

ORIGINAL ARTICLE

Provoking allergens and treatment of anaphylaxis in children and adolescents – data from the anaphylaxis registry of German-speaking countries

Stephanie Hompes¹, Alice Köhli², Katja Nemat³, Kathrin Scherer⁴, Lars Lange⁵, Franziska Rueff⁶, Ernst Rietschel⁷, Thomas Reese⁸, Zsolt Szepefalusi⁹, Nicolaus Schwert¹⁰, Kirsten Beyer¹¹, Thomas Hawranek¹², Bodo Niggemann¹³, Margitta Worm¹

¹Department of Dermatology and Allergy, University Hospital Charité Berlin, Germany, ²Division of Allergy, Department of Paediatrics, University Children's Hospital Zurich, Switzerland, ³Department of Paediatrics, University Hospital Carl Gustav Carus, Technical University of Dresden, Germany, ⁴Allergy Unit, Department of Dermatology, University Hospital Basel, Switzerland, ⁵Children's Hospital, St. Marien-Hospital Bonn, Germany, ⁶Department of Dermatology and Allergology, Ludwig-Maximilians-University Munich, Germany, ⁷Children's Hospital, University of Cologne, Germany, ⁸Children's Hospital, Mathias-Spital Rheine, Germany, ⁹Department of Paediatrics, Medical University of Vienna, Austria, ¹⁰Clinic of Paediatric Pneumology and Neonatology, Hannover Medical School, Hannover, Germany, ¹¹Department of Paediatric Pneumology and Immunology, University Hospital Charité Berlin, Germany, ¹²Department of Dermatology, Paracelsus Medical University Salzburg, Austria, ¹³Paediatric Allergology and Pneumology, German Red Cross Hospital Westend, Berlin, Germany

To cite this article: Hompes S, Köhli A, Nemat K, Scherer K, Lange L, Rueff F, Rietschel E, Reese T, Szepefalusi Z, Schwert N, Beyer K, Hawranek T, Niggemann B, Worm M. Provoking allergens and treatment of anaphylaxis in children and adolescents – data from the anaphylaxis registry of German-speaking countries. *Pediatr Allergy Immunol* 2011; Doi: 10.1111/j.1399-3038.2011.01154.x.

Keywords:

anaphylaxis; children and adolescents; provoking allergens; adrenaline; aggravating factors

Correspondence

Prof. Dr. med. Margitta Worm, Allergy-Center-Charité, Department of Dermatology and Allergy, Charité Campus Mitte, Charitéplatz 1, D – 10117, Berlin
Fax: +49 30 450 518 919
E-mail: margitta.worm@charite.de

Accepted for publication 20 January 2011

DOI:10.1111/j.1399-3038.2011.01154.x

Abstract

Anaphylaxis is the most severe reaction of an IgE-mediated hypersensitivity. Data about affected patients may help to improve our knowledge of anaphylaxis and its medical care. We analysed data from the anaphylaxis registry of German speaking countries with regard to the provoking allergens and treatment modalities of anaphylaxis in children and adolescents.

Inclusion criteria were severe systemic allergic reactions with concomitant pulmonary and/or cardiovascular symptoms. The data are collected by a password-controlled online-questionnaire. For this analysis, data of 197 reported anaphylactic reactions from children and adolescents registered between 2006 and 2009 were included.

The data show that within the registered cases the most frequently affected organ systems for children and adolescents were the skin (89%) and the respiratory tract (87%) followed by symptoms of the cardiovascular system (47%) and the gastrointestinal tract (43%). The most frequent elicitors were food allergens accounting for 58% of cases, followed by insect venom (24%) and drugs (8%). The most frequent food allergens were peanuts followed by tree nuts and animal related food products. In 18% aggravating factors such as physical exercise were noted by the clinicians. 26% of the analysed patients had experienced more than one reaction. The data regarding the emergency treatment show that antihistamines (87%) and corticosteroids (85%) were often used but that adrenaline was rarely used (22% of the registered cases).

Taken together these data show that the analysis of anaphylaxis by registration of affected individuals can provide data about provoking allergens and treatment measures but also suggest the impact of aggravating factors on anaphylactic reactions. The under-represented usage of adrenaline indicates the need of educational measures for patients and their physicians.

