Prevalence triggers and clinical severity associated with anaphylaxis at a tertiary care facility in Saudi Arabia

A cross-sectional study

Raghad Alkanhal, MD Studenta, Ibrahim Alhoshan, MD Studentb, Sadal Aldakhil, MD Studentb, Nouf Alromaih, MD Studentb, Nesrin Alharthy, MDc, Mahmoud Salam, MSNa, Adel F. Almutairi, MANP, DHCScie, Raghad Alkanhal, MD Studenta, Ibrahim Alhoshan, MD Studentb, Sadal Aldakhil, MD Studentb, Nouf Alromaih, MD Studentb, Nesrin Alharthy, MDc, Mahmoud Salam, MSNa, Adel F. Almutairi, MANP, DHCScie

Abstract

Anaphylaxis is a systemic and hypersensitive allergic reaction caused by various triggers such as environmental, food, drug, and insects. The aim of this study was to identify the prevalence, triggers, and clinical severity of anaphylaxis in 2 emergency departments (EDs) in Saudi Arabia.

A cross-sectional study based on a screening of medical records was conducted between January 2015 and August 2017, to identify confirmed cases of anaphylaxis. Patient characteristics were age, sex, previously known allergies, and the triggering allergens. The clinical severity was measured on the basis of the anaphylaxis international assessment tool (mild, moderate, severe). Factors associated with triggers and severities were identified.

The period prevalence of anaphylaxis among ED admissions was 0.00026%. Pediatric cases (age 1–16 years) were 98 (60.9%), while adults (age 17–40 years) were 63 (39.1%). Triggers of anaphylaxis were food 63 (39.1%), insects 62 (38.5%), drugs 28 (17.4%), and environmental 9 (5.0%). Mild symptoms were observed in 41 (25%) of the sample, while moderate and severe symptoms were observed in 116 (72%) and 4 (3%) of the cases, respectively. Adults were 1.25 times more likely to endure drug allergy rather than food allergy, than pediatrics with adj.P = .015. ED admissions in summer season were 1.29 less likely to be due to drug allergy rather than insect allergy, compared with admissions in winter season, adj.P = .01. Cases with known allergy were 1.72 times less likely to endure drug allergy rather than food allergy, compared with those with unknown allergy, adj.P = .001. Adults were 4.79 more likely to endure severe symptoms than pediatrics with adj.P = .001.

Although the prevalence of anaphylaxis was higher in pediatrics, yet the disease was more severe in adults. Special consideration should be paid to anaphylaxis triggered by insect bites in summer, and food allergy among cases with unknown allergy upon ED admission.

Abbreviation: ED = emergency departments.

Keywords: adults, anaphylaxis, drug, food, insects., pediatrics, severity

1. Introduction

Anaphylaxis is a systemic and hypersensitive allergic reaction in which histamine and other vasoactive mediators are released in the body. According to the guidelines by World Allergy Organization for the assessment and management of anaphylaxis, clinical features can vary between patients. Further, the reactions have been classified into 4 grades, ranging from mild (only skin reactions), to moderate (respiratory, cardiovascular, or gastrointestinal involvement), to severe (hypoxia, hypotension, or neurologic compromise reactions), or even death. The reaction pattern might be uniphasic (resolves by treatment), biphasic (resolves by treatment, then reoccurs), or protracted (not responsive to treatments). The diagnostic criterion of anaphylaxis is primarily based on the observed clinical signs and symptoms. Laboratory tests may be requested to confirm anaphylaxis, as Tryptase enzyme level exceeds 11.4 μg/L at a 2-hour peak after the event. In rare cases when Tryptase levels remain high, anaphylaxis may progress to cutaneous or even systemic mastocytosis. In a study conducted in a large city in Saudi Arabia, there were 238 reported cases of anaphylaxis in a 2-year period. Food allergies are more common among children and adolescents, whereas insect and drug-induced allergies are more prevalent in adults. A Turkish study reported that the most common cause of anaphylaxis in children was food, and that there was a significant male predominance among children younger than 10 years of age. Similarly, a study in Saudi Arabia found that 46% of the patients in the examined cases of...
Eligibility criteria for subject selection were being of any age to validate the collected data and fulfill obtaining the data of interest. Additional 2 persons were assigned to tertiary care facilities in the Middle East.

