525–531, doi: 10.1097/SHK.0000000000000899.
80. Jeppesen A.N., Christiansen C.F., Frøslev T., Sørensen H.T. Hospitalization rates and prognosis of patients with anaphylactic shock in Denmark from 1995 through 2012. J. Allergy Clin. Immunol. 2016; 137(4): 1143–1147, doi: 10.1016/j.jaci.2015.10.027.
81. Sterzik V., Drendel V., Will M., Bohnert M. Suicide of a man with known allergy to fish protein by ingesting tinned fish. Forensic Sci. Int. 2012; 221(1–3): e4–6, doi: 10.1016/j.forsciint.2012.02.002.
82. Tambuzzi S., Gentile G., Boracchi M., Di Candia D., Bianchi R., Zoja R. Postmortem diagnostics of assumed suicidal food anaphylaxis in prison: a unique case of anaphylactic death due to peach ingestion. Forensic Sci. Med. Pathol. 2021; 17(3): 449–455, doi: 10.1007/s12024-021-00373-1.
83. Heldring N., Kahn L., Zilg B. Fatal anaphylactic shock: A review of postmortem biomarkers and diagnostics. Forensic Sci. Int. 2021; 323:110814, doi: 10.1016/j.forsciint.2021.110814.
84. Yilmaz R., Yuksekbas O., Erkol Z., Bulut E.R., Arslan M.N. Postmortem findings after anaphylactic reactions to drugs in Turkey. Am. J. Forensic Med. Pathol. 2009; 30(4): 346–349, doi: 10.1097/PAF.0b013e3181c0e7bb.
85. Shen Y., Li L., Grant J., Rubio A., Zhao Z., Zhang X. et al. Anaphylactic deaths in Maryland (United States) and Shanghai (China): A review of forensic autopsy cases from 2004 to 2006. Forensic Sci. Int. 2009; 186(1–3): 1–5, doi: 10.1016/j.forsciint.2008.12.007.
86. Da Broi U., Moreschi C. Post-mortem diagnosis of anaphylaxis: A difficult task in forensic medicine. Forensic Sci. Int. 2011; 204(1–3): 1–5, doi: 10.1016/j.forsciint.2010.04.039.
87. Esposito M., Montana A., Liberto A., Filetti V., Nunno N.D., Amico F. et al. Anaphylactic death: A new forensic workflow for diagnosis. Healthcare 2021; 9(2): 117, doi: 10.3390/healthcare9020117.
88. Radheshi E., Reggiani Bonetti L., Confortini A., Silingardi E., Palmiere C. Postmortem diagnosis of anaphylaxis in presence of decompositional changes. J. Forensic Leg. Med. 2016; 38: 97–100, doi: 10.1016/j.jflm.2015.12.001.
89. Kobek M., Jankowski Z., Chowaniec C., Chowaniec M., Jabłoński C., Skowronek R. Possibilities of post-mortem diagnostics, including immunodiagnostics, in cases of sudden death due to anaphylactic and anaphylactoid reactions. Arch. Med. Sadowej Kryminol. 2014; 64(2): 102–111, doi: 10.5114/amsik.2014.47745.
90. Reggiani Bonetti L., Maccio L., Trani N., Radheshi E., Palmiere C. Splenic hypereosinophilia in anaphylaxis-related death: different assessments depending on different types of allergens? Int. J. Legal Med. 2015; 129(1): 97–103, doi: 10.1007/s00414-014-1004-2.
91. Cecchi R. Diagnosis of anaphylactic death in forensics: Review and future perspectives. Leg. Med. 2016; 22: 75–81, doi: 10.1016/j.legalmed.2016.08.006.
92. Tattoli L., Tsokos M., Sautter J., Anagnostopoulos J., Maselli E., Ingravallo G. et al. Postmortem bone marrow analysis in forensic science: study of 73 cases and review of the literature. Forensic Sci. Int. 2014; 234: 72–78, doi: 10.1016/j.forsciint.2013.10.040.
93. Del Duca F., Manetti A.C., Maiese A., Napoletano G., Ghamlouch A., Pascale N. et al. Death due to anaphylactic reaction: the role of the forensic pathologist in an accurate postmortem diagnosis. Medicina 2023; 59(12): 2184, doi: 10.3390/medicina59122184.
94. Payne V., Kam P.C.A. Mast cell tryptase: a review of its physiology and clinical significance. Anaesthesia 2004; 59(7): 695–703, doi: 10.1111/j.1365-2044.2004.03757.x.
95. Schwartz L.B. Tryptase, a mediator of human mast cells. J. Allergy Clin. Immunol. 1990; 86(4 Pt 2): 594–598, doi: 10.1016/S0091-6749(05)80222-2.
96. Laroche D., Vergnaud M.C., Sillard B., Soufarapis H., Bricard H. Biochemical markers of anaphylactoid reactions to drugs: comparison of plasma histamine and tryptase. Anesthesiology 1991; 75(6): 945–949, doi: 10.1097/00000542-199112000-00004.
97. Vitte J. Human mast cell tryptase in biology and medicine. Mol. Immunol. 2015; 63(1): 18–24, doi: 10.1016/j.molimm.2014.04.001.
98. Mayer D.E., Krauskopf A., Hemmer W., Moritz K., Jarisch R., Reiter C. Usefulness of post mortem determination of serum tryptase, histamine and diamine oxidase in the diagnosis of fatal anaphylaxis. Forensic Sci. Int. 2011; 212(1–3): 96–101, doi: 10.1016/j.forsciint.2011.05.020.
99. Tejedor-Alonso M.A., Vallejo-de-Torres G., Escayola E.N., Martínez-Fernandez P., Moro-Moro M., Masgrau NA. Postmortem tryptase cutoff points and main causes of fatal anaphylaxis. J. Allergy Clin. Immunol. Pract. 2020; 8(2): 761–763.e6, doi: 10.1016/j.jaip.2019.07.015.
100. Sun K.J., He J.T., Huang H.Y., Xue Y., Xie X.L., Wang Q. Diagnostic role of serum tryptase in anaphylactic deaths in forensic medicine: a systematic review and meta-analysis. Forensic Sci. Med. Pathol. 2018; 14(2): 209–215, doi: 10.1007/s12024-018-9980-z.
101. Edston E., Eriksson O., van Hage M. Mast cell tryptase in postmortem serum—reference values and confounders. Int. J. Legal Med. 2007; 121(4): 275–280, doi: 10.1007/s00414-006-0101-2.
102. Edston E., van Hage-Hamsten M. β-Tryptase measurements post-mortem in anaphylactic deaths and in controls. Forensic Sci. Int. 1998; 93(2–3): 135–142, doi: 10.1016/S0379-0738(98)00040-1.
103. Rook E.J., van Zanten A.P., Van den Brink W., van Ree J.M., Beijnen J.H. Mast cell mediator tryptase levels after inhalation or intravenous administration of high doses pharmaceutically prepared heroin. Drug Alcohol Depend. 2006; 85(3): 185–190, doi: 10.1016/j.drugalcdep.2006.04.013.
104. Comment L., Reggiani Bonetti L., Mangin P., Palmiere C. Measurement of β-tryptase in postmortem serum, pericardial fluid, urine and vitreous humor in the forensic setting. Forensic Sci. Int. 2014; 240: 29–34, doi: 10.1016/j.forsciint.2014.04.006.
105. Tran L., Astengo B., Palmiere C. Determination of specific IgE in pericardial and cerebrospinal fluids in forensic casework. Forensic Sci. Int. 2016; 267: 204–209, doi: 10.1016/j.forsciint.2016.08.021.
106. Zheng Z., Zhao C., Xiong H., Zhang L., Wang Q., Li Y. et al. Significance of detecting postmortem serum IgE in frozen corpses for the diagnosis of anaphylaxis in forensic. Leg. Med. 2021; 53: 101930, doi: 10.1016/j.legalmed.2021.101930.
107. Palmiere C. Postmortem diagnosis of drug-induced anaphylactic death. J. Forensic Leg. Med. 2016; 41: 28–29, doi: 10.1016/j.jflm.2016.04.005.
108. Kounis N.G. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. Clin. Chem. Lab. Med. 2016; 54(10): 1545–1559, doi: 10.1515/cclm-2016-0010.