Anaphylaxis is the most severe reaction associated with IgE-mediated hypersensitivity. Recent epidemiological data suggest that the prevalence of anaphylaxis has increased over the last years (1, 2). In general, only limited epidemiological data about anaphylaxis are available, in particular for children and adolescents. The calculated incidence rates for this age group have been suggested to range between 0.2 (UK) and 10.5 (USA) per 100 000 person-years (3, 4). Whenever data about anaphylaxis is assessed it has to be considered that there is no commonly agreed definition of anaphylaxis and the acquirement of data varies widely (5–9). More data are available about the causes of anaphylaxis in children and adolescents. Tree nuts, peanuts, fish, hen's egg and cow's milk have been reported as the most frequent allergens (4, 7, 10, 11).

Augmentation factors, also called cofactors or aggravating factors, are suggested to be involved in the activation of some anaphylactic reactions. This means, while exposure to the allergen alone is tolerated, the combination of the allergen with augmentation factors may lead to an anaphylactic reaction (12). In children, physical exercise seems to be the most important augmentation factor (10, 11, 13). With respect to food, wheat-dependent exercise-induced anaphylaxis is most frequent, but other augmentation factors such as infections, drugs, psychological factors or menstruation have been previously suggested (10, 11, 14). However, clinical studies exploring the exact role of such augmentation factors are missing.

Adrenaline is the generally agreed first line treatment for anaphylaxis. In addition, patients who had been suffering from anaphylaxis should receive an adrenaline autoinjector for the case of a future emergency (15, 16). The need for the prescription of additional antiallergic drugs for the use in an emergency situation by the patient is controversial. In the US it is common to prescribe only the adrenaline autoinjector solely, although sometime it is accompanied by a H1-antihistamine (16, 17). However, in Europe it is recommended that patients who have had a severe allergic reaction should receive oral antihistamines and oral corticosteroids besides the adrenaline autoinjector (18, 19). For those patients, who suffer in addition from allergic asthma, inhaled short acting beta-2-agonists are another important class of drugs (9, 19).

The few previously published data of the German-speaking area concerning the treatment of anaphylaxis in an emergency indicate a need of improvement. Adrenaline is prescribed by few doctors and the use of emergency drugs by the patient is low (7, 20).

In the present study we report clinical data from affected children and adolescents in the German speaking area, who had experienced anaphylaxis. Our objectives were to characterize the clinical features, the site of reaction and the most common provoking allergens of anaphylaxis in children and adolescents. Furthermore, we wish to describe additional factors – possibly aggravating factors, which may contribute to the elicitation of an anaphylactic reaction in children and adolescents and finally we describe the medical care of the cases.

Methods

Since July 2006 voluntarily reported data from allergy specialized centres about patients who experienced a severe systemic allergic reaction have been registered in Germany, Austria and Switzerland. 71 allergy clinics and 4 allergy private practices are connected to the registry. The registry consists of an online, security protected questionnaire. The questionnaire includes demographical data and data about the clinical symptoms, the cause of the reaction, possible augmentation factors, location of the reaction and frequency of the reaction in addition to data about diagnostic and therapeutic measures, which have been performed in the affected individuals.

To consider possible augmentation factors the following features were asked in the questionnaire: if the reaction started during or shortly after physical exercise, if the patient was under stress at the time point of the reaction, if an acute infection was ongoing, if the patient has drunken alcohol or taken drugs (specifically asked about acetylsalicylic acid (ASA), ACE-inhibitor, AT-2-antagonist and beta-blocker), if women had their menses or if some other considerably conditions were present at the time point of the reaction. These items are obtained by the history of the attending physicians and are not proven by provocation tests.

In regard to the frequency of the reaction, it was asked if the patient had previous severe reactions comparable to the one which is reported to the registry. The information about the emergency treatment were gathered through the patient's history and through reports from the emergency hospitalizations. The information about the use of the self-administered emergency drugs is obtained from the patients or their parents.

Inclusion criteria for being accepted to the registry are severe systemic allergic reactions with at least one pulmonary and/or cardiovascular symptom. At least one of the following symptoms had to be present: dyspnoea, stridor, apnoea, tachycardia, drop in blood pressure, collapse or cardiac arrest. Our focus is on life-threatening symptoms independent of an existing definition of anaphylaxis. Accompanying symptoms of the skin and the gastrointestinal tract and mild symptoms of the respiratory tract and the cardiovascular system are registered as well.