2.2. Data collection

Between January 2015 and August 2017, 161 cases were identified suffering of anaphylaxis out of 617,401 ED admissions, with a prevalence of 0.00026%. Excluded cases are those where the type of trigger is not specified or those with more than 1 type of trigger were also excluded. Other forms of allergies such as allergic rhinitis, sinusitis, asthma, and conjunctivitis were also not included in this study.

Medical records contained the detailed medical history as reported by the patients and/or their companions. These included patient characteristics such as age (pediatrics <17 years and adults ≥17 years), sex, previous history of asthma or allergy, season of event that is summer (April to September) versus winter (October to March). Anaphylaxis event characteristics assessed were type of trigger (insect bites, environmental, food, and drugs) and route of exposure (oral, inhalations, parenteral, skin). Outcomes were period prevalence, clinical severity based on the anaphylaxis international assessment tool; mild (only skin reactions), moderate (respiratory, cardiovascular, or gastrointestinal involvement), severe (hypoxia, hypotension, or neurologic compromise reactions), or unfortunate death. Other outcomes included pattern of event (uniphasic vs biphasic), referral rate to specialist, medications given, and in-hospital admission.

2.3. Data analysis and management

Data were entered and analyzed by using the SPSS statistical software (IBM, SPSS Inc, NY). The period prevalence of anaphylaxis was calculated by dividing the number of events over the number of ED admissions within the study period (*100). Descriptive statistics such as mean, standard deviation, as well as frequency and percentage, were used to describe various continuous and categorical variables, respectively. Identification of any age group differences was made by testing various exposures using Pearson Chi-square. Multinomial logistic regression was performed to model the relationship between the predictors (gender, age group, season, asthmatic status, allergy known prior ED admission) and 4 levels of outcomes (types of triggers). The reference group was the drug trigger. Moreover, a cumulative odds ordinal regression was constructed to identify which of the variables (gender, age, asthmatic status, and type of trigger) were predictors of 3 ordinal levels of severity (mild, moderate, severe). These models passed the required assumptions and contained the intercepts that significantly improved the fit between the model and data and they also both passed the goodness of fit. P value was statistically significant at <.05.

2.4. Ethical consideration

Ethical approval of this study was obtained from the Institutional Review Board (RSS 17/022) at the Saudi Ministry of National Guards Health Affairs. No patient informed consent was obtained, as it was a secondary analysis from medical records.

3. Results

3.1. Anaphylaxis event characteristics

Between January 2015 and August 2017, 161 cases were identified suffering of anaphylaxis out of 617,401 ED admissions, with a prevalence of 0.00026%. Excluded cases are presented in Fig. 1. No cases of cutaneous or systemic mastocytosis were identified. There were 98 (60.9%) pediatrics with a mean of age ± standard deviation 6.6 ± 4.4 years, while
adults were 63 (39.1%) with mean age ± standard deviation 28.4 ± 6.4 years. Prevalence of anaphylaxis in pediatrics was 0.0005%, significantly higher Risk ratio = 3.16 (95% CI 2.30–4.33) than the prevalence in adults, which was 0.0002%, \( P < .001 \). Among the 161 cases, almost equal gender distribution was observed, in which males constituted 53.7% versus 46.3% for females. Season variations were observed between winter season 58 (36%) and summer season 103 (64%). Those with a previous history of asthma were 29 (18%), while those with a previous history of allergy were 68 (42.2%). Triggers of anaphylaxis included environmental triggers 8 (5.0%), insect bites 62 (38.5%), food 63 (39.1%), and drug 28 (17.4%). Table 1 summarizes all types of triggers identified in the study samples. Routes of exposure were oral 85 (52.8%), inhalation 4 (2.5%), parenteral 6 (3.7%), bites 62 (38.5%), and skin contact 4 (2.5%).

### 3.2. Outcome characteristics

Almost 41 (25%) of the cases were classified as level 1 severity (mild), 116 (72%) were level 2 (moderate), and 4 (3%) were level 3 (severe). No death cases were reported. Table 2 describes the severity level of anaphylaxis associated with various triggers. Majority of cases, that is, 151 (93.8%) were uniphasic, while 10 (6.2%) were biphasic and protracted. In-hospital admission rate was 53 (32.9%) and the rate of referral to specialist was 60 (37.3%). The rates of epinephrine administered in the EDs were 143 (88.8%), steroids 149 (92.5%), and antihistamine 156 (96.9%).