109. Kounis N.G., Soufras G.D., Hahalis G. Accumulation of eosinophils, mast cells, and basophils in the spleen and the coronary arteries in anaphylactic deaths: is the Kounis hypersensitivity associated syndrome present? Forensic Sci. Med. Pathol. 2014; 10(1): 150–151, doi: 10.1007/s12024-013-9489-4.

110. Kounis N.G. Coronary hypersensitivity disorder: the Kounis syndrome. Clin. Ther. 2013; 35(5): 563–571, doi: 10.1016/j.clinthera.2013.02.022.

111. Forzese E., Pitrone C., Cianci V., Sapienza D., Ieni A., Tornese L. et al. An insight into Kounis syndrome: bridging clinical knowledge with forensic perspectives. Life 2024; 14(1): 91, doi: 10.3390/life14010091.

112. Kounis N.G., Koniari I., Tsigkas G., Chourdakis E., Velissaris D., Soufras G.D. et al. Death following ceftazidime-induced Kounis syndrome: Diagnostic considerations in the realm of forensic pathology. Med. Leg. J. 2020; 88(1): 48–49, doi: 10.1177/0025817220902057.

113. Kitulwatte I., Gangahawatte S., Perera U., Edirisinghe P. Death following ceftazidime-induced Kounis syndrome. Med. Leg. J. 2017; 85(4): 215–218, doi: 10.1177/0025817217695904.

114. Kounis N.G. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int. J. Cardiol. 2006; 110(1): 7–14, doi: 10.1016/j.ijcard.2005.08.007.

115. Kounis N.G., Davlouros P., Hahalis G., Mazarakis A. The heart seems to be the primary site and the target of anaphylaxis resulting in the development of Kounis syndrome. Intern. Emerg. Med. 2012; 7(Suppl 2): S119–120, doi: 10.1007/s11739-012-0786-9.

116. Kounis N.G., Kounis G.N., Soufras G.D., Lianas D., Patsouras N. Postmortem diagnosis of drug-induced anaphylactic death: Kounis syndrome and hypersensitivity myocarditis are the likely culprit in death of severe anaphylactic reactions. J. Forensic Leg. Med. 2016; 40: 40–41, doi: 10.1016/j.jflm.2016.03.001.