Every anaphylactic reaction in patients visiting the centre, which meets the inclusion criteria, should be reported to the registry (independent of the age of the patient or the cause of the anaphylactic reaction). For acceptance in this data analysis, reactions are only considered if they had happened less than 12 months ago before the first visit date in the centre. This rule and the fact that the reactions should be reported after the diagnostic work up should increase the data quality.

The data acquirement was approved by the local ethics committee. Data processing and analysis was done with SPSS for Windows (Version 16.0).

Results

Patients and clinics

A total of 1281 anaphylactic reactions, which occurred from 2005 to 2008, were registered. Seventy-one reactions had to

be excluded because they occurred before 2005. Further 45 reactions were excluded due to the missing inclusion criteria of pulmonary or cardiovascular symptoms or due to unproven diagnosis of anaphylaxis. Consequently 1165 reactions went into the overall analysis, these were 968 reactions in adults (18–85 yr) and 197 reactions in children and adolescents (3 months–17 yr).

Within this survey the 197 reactions of children and adolescents were analysed. The analysed data of children and adolescents were delivered by 36 centres. These were 21 paediatric clinics, 1 private paediatric allergy practice, 13 dermatology clinics and 1 pulmonology clinic, all of them specialized in allergy. Among the different German speaking countries 3 reporting centres were from Austria, 5 from Switzerland and 28 from Germany. Approximately one fourth of the 75 centres did not report cases. The other centres not contributing data to the present analysis see adult patients only.

Since 30 registered cases were from the pilot phase, where a detailed symptom registration was not realised, the analysis of symptoms of the anaphylactic reactions covers 167 cases.

The patient cohort included in this analysis were 197 children and adolescents each with one anaphylactic reaction. The median patient age of that cohort was 10 yr with a minimum of 3 months to a maximum of 17 yr. The majority of patients were male (68%).

Symptoms of anaphylaxis

In the cohort of 167 registered anaphylactic reactions in children and adolescents the most frequently affected organ systems were the skin (89%) and respiratory tract (87%) followed by symptoms of the cardiovascular system (47%) and the gastrointestinal tract (43%) (Table 1). If single symptoms were considered, dyspnoea was the most common registered symptom (75%), followed by symptoms of the skin such as urticaria (67%), angioedema (47%) and pruritus (29%). The fifth most common sign was stridor (23%) followed by the gastrointestinal symptom of vomiting (22%) and the cardiovascular symptom of vertigo (22%) (Table 1). One fatal reaction of a 13-yr-old girl caused by peanut allergy was registered.

Provoking allergens

Among the most frequent elicitors of anaphylaxis, food allergens accounted for 58% (n = 115) of the cases, followed by insect venom (24%; n = 47) and drugs (8%; n = 16). Interestingly, specific immunotherapy was also registered by 1.5% (n = 3) of all cases as a cause of a severe systemic allergic reaction. Other causes accounted for 2.5% (n = 5) and latex for 0.5% (n = 1) of the cases. In 5% (n = 10) of the cases the provoking allergen was given as unknown.

A detailed analysis of food allergens revealed that legumes (n = 36), and in particular peanuts (n = 26), are the most frequent food allergens causing severe allergic reactions. This was followed by tree nuts (n = 29), in detail 11 cases of hazelnut and 5 cases of cashew. The third most frequent food

Table 1 Symptoms of registered anaphylactic cases in children and adolescents (659 registered symptoms in 167 cases)

Symptoms of registered cases	n (%)
Cutaneous	148 (89)
Urticaria	111 (67)
Angioedema	78 (47)
Pruritus	49 (29)
Flushing	21 (13)
Erythema	16 (10)
Respiratory	145 (87)
Dyspnoea	125 (75)
Stridor	39 (23)
Apnoea	4 (2)
Cardiovascular	78 (47)
Vertigo	36 (22)
Drop in blood pressure	23 (14)
Tachycardia	15 (9)
Reduction of consciousness	15 (9)
Collapse	14 (8)
Cardiac arrest	1 (1)
Gastrointestinal	72 (43)
Vomiting	36 (22)
Nausea	34 (20)
Abdominal pain	27 (16)
Diarrhoea	8 (5)

allergens were animal-related food products (n = 26) such as cow's milk (n = 11) and hen's egg (n = 8). Other food allergens like fruits, vegetables or cereals accounted for severe allergic reactions only in single cases (Table 2). Combinations of food like e.g. tree nuts and legumes were registered in five cases all together. In addition some cases were only given with the food group name, e.g. animal-related food, tree nuts (Table 2). In these cases the food was not specified in more detail. In three cases the food, which caused anaphylaxis, was not specified at all and was only indicated as 'food'.