Age group differences were tested in a series of bivariate analysis as indicated in Table 3. It showed that within the pediatric group, males were significantly at a higher risk for anaphylaxis (61.2%) than females (38.8%), while within the adult group, females (57.1%) were at a higher risk than males (42.9%), \( P = .022 \). Pediatrics with anaphylaxes were significantly more likely to be referred to a specialist, that is, 53 (54.1%) compared with adults 7 (11.1%), \( P < .001 \). Pediatrics were also significantly more likely to receive epinephrine 91 (92.9%), compared with adults 52 (82.5%), \( P = .043 \). Pediatrics were also significantly more likely to receive antihistamine 98 (100%), compared with adults 58 (92.1%), \( P = .005 \).

### 3.3. Predictors of anaphylaxis triggers and clinical severity

Although the prevalence of anaphylaxis was higher among pediatrics, more clinical severity was observed in adults as shown in Fig. 2. Multinomial logistic regression showed that adults were 1.25 times more likely to suffer from drug allergy rather than food allergy, than pediatrics, adj.\( P = .015 \). ED admissions in summer season are 1.29 less likely to be due to drug allergy rather than insect allergy, compared with winter season admissions, adj.

### Table 1

| Category         | Type         | n  |
|------------------|--------------|----|
| Environment (n=8, 5.0%) | Dust         | 4  |
|                  | Horse fur    | 1  |
|                  | Detergents   | 2  |
|                  | Plant leaves | 1  |
|                  | Penicillin   | 2  |
|                  | Cephalexin   | 2  |
|                  | Other antibiotics | 12 |
|                  | Aspirin      | 9  |
|                  | Antifungal   | 1  |
| Insect bites (n=62, 38.5%) | Ants         | 55 |
|                  | Hornets      | 2  |
|                  | Unknown insect | 5  |
|                  | Nuts         | 27 |
|                  | Bears        | 2  |
|                  | Wheat        | 1  |
|                  | Sesame products | 6  |
|                  | Fish         | 2  |
|                  | Eggs         | 5  |
|                  | Milk/Yogurt  | 4  |
|                  | Eggplant     | 1  |
|                  | Shrimps      | 4  |
|                  | Strawberry   | 2  |
|                  | Mango        | 1  |
|                  | Kiwi         | 1  |
|                  | Coconut      | 1  |
|                  | Spices       | 4  |
|                  | Soft drinks/Juices | 2  |

n=frequency.
Cases with known allergy were 1.72 times less likely to endure drug allergy rather than food allergy, compared with those with unknown allergy, adj. P = .001 (Table 4). Ordinal logistic regression showed that adults were 4.79 more likely to endure severe symptoms than pediatrics, adj. P = .001, (Table 5).

4. Discussion

As anaphylaxis remains a great public health concern, investigating the factors associated with it is of great significance. The prevalence of anaphylaxis in pediatrics was significantly higher than that in adults, which contradicts a recent report by the World Allergy Organization, which stated that anaphylaxis is higher in adults than in pediatrics.[13,14] However, the prevalence in Australia was equal in both adults and pediatrics, probably due to the distinct desert environment of Saudi Arabia. In countries with humid or tropical climates, different types of insects are prevalent and plant pollens travel around, both of which may contribute to anaphylaxis.[15] This was reflected in the findings of the current study, in which the environmental triggers were found to be the most common in adults, while food was the most common trigger in pediatrics. It is also congruent with the results reported in the literature.[13]

One of the environmental triggers in the setting was insects, which were apparently influenced by climate characteristics. Most of the anaphylaxis events occurred in the summer (64%), during which insects tend to be more active, foraging for food and seeking cooler temperature indoors.[16] Systemic allergic reactions to insect stings affect up to 5% of the population during their lifetime, with only 2% who might develop cardiorespiratory arrests.[17,18] These rates vary between countries, as 40 deaths are reported annually in the US, while 16 to 18 in France.[19]

| Table 2 | Severity levels in association with various anaphylaxis triggers. |
|---------|------------------------------------------------------------------|
|         | Mild                | Moderate          | Severe             |
|         | 41 (25.5%)          | 116 (72.0%)       | 4 (2.5%)           |
| Environmental | 1 (12.5%)        | 7 (87.5%)         | 0 (0%)             |
| Food     | 20 (31.7%)          | 42 (66.7%)        | 1 (1.6%)           |
| Drugs    | 6 (21.4%)           | 21 (75.0%)        | 1 (3.6%)           |
| Insects  | 14 (22.6%)          | 46 (74.2%)        | 2 (3.2%)           |

