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FOOD-INDUCED ANAPHYLAXIS MORBIDITY: EMERGENCY DEPARTMENT AND HOSPITALIZATIONS DATA SUPPORT PREVENTIVE STRATEGIES

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Key message: Food-induced anaphylaxis (FIA) admissions are increasing worldwide and most cases seem to be accidental. We review published morbidity epidemiological data relating to FIA and potential risk factors, in order to provide evidence-based recommendations to reduce the risk of severe adverse outcomes.

ABSTRACT:

BACKGROUND: Anaphylaxis is a recognized public health issue. There is no doubt that food-induced anaphylaxis (FIA) has tremendous impact on the quality of life of patients and their families and increases direct and indirect costs. FIA is associated with increasing rates of emergency department admissions and hospitalizations and implies the risk of death. Morbidity epidemiological data is key to tailor public health actions to this non-communicable disease. The aim of this article is to review published morbidity epidemiological data relating to FIA and potential risk factors, in order to provide evidence-based recommendations to reduce the risk of severe adverse outcomes.

METHODS: We identified published studies available in PUBMED/MEDLINE (1966–2020), EMBASE (1980–2020), CINAHL (1982–2020). The systematic review was carried out using MeSH terms related to FIA ED admissions and hospitalizations.

RESULTS: A total of 25 articles were selected, 80% published in the last 5 years. After critical analysis of methodological and clinical characteristics reported in the data selected, we were able to propose preventive strategies.

CONCLUSION: Anaphylaxis is a recognized public health issue. FIA is associated with increasing rates of ED admissions and hospitalizations and imply in risk of death. More than reviewing and critically interpreting the key patterns related to FIA morbidity published data, we proposed strategies in order to promote quality care of patients suffering from FIA. Our World Health Organization Collaborative Center is deeply involved in this process and we believe that the proposed strategies will inform future healthcare policies on anaphylaxis. The long-term objective would be to improve clinical care and quality of life of patients and their families, and develop risk-stratified, cost-effective preventive measures.

KEYWORDS: anaphylaxis admission, emergency visit, hospitalization, food allergy, food-induced anaphylaxis, morbidity

90 **BACKGROUND:**

91 *Anaphylaxis morbidity*

92 The World Health Organization (WHO) defines health statistics as estimates related to health, such as
93 mortality, morbidity, risk factors, health service coverage, and health systems. Morbidity statistics
94 measure the extent of a nation's health and provision of health facilities, which can be also used to
95 investigate patterns of occurrence of an illness, it can be a powerful tool in the anaphylaxis epidemiology
96 and public health planning (1,2). Although with limitations, hospital and emergency admissions data sets
97 represent the largest and most robust data available to understand trends in anaphylaxis and gather
98 anaphylaxis morbidity data (3).

99 Measuring and evaluating epidemiological data related to anaphylaxis are recognized means to tailor
100 public health actions by identifying trends, burden of disease and potential risk factors can be identified.
101 Morbidity and mortality data have been used as the main epidemiological and outcome variables.
102 Updated information regarding anaphylaxis epidemiology is usually generated from analyses of general
103 population surveys, large clinical registries, and administrative databases (4). The lack of accurate
104 epidemiological data implies in practical negative health coverage outcomes, such as the lack of
105 adrenaline auto-injectors in more than 60% of world countries (5).

106

107 *Food-induced anaphylaxis*

108 Epidemiology data of food-induced anaphylaxis (FIA) is heterogeneous, and FIA is a major cause of
109 anaphylaxis which lifetime risk has been estimated to be at least 1.6% (6). Anaphylaxis is a recognized
110 cause of death in all ages, and anaphylaxis related mortality rate is less than 1 per million per year.
111 However, difficulties in the collection and interpretation of epidemiological anaphylaxis data must be
112 acknowledged (4). In infancy there is a paucity of anaphylaxis data due to under-recognition and under-
113 diagnosis, worsened by different age-related patterns of specific manifestation (7).

114 Over the last few decades, with increasing prevalence, FA has emerged as a global health problem
115 affecting up to 10% of the paediatric population and 2-3% of adults in Western countries (8-12). FA is
116 known as having significant effects on the health-related quality of life for patients and their families, with
117 incremental increases in social, emotional and financial burdens (3). Patients with milder clinical
118 presentations, such as manifestations restricted to oral symptoms, undoubtedly need diagnostic care, but
119 may not require as much therapeutic and management resources as required in life-threatening
120 conditions, such as food-induced anaphylaxis (FIA).

121 Although publications on FIA have been increasing over the last 10 years and published data have
122 indicated increasing prevalence in some countries, there is still a lack of knowledge of precise populations

123 at risk and accurate epidemiological data. This information could in turn support better clinical practice
124 and possibly prevent future severe reactions and avoidable fatalities. Emergency department (ED) and
125 hospital admissions provide the most robust and largest datasets to understand trends of FIA.

126 The aim of this article is to review published morbidity and epidemiological data relating to FIA through
127 populational-studies on hospitalization and emergency admissions, in order to identify possible
128 populations at-risk and provide evidence-based recommendations to reduce the risk of severe adverse
129 outcomes in food anaphylaxis.

130

131 **COLLECTING FOOD-INDUCED ANAPHYLAXIS MORBIDITY DATA**

132 **METHODS:**

133 We identified published studies available in PUBMED/MEDLINE (1966–2020), EMBASE (1980–2020),
134 CINAHL (1982–2020). The search was performed in 13th July 2020, with terms generated using known
135 terms and synonyms suggested by librarians and allergy specialists to capture all text words and Medical
136 Subject Heading (MeSH) terms. The strategy of search was based in the combinations of used MeSH
137 terms: “Food-induced anaphylaxis”, “hospitalization”, “Food-induced anaphylaxis morbidity”, “Food-
138 induced anaphylaxis admission” and “emergency department”. We included only populational-based
139 studies related to hospital and emergency admissions. All the articles were screened in parallel by two
140 independent authors. In all cases, disagreements were openly discussed among the co-authors. The
141 Cohen's kappa coefficient demonstrated high agreement between the two reviewers (Kappa = 0.83).
142 We included 25 reports describing epidemiological data and risk factors for FIA admissions and/or
143 strategies to reduce FIA morbidity. Studies were reviewed by two authors, who screened full-text articles
144 and were finally approved by all co-authors. The eligible studies formed the basis of analysing qualitative
145 data related to study design, population characteristics, rates of anaphylaxis morbidity (Table 1), food
146 triggers, clinical patterns and management (Table 2).

147

148 **RESULTS:**

149 A total of 25 articles were selected, 80% published in the last 5 years. Most publications (76%) originated
150 from the European Union (EU, 44%) and United States (US, 32%). Half of the manuscripts dealt specifically
151 with the paediatric population and ethnicity was addressed in 25% of the documents.

152 Table 1 demonstrates that most of FIA related admissions occurred in the male gender before the age of
153 15 and the trends seem to change after adolescence with higher numbers in the female population (56%).

154 Detailed clinical description of the manifestations and severity are missing in most of the studies in which
155 national databases were used (60%), but skin manifestations (24%), respiratory (24%), gastrointestinal

(16%) and cardiovascular (8%) manifestations seemed to be the main clinical presentations. Peanuts were the main triggers of FIA in all ages (52% of the studies), and cow's milk (52%) and egg (