Accompanying factors

Accompanying factors – which might be regarded as aggravating factors – were observed in 18.3% (n = 36) of all cases. The most frequent factors were exercise (n = 19; 10%) and drugs (n = 12; 6%). Among drugs the most common substances were non-steroidal anti-inflammatory agents (n = 5) and antipsychotic drugs (n = 4). Five children (3%) were suffering from an infection when experienced the severe allergic reaction. Psychological stress was given in three cases (2%). Menstruation was given in 3 (10%) among 29 female adolescents aged from 13 to 17 yr. Alcohol consumption was not reported in this series of registered cases. In four patients, more than one accompanying factor was registered. The most frequent observed combination of an allergen with another factor was the consumption of food allergens followed by physical exercise (n = 10). This was most frequently the case when tree nuts (n = 3) were the eliciting food allergens, but also the following food allergens were given once each: apple, pepper, wheat, fish, peanut, sesame and a combination of

Table 2 Food allergen panel eliciting anaphylaxis in children and adolescents (proportion of food allergen groups and number of single food allergens eliciting anaphylaxis; n = 115)

Food groups	Single food	n
Legumes (n = 36; 31.3%)	Peanut	26
	Legumes*	5
	Pea	2
	Chickpea	1
	Lupine	1
	Soy	1
Tree nuts (n = 29; 25.2%)	Hazelnut	11
	Cashew	5
	Almond	4
	Walnut	3
	Tree nuts*	3
	Pistachio	2
	Para nut	1
Animal-related food (n = 26; 22.6%)	Cow's milk	11
	Hen's egg	8
	Fish	4
	Shellfish	2
	Animal-related food*	1
Fruits (n = 5; 4.3%)	Apple	2
	Mango	2
	Lychee	1
Spices and other (n = 5; 4.3%)	Sesame	3
	Garlic	1
	Spices*	1
Combination of food (n = 5; 4.3%)	Tree nut & Legume	4
	Animal food & Vegetables	1
Vegetables (n = 3; 2.6%)	Celery	2
	Pepper	1
Cereals (n = 3; 2.6%)	Cereals*	2
	Wheat	1
Food (n = 3; 2.6%)	Food†	3

* In these cases the exact eliciting food was not specified.

† In these cases the food was not specified at all.

hazelnut and peanut. The second most common combination of an allergen with another factor were insect venoms and exercise (n = 6).

Recurrent reactions

Recurrent reactions may happen throughout childhood and may be a risk factor for fatal reactions. Indeed, in 26% of the affected patients a previous reaction before the one reported in this study was registered. Seventy-five per cent of these repetitive reactions were caused by foods. Among these most frequently peanut (26%) was given as the eliciting food.

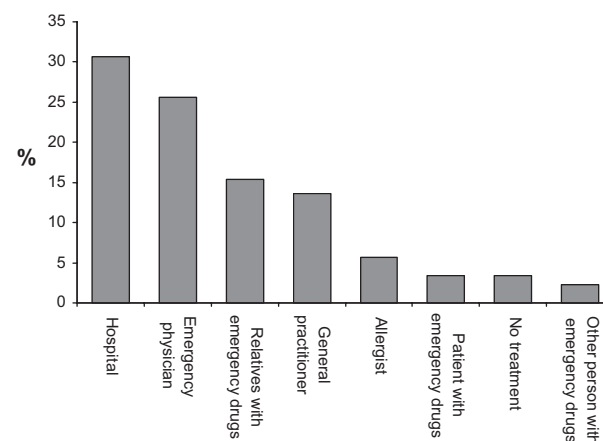
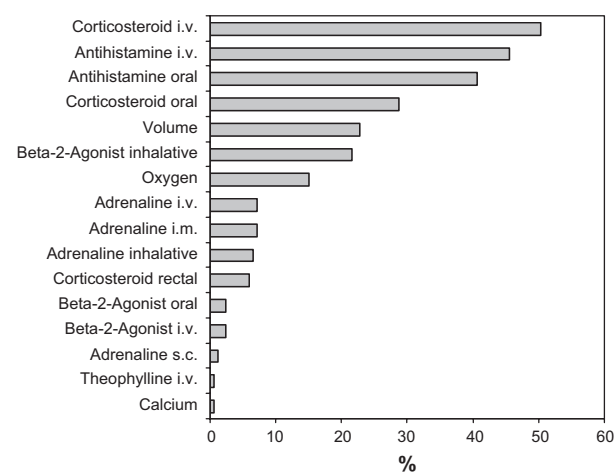
Treatment of anaphylactic reactions