P = .01. Cases with known allergy were 1.72 times less likely to endure drug allergy rather than food allergy, compared with those with unknown allergy, adj. P = .001 (Table 4). Ordinal logistic regression showed that adults were 4.79 more likely to endure severe symptoms than pediatrics, adj. P = .001, (Table 5).

| Table 3 | Age group differences in relation to anaphylaxis event characteristics and its outcomes. |
|---------|-----------------------------------------------------------------------------------------|
|         | Adults (≥17)                                                                 | Pediatrics (0–16) | OR (95% CI) |
| Sex     |                                                                                          |                  |
| Females | 63 (39.1%)                                                                                | 98 (60.9%)       | 2.11 (1.11–4.01) |
| Males   | 27 (42.9%)                                                                                 | 60 (61.2%)       |                       |
| Season  |                                                                                          |                  |
| Summer  | 39 (61.9%)                                                                                 | 64 (65.3%)       | 1.16 (0.60–2.23)   |
| Winter  | 24 (38.1%)                                                                                 | 34 (34.7%)       |                       |
| Previous history of asthma |                                                                                     |                  |
| No      | 35 (57.1%)                                                                                 | 60 (61.2%)       |                       |
| Yes     | 26 (42.9%)                                                                                 | 38 (38.8%)       |                       |
| Previous known allergy |                                                                                      |                  |
| No      | 42 (57.1%)                                                                                 | 62 (63.3%)       |                       |
| Yes     | 33 (42.9%)                                                                                 | 36 (36.7%)       |                       |
| Triggers |                                                                                          |                  |
| Insects vs others |                                                                                     |                  |
| No      | 28 (44.4%)                                                                                 | 34 (34.7%)       | 1.51 (0.79–2.87)   |
| Yes     | 35 (42.9%)                                                                                 | 64 (65.3%)       |                       |
| Food vs others |                                                                                       |                  |
| No      | 28 (44.4%)                                                                                 | 45 (45.9%)       | 2.12 (1.08–4.17)   |
| Yes     | 35 (42.9%)                                                                                 | 34 (34.7%)       |                       |
| Drugs vs others |                                                                                      |                  |
| No      | 28 (44.4%)                                                                                 | 45 (45.9%)       | 2.12 (1.08–4.17)   |
| Yes     | 35 (42.9%)                                                                                 | 34 (34.7%)       |                       |
| Environmental vs others |                                                                                     |                  |
| No      | 28 (44.4%)                                                                                 | 45 (45.9%)       | 2.12 (1.08–4.17)   |
| Yes     | 35 (42.9%)                                                                                 | 34 (34.7%)       |                       |
| Referral to specialist |                                                                                      |                  |
| No      | 7 (11.1%)                                                                                  | 53 (54.1%)       | 9.42 (3.91–22.73)  |
| Yes     | 56 (88.9%)                                                                                 | 45 (45.9%)       |                       |
| Epinephrine used |                                                                                       |                  |
| No      | 52 (82.5%)                                                                                 | 91 (92.9%)       | 2.75 (1.01–7.53)   |
| Yes     | 11 (17.5%)                                                                                 | 8 (8.1%)         |                       |
| Steroids used |                                                                                       |                  |
| No      | 68 (82.5%)                                                                                 | 98 (100.0%)      | 2.69 (2.19–3.29)   |
| Yes     | 58 (77.8%)                                                                                 | 91 (91.8%)       |                       |
| Anti-histamine used |                                                                                       |                  |
| No      | 58 (82.1%)                                                                                 | 98 (100.0%)      | 2.69 (2.19–3.29)   |
| Yes     | 58 (77.8%)                                                                                 | 91 (91.8%)       |                       |
| Category of anaphylaxis |                                                                                     |                  |
| Uniphasic| 58 (92.1%)                                                                                 | 93 (94.9%)       | 1.60 (0.45–5.78)   |
| Bilphasic| 5 (7.9%)                                                                                   | 5 (5.1%)         |                       |
| In-hospital admission |                                                                                       |                  |
| No      | 58 (92.1%)                                                                                 | 93 (94.9%)       | 1.60 (0.45–5.78)   |
| Yes     | 5 (7.9%)                                                                                    | 5 (5.1%)         |                       |

\( \chi^2 = \) Pearson Chi-square, \( F = \) Fisher exact test.