The primary care of the affected patients was provided by different persons or institutions, including emergency settings (57%), relatives using the emergency drugs (15%), general practitioners (14%), allergists (6%), patients (3%) and other

persons (2%) using the emergency drugs. Six out of 176 patients (3%) did not receive any treatment (Fig. 1). In 21 patients no information concerning the primary care was available.

The most frequently applied drugs were intravenously administered corticosteroids (50%) and antihistamines (46%), but also the oral application of these drugs (oral corticosteroids = 29%, oral antihistamines = 41%) and rectal application in case of corticosteroids (6%). In total, antihistamines were given in 144 (87%) cases and corticosteroids in 142 (85%) cases. Other emergency measures such as volume support (23%), inhalant beta-2-agonists (22%) and oxygen (15%) were also given.

Adrenaline was administered 12 times intramuscularly, 12 times intravenously, 11 times by inhalant applications and surprisingly 2 times subcutaneously (Fig. 2). Overall, adrenaline was used in 37 out of 167 cases (22.2%).

**Figure 1** Persons or institutions providing primary care to anaphylactic patients (n = 176). In 21 patients no information was available.**Figure 2** Panel of applied drugs among registered cases (432 applied drugs in 167 cases). In 30 cases no information was available.

In 6 out of 167 cases the patient did not receive any therapy at all. In 30 cases no information concerning the treatment given were available.

Discussion

The registry of German speaking countries is a clinical registry with the aim to characterize a patient cohort suffering from anaphylaxis and to obtain information about the medical care of these patients. It provides clinical data in its present form and cannot deliver epidemiological data like rates of incidence or prevalence.

We observed that the life-threatening respiratory symptoms were more frequent (87%) than cardiovascular ones (25%). The most common concomitantly affected organ was the skin [urticaria (67%) and angioedema (47%)]. Although food is the main cause of anaphylaxis in children, symptoms of the gastrointestinal tract occurred less frequently (43%). Considering the overall appearance of anaphylaxis in children and adolescents we identified in our cohort the skin (89%) and the respiratory tract (87%) as major target organs, which has also been shown in previously published data (3, 7, 21). Also the dominance of the life-threatening respiratory symptoms has been described previously. Pumphrey described that most fatal food anaphylaxis were caused due to difficulty in breathing and most iatrogenic and venom reactions due to shock (9). Furthermore it was assumed that the age of patients does not influence the mode of symptoms. To clarify these observations in more detail large patient cohorts are needed.

Several previous studies have shown that food allergens are the most frequent provoking allergens in anaphylaxis in children and adolescents (4, 7, 13). The proportion of 58% for food as an allergen in our study is within a comparable range from other European studies (7, 13).

Insect venom and drugs were the second and third most frequent cause of anaphylaxis in children and adolescents. These data are in line with data from the German study of Mehl et al., in which insect venom was the second most frequent allergen of anaphylaxis (7). However, in this study specific immunotherapy was the third most frequent cause of anaphylaxis in children (7). This finding was not confirmed in our study. One reason for this difference might be that the inclusion criteria by Mehl et al. were not as strict as for the anaphylaxis registry resulting in 24% of their cases not showing life-threatening symptoms. Another reason might be that the study from Mehl et al. considered primarily paediatricians from private practices (77% of the responding physicians), whereas within the anaphylaxis registry the majority of reporting doctors are from clinic based allergy centres (95%). This assumption is strengthened by the observation that specific immunotherapy is more frequently determined as an allergen for severe allergic reactions if cases from private practices are considered (22).

Which medical doctor is reporting also has an impact on the registration of fatal reactions, which are probably under-represented in this German-speaking registry. The specialized centres see patients, who have suffered from an anaphylactic

reaction, to perform the allergy follow-up, but do not have information about fatal reactions. To receive reliable data on fatal reactions information, data from emergency rooms or other hospital departments must be considered.

Among food allergens, peanut was the most frequent food allergen – also for recurrent reactions. The only registered fatal reaction was caused by peanut as well. Peanut is well-known to be responsible for severe allergic reactions even after the ingestion or inhalation of very small amounts (3, 9, 11).

Data about the identified causes of the anaphylactic reaction are reliable, as they were delivered from specialized allergy-clinics, which perform a detailed diagnostic work-up in a standardized manner. However, the data about accompanying factors need to be taken with great care as these have not been verified by provocation tests. Nevertheless we suppose this is an important observation.

Accompanying factors were supposed in 18% of the cases. Among these the most frequent suspected factor was exercise (10%). A similar percentage (9%) was also observed in a children-cohort by Novembre et al. (13), another study by Uguz et al. (10) reported only 2.5%. Several reports have proven the influence of exercise on anaphylaxis (10, 12, 23, 24). It is presumed that exercise leads to an increased mast cell releasability and a dysfunction of the autonomic nervous system (25, 26). In addition an increased gut permeability may enhance the availability of allergenic proteins to the gut-associated immune system (24).

Although we cannot prove the clinical relevance of the supposed factors our observation together with numerous reports from the literature suggest that they are most likely important and that further investigations to clarify their exact role are urgently needed.

Concerning the data about the emergency treatment it should be taken into consideration that these data are gathered from secondary and not from primary sources, e.g. emergency physicians.

Only 20% of patients, relatives or other persons respectively used their emergency drugs. Considering that in 26% of the cases the reactions occurred repeatedly, patients should always carry their emergency drugs with them and should know how to use it. To achieve an improved handling of the adrenaline autoinjector standardized educational programmes with defined training items how to use the emergency drugs and with information about the handling of allergens in daily life are important. In Germany such a programme is currently under evaluation (27).

The finding that up to 50% of the severe allergic reactions were observed and treated by emergency doctors supports the view that the inclusion criteria of severity were fulfilled. However, although pulmonary and/or cardiovascular symptoms were present in all registered cases, adrenaline was only used in 22.2% of the registered cases. From previous studies it became obvious that the frequency of the use of adrenaline differs in Europe compared to the US. Adrenaline is much more often used in the US (79–84%) whereas in Europe the numbers are remarkably lower (11–18%) (3, 10, 13, 21). This may reflect different views on treatment indications, but may

also indicate the need for educational programmes in Europe, not only for affected patients and their parents but also for physicians. On the other hand, there are no data so far which indicate that the more restrictive use of adrenaline in Europe is accompanied by a higher rate of deaths. One may hypothesize that even severe anaphylactic reactions may be self-limiting. Due to ethical reasons no prospective controlled studies on the effectiveness of adrenaline in anaphylaxis are available. Appropriate models, which allow studying such effects, are warranted.

In summary, the present data confirm that food allergens are the main triggers of anaphylaxis in children and adolescents in German speaking countries. Additionally the data indicate that possible aggravating factors should always be considered in the allergic assessment of severe allergic reactions in children and young adults. The high number of recurrent reactions and the low usage of adrenaline in emergencies underline the need for educational programmes for the patients as well as for the physicians.

Acknowledgments

The following persons and centres are participating in the registry and have contributed cases to this publication: A. Bircher, Allergy Unit, Department of Dermatology, University Hospital Basel, Switzerland; B. Przybilla, Department of Dermatology and Allergology, Ludwig-Maximilian-University Munich, Germany; G. Hansen, Department of Paediatric Pneumology and Neonatology, Hannover Medical School, Germany; R. Lang, Department of Dermatology, Paracelsus Medical University Salzburg, Austria; M. Rett, Children's Hospital, Clinic Itzehoe, Germany; A. Nordwig, Children's Hospital Dresden-Neustadt, Dresden, Germany; P. Eng, Paediatric Pulmonology and Allergy/Immunology, Children's Hospital Lucerne and Paediatric Pulmonology and Allergy/Immunology, Children's hospital Aarau, Switzerland; C. Pfohler, Department of Dermatology, The Saarland University Hospital Homburg/Saar, Germany; V. Mahler, Department of Dermatology, University Hospital Erlangen, Germany; T. Fuchs, Department of Dermatology, Venerology and Allergy, Georg-August-University Goettingen, Germany; I. Yildiz, Children's Hospital, Friedrich-Ebert-Hospital Neumuenster, Germany; G. Stichtenoth, Department of Paediatrics, University of Luebeck, Germany; A. Schuster, Department of paediatrics, University of Duesseldorf, Germany; M. Polz, Children's Hospital, GPR Hospital Ruesselsheim, Germany; M. Henzgen, Pneumology/Allergology of the Department of Internal Medicine I, Friedrich-Schiller-University Jena, Germany; R. Bruns, Department of Paediatrics, Ernst-Moritz-Arndt-University of Greifswald, Germany; A. Heinzmann, Paediatrics and Adolescent Medicine, University of Freiburg, Germany; P. Schmid-Grendelmeier, Department of Dermatology, University Hospital of Zurich, Switzerland; R. Treudler, Department of Dermatology, Venerology and Allergy, University Hospital of Leipzig, Germany; H. Dickel, Department of Dermatology and Allergology, Ruhr-University Bochum, Germany; F. Friedrichs,