\* Statistically significant at \(< .05.\)
The risk of developing anaphylaxis will never be zero, and the severity of its signs/symptoms will vary depending on various confounding factors. Interestingly, in this study, anaphylaxis was found to be more prevalent in pediatrics, though the results illustrated that adults endured more severe clinical presentations than pediatrics (adj. OR = 4.79). This finding was comparable to that reported by a clinical review study that stated that the odds of severe reactions are 9-fold for adults compared with children. Cardiac and lung diseases, such as asthma, have also been known to increase the clinical severity of anaphylaxis, as 75% of asthmatic patients were reported to present with severe or fatal anaphylaxis. Although it was not statistically significant in this study, the findings indicated that an asthmatic is 1.54 times more likely to experience severe symptoms than a nonasthmatic patient.

Only 1.6% of the cases of food allergies in this study experienced severe symptoms, while 66.7% experienced moderate symptoms and 31.7% experienced mild symptoms. These figures were higher than those reported in the literature, which stated that up to 20% of cases of food anaphylaxis may present without even cutaneous symptoms. Normally, the leading causative food allergens are seafood and shellfish (34.8%), while in this study setting, they were mainly beans, nuts, and seeds (31.7%) in comparison to seafood (3.7%). This can be explained by the study’s geographical location, which was inland, so the population might not be as likely to consume fish as those living in coastal cities.

Adults were 1.25 times more likely to suffer from drug allergies rather than food allergies than pediatrics. However, 1 study stated that among children and adolescents who suffered from anaphylaxis, the trigger was predominantly (75%) drug hypersensitivity. Food allergies in adults are often under reported, as people usually self-adjust their diet on the basis of experiencing unpleasant signs/symptoms after a meal. Sensitivity to food allergens might emerge among infants and toddlers, who have just started experimenting with various foods for the first time in their lives, with a worldwide prevalence of 1% to 10%. This explains why food allergies in this study were more prevalent among pediatrics than adults. High-risk individuals will probably become hypervigilant about avoiding food allergens throughout their lives.

### Table 4

| IV                          | Environmental vs drug triggers | Food vs drug triggers | Insect vs drug trigger |
|-----------------------------|--------------------------------|----------------------|-----------------------|
|                             | Adj. OR (SE) | Adj. P | Adj. RR (95% CI) | Adj. OR (SE) | Adj. P | Adj. RR (95% CI) | Adj. OR (SE) | Adj. P | Adj. RR (95% CI) |
| Intercept                   | -0.85 (1.44) | .557  | 2.38 (0.99) | .100  | 1.39 (0.95) | .144  |
| Gender                      | 0.04 (0.83) | .962  | 1.04 (0.20–5.51) | .695  | 0.82 (0.30–2.21) | 0.79 (0.49) | .103  | 2.21 (0.85–5.71) |
| Female = 0, Male = 1        |                 |       |                      |       |                    |       |                   |       |
| Age group                   | 1.28 (0.92) | .165  | 1.25 (0.51) | .151  | 0.22 (0.02–1.95) | 0.144 (0.83) | .746  | 0.85 (0.32–2.29) | 1.29 (0.50) | .010  | 0.28 (0.10–0.73) |
| Pediatrics = 0, Adults = 1  |                 |       |                      |       |                    |       |                   |       |
| Season                      | 0.16 (0.82) | .846  | 1.17 (0.23–5.88) | .746  | 0.85 (0.32–2.25) | 1.29 (0.50) | .010  | 0.28 (0.10–0.73) | 1.29 (0.50) | .010  | 0.28 (0.10–0.73) |
| Winter = 0, Summer = 1      |                 |       |                      |       |                    |       |                   |       |
| Asthmatic                   | -1.53 (1.12) | .737  | 0.22 (0.02–1.95) | 0.144 (0.83) | 0.80 (0.24–3.19) | -0.88 (0.83) | .291  | 0.42 (0.08–2.12) | 1.29 (0.50) | .010  | 0.28 (0.10–0.73) |
| No = 0, Yes = 1             | 0.02 (0.94) | .983  | 1.02 (0.16–6.38) | 1.72 (0.52) | .001* | 0.18 (0.06–0.50) | 0.02 (0.53) | .969  | 1.02 (0.36–2.89) |
| Allergy known               |                 |       |                      |       |                    |       |                   |       |
| No = 0, Yes = 1             |                 |       |                      |       |                    |       |                   |       |

Drug trigger: reference group in DV; 0: reference group in IV; Adj.OR: beta coefficient; Adj.RR: exponential of beta coefficient.

Adj = adjusted; CI = confidence interval; DV = dependent variable; IV = independent variables; OR = odds ratio; RR = relative risk; SE = standard error.

* Statistically significant at <0.05.
4.1. Limitations

Although this study provided significant findings, the small sample size may have limited its statistical power. Accordingly, the most suitable statistical tests were utilized to identify factors associated with triggers and severity of allergic reactions. Pooling of data about anaphylaxis from multicenters in national data bases will reinforce the generalizability of such findings. The low prevalence in this setting could be an indicator that not all allergic cases in the targeted population had received medical treatments in the addressed EDs, but rather resolved either spontaneously or by using over-the-counter drugs at home or sought help at the primary health care clinics. Findings in this study can be generalized to populations residing in similar climates such that in the neighboring Gulf countries, African countries, some USA states such as Arizona, cities proximal to the Australian outback, and so on. Furthermore, Saudi Arabia has been known to be a common work destination for expatriates from all over the world, driven by the higher paid salaries and low taxes. Findings in this paper might be of interest for those planning to move and reside in Saudi Arabia, with or without their families. One of the potentially associated factors with anaphylaxis is having a family history of allergies, yet it was not addressed in this study due to the fact that the initial data were obtained and recorded for clinical, rather than research purposes. Another limitation is the fact that most of the published studies focused on anaphylaxis among specific populations or that was associated with certain triggers, with very little attention having been paid to generating a universal language or coding to diagnose anaphylaxis.

5. Conclusion

The prevalence of anaphylaxis in 2 Middle Eastern EDs showed that although the prevalence of anaphylaxis reaction was higher in pediatrics, the reactions were more severe in adults. Anaphylaxis in pediatrics was more common in males yet in adults the prevalence was higher in females. Food was the most common trigger of anaphylaxis in pediatrics. Findings also showed a poor referral rate of anaphylactic cases to allergy immunologists.

5.1. Recommendations

The concept of prevention, rather than the clinical prediction or management, of anaphylaxis is of great importance. Any person classified as a high-risk individual because they reside in a high-risk environment, have a family history of allergies, and/or have a known allergy should receive a sensitivity profile as part of primary or secondary prevention measures. Prompt recognition of anaphylaxis symptoms is vital, as these conditions require immediate clinical management to avoid a drastic deterioration to more life-threatening conditions. It is also crucial for health care practitioners to increase awareness and ensure proper education on the self-administration of epinephrine injections and emphasize that those experiencing a reaction should report directly to the nearest health facility. Emergency hotlines ought to be accessible in houses, schools, and public areas so that any person suspecting the early signs of anaphylaxis can receive proper instructions. It is also crucial for all health care professionals to follow the international guidelines for the treatment and management of anaphylaxis, including referring cases to allergy immunologists.

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Author contributions

Conceptualization: Raqhad Alkanhal, Ibrahim Alshoushan, Sadal Aldakhl, Nouf Alromaih, Nesrin Alharthy, Adel F Almutairi.
References