Private paediatric practice Laurensberg Aachen, Germany; T. Spindler, Waldburg-Zeil Hospitals, Department of Paediatrics, Clinics Wangen im Allgäu, Germany; N. Hunzelmann and G. Siebenhaar, Department of Dermatology and Venerology, University Hospital of Cologne, Germany; E. Coors, Department of Dermatology and Venerology, University Medical Center Hamburg-Eppendorf, Germany; S. Schweitzer-Krantz, Children's Hospital, Evangelic Hospital Duesseldorf, Germany; W. Aberer, Department of Dermatology, Medical University of Graz, Austria.

The following persons and centres are participating in the registry: H. Merk, Department of Dermatology, University Hospital Aachen, Germany; K. Tenbrock and S. Lehmann, Department of Paediatrics, University Hospital Aachen, Germany; M. Gerstlauer, Clinic for children and juvenile, Clinical Centre Augsburg, Germany; J. Kleine-Tebbe, Allergie- u. Asthma-Zentrum Westend, Berlin, Germany; M. Bücheler, Department of Otorhinolaryngology, Head and Neck Surgery, Allergology, Evangelical Hospital Bonn, Germany; T. Bieber and J. Hanfland, Department of Dermatology, University Hospital Bonn, Germany; S. Schmitt-Grohe and D. Vlainic, Department of Paediatrics, University Hospital Bonn, Germany; V. Heckmann, Department of Paediatrics, Prof. Hess Hospital Bremen, Germany; J. Fischer, Department of Dermatology, University of Tuebingen, Germany; K. Schäkel, Department of Dermatology, University Hospital Carl Gustav Carus, Technical University of Dresden, Germany; U. Hillen, Department of Dermatology, University Hospital Essen, Germany; C. Szliska, Department of Dermatology Hospital Bethesda, Freudenberg, Germany; J. Klinge and I. Neustädter, Department for children and adolescents, Hospital Fuerth, Germany; B. Kreft, Department of Dermatology and Venerology, Martin-Luther-University Halle-Wittenberg, Germany; W. Rebien, Allergological private practice Rebien Hamburg, Germany; B. Wedi, Department of Dermatology, Hannover Medical School, Germany; P. Vöhringer, Department of Paediatrics, Hospital Karlsruhe, Germany; R. Fölster-Holst, Department of Dermatology, University of the Clinics of Schleswig-Holstein, Kiel, Germany; S. Nestoris, Department of Dermatology, Medical Center Lippe-Deilmold, Germany; C. Schirpke, Department of Pneumology, Lungenklinik Lostau, Germany; J. Grabbe, Department of Dermatology and Allergy, University of Luebeck, Germany; J. Ring and K. Brockow, Department of Dermatology and Allergy Biederstein, Technical University Munich, Germany; R. Brehler, Department of Dermatology, University Hospital Muenster, Germany; S. Volkmuth, Department of Paediatrics, Hospital Niederrhein Velbert, Germany; M. Geißler, ENT-Unit Otto-Körner Rostock, Germany; F. Riffelmann, Allergology Unit, Hospital Kloster Grafschaft/Schmallenberg, Germany; S. Thies, Department of Dermatology and Allergy, Asklepios Hospital Uckermark Schwedt, Germany; U. Lepp, Private practice of cardiology and pneumology Stade, Germany; U. Rabe, Clinic of Pneumology, Johanniter-Hospital Treuenbrietzen, Germany; H. Rebmann, Department I (General Pediatrics, Hematology and Onkology), University Children's Hospital Tuebingen, Germany; L. Klimek and O. Pfaar, Department