[1] Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004;114:371-6.
[2] Golden DB. Patterns of anaphylaxis: Acute and late phase features of allergic reactions. In: Novartis Foundation Symposium. Vol. 257. 2004. p. 101-110. (Novartis Foundation Symposium).
[3] Tejedor-Alonso MA, Moro-Moro M, Míguez-García MV. Epidemiology of anaphylaxis: contributions from the last 10 years. J Investig Allergol Clin Immunol 2015;25:163–75.
[4] National Clinical Guideline Centre. Patterns of Anaphylaxis: Acute and Late Phase Features of Allergic Reactions. London, UK: National Institute for Health and Care Excellence; 2014. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0068956/pdf/PubMedHealth_PMH0068956.pdf. Accessed June 2018.
[5] Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. Br J Haematol 2014;166:521–8.
[6] Sheikh F, Amin R, Rehan Khaliq AM, et al. First study of pattern of anaphylaxis in a large tertiary care hospital in Saudi Arabia. Asia Pac Allergy Immunol Res 2016;8:353–40.
[7] Civelek E, Erkoçoğlu M, Akan A, et al. The etiology and clinical features of anaphylaxis in a developing country: nationwide survey. Asian Pac J Allergy Immunol 2017;35:212–9.
[8] Iribarren C, Tolstykh IV, Miller MK, et al. Asthma and the prospective risk of anaphylactic shock and other allergy diagnoses in a large integrated health care delivery system. Ann Allergy Asthma Immunol 2010;104:371–7.
[9] Simon AK, Hollander GA, McMiechael A. Evolution of the immune system in humans from infancy to old age. Proc R Soc B 2015;282:20143085.
[10] El-Hazmi M, Al-Swailem A, Warsy A, et al. Consanguinity among the Saudi Arabian population. J Med Genetics 1995;32:623–6.
[11] BenShoshan M, Clarke A. Anaphylaxis: past, present and future. Allergy 2011;66:1–4.
[12] World Allergy Organization. Anaphylaxis: Global Overview: World Allergy Organization; 2017. Available at: http://www.worldallergy.org/professional/allergic_diseases_center/anaphylaxis/anaphylaxisglobal.php. Accessed October 26, 2017.
[13] Jiang N, Yin J, Wen L, et al. Characteristics of anaphylaxis in 907 Chinese patients referred to a tertiary allergy center: a retrospective study of 1,952 episodes. Allergy Asthma Immunol Res 2016;8:353–61.
[14] Asthma and Allergy Foundation of America. Anaphylaxis: A Severe Allergic Reaction. Landover, MD: Asthma and Allergy Foundation of America; 2007. Available at: http://www.aafa.org/page/anaphylaxis-severe-allergic-reaction.aspx. Accessed October 26, 2017.
[15] Jayatilaka P, Narendra A, Reid SF, et al. Different effects of temperature on foraging activity schedules in sympatric Myrmecia ants. J Exp Biol 2011;214:2730–8.
[16] Ludman SW, Boyle RJ. Stinging insect allergy: current perspectives on venom immunotherapy. J Asthma Allergy 2015;8:75.
[17] Golden D. Stinging insect allergy. Am Fam Phys 2003; 67:2541–2346.
[18] Jerschow E, Lin RY, Scaperotti MM, et al. Fatal anaphylaxis in the United States, 1999–2010: temporal patterns and demographic associations. J Allergy Clin Immunol 2014;134:1318–28.
[19] Sarinho E, Lins MdGM. Severe forms of food allergy, J Pediatr (Vasco em Português) 2017;93:53–9.
[20] Castells M. Diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol 2017;140:521–33.
[21] Turner PJ, Jerschow E, Umasunthar T, et al. Fatal anaphylaxis: mortality rate and risk factors. J Allergy Clin Immunol 2017;135:1169–78.
[22] Mansoor DK, Sharma HP. Clinical presentations of food allergy, Pediatr Clin North Am 2011;58:315–26.
[23] Lee S-H, Ban G-Y, Jeong K, et al. A retrospective study of Korean adults with food allergy: differences in phenotypes and causes. Allergy Asthma Immunol Res 2017;9:534–9.
[24] Burger J, Goehfeld M, Batang Z, et al. Fish consumption behavior and rates in native and non-native people in Saudi Arabia. Environ Res 2014;133:141–81.
[25] Cavaktyar Q, Karaatzamac B, Betinkaya PG, et al. Characteristics of drug-induced anaphylaxis in children and adolescents. Allergy Asthma Proc 2017;38:56–63.
[26] Chin B, Chan ES, Goldman RD. Early exposure to food and food allergy in children. Can Fam Phys 2014;60:338–9.
[27] Sousa-Pinto B, Fonseca JA, Gomes ER. Frequency of self-reported drug allergy: a systematic review and meta-analysis with meta-regression. Ann Allergy Asthma Immunol 2017;119:362–73. e2.
[28] Coninho-Cohen R, Goldberg A. Allergen immunotherapy–induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective study. Ann Allergy Asthma Immunol 2010;104:73–8.
[29] Scantoni SE, Gonzalez EG, Waiibel KH. Incidence and characteristics of biphasic reactions after allergen immunotherapy. J Allergy Clin Immunol 2009;123:493–8.