of Otorhinolaryngology, Head and Neck, University Hospital Mannheim, Germany; W. Brosi, Paediatric pneumology and allergology, private practice am Dom Würzburg, Germany; E. Varga, Department of Paediatrics, Medical University of Graz, Austria; N. Reider, Department of Dermatology and Venerology, Medical University of Innsbruck, Austria; I. Huttegger, Clinic of Paediatrics, University Hospital Salz-

burg, Austria; T. Kinaciyan and K. Hoffmann-Sommergruber, Department of Dermatology and Centre of Physiology and Pathophysiology, Medical University of Vienna, Austria; A. Helbling, Clinic of Allergology, University Hospital Bern, Switzerland; P. Eigenmann, Clinic of Paediatrics, University Hospital Genf, Switzerland; R. Guggenheim, Department of Paediatrics, Triemli City Hospital Zurich, Switzerland.

References

- Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* 2007; **120**: 878–84.
- Wilson R. Upward trend in acute anaphylaxis continued in 1998–1999. *BMJ* 2000; **321**: 1021–2.
- Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol* 2004; **113**: 536–42.
- Macdougall CF, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child* 2002; **86**: 236–9.
- Sampson HA, Munoz-Furlong A, Campbell RL, 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. *Ann Emerg Med* 2006; **47**: 373–80.
- Johansson SG, Bieber T, Dahl R, 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**: 832–6.
- Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children – a questionnaire-based survey in Germany. *Allergy* 2005; **60**: 1440–5.
- Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; **1**: 466–9.
- Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000; **30**: 1144–50.
- Uguz A, Lack G, Pumphrey R, et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy* 2005; **35**: 746–50.
- Wang J, Sampson HA. Food anaphylaxis. *Clin Exp Allergy* 2007; **37**: 651–60.
- Romano A, Di Fonso M, Giuffreda F, et al. Food-dependent exercise-induced anaphylaxis: clinical and laboratory findings in 54 subjects. *Int Arch Allergy Immunol* 2001; **125**: 264–72.
- Novembre E, Cianferoni A, Bernardini R, et al. Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 1998; **101**: E8.
- Burstein M, Rubinow A, Shalit M. Cyclic anaphylaxis associated with menstruation. *Ann Allergy* 1991; **66**: 36–8.
- Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy* 2007; **62**: 857–71.
- Sicherer SH, Simons FE. Quandaries in prescribing an emergency action plan and self-injectable epinephrine for first-aid management of anaphylaxis in the community. *J Allergy Clin Immunol* 2005; **115**: 575–83.
- Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics* 2003; **111**: 1601–8.
- Ring J, Brockow K, Duda D, et al. Akuttherapie anaphylaktischer Reaktionen. *Allergo J* 2007; **16**: 420–34.
- Pouessel G, Deschildre A, Castelain C, et al. Parental knowledge and use of epinephrine auto-injector for children with food allergy. *Pediatr Allergy Immunol* 2006; **17**: 221–6.
- Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy* 2004; **34**: 285–90.
- Dibs SD, Baker MD. Anaphylaxis in children: a 5-year experience. *Pediatrics* 1997; **99**: E7.
- Worm M, Hompes S, Vogel N, Kirschbaum J, Zuberbier T. Care of anaphylaxis among practising doctors. *Allergy* 2008; **63**: 1562–3.
- Aihara Y, Kotoyori T, Takahashi Y, Osuna H, Ohnuma S, Ikezawa Z. The necessity for dual food intake to provoke food-dependent exercise-induced anaphylaxis (FEIAN): a case report of FEIAN with simultaneous intake of wheat and umeboshi. *J Allergy Clin Immunol* 2001; **107**: 1100–5.
- Du Toit G. Food-dependent exercise-induced anaphylaxis in childhood. *Pediatr Allergy Immunol* 2007; **18**: 455–63.
- Fukutomi O, Kondo N, Agata H, Shinoda S, Shinbara M, Orii T. Abnormal responses of the autonomic nervous system in food-dependent exercise-induced anaphylaxis. *Ann Allergy* 1992; **68**: 438–45.
- Kivity S, Sneh E, Greif J, Topilsky M, Mekori YA. The effect of food and exercise on the skin response to compound 48/80 in patients with food-associated exercise-induced urticaria-angioedema. *J Allergy Clin Immunol* 1988; **81**: 1155–8.
- Brockow K, Ring J. Food anaphylaxis. *Anal Bioanal Chem* 2009; **395**: 17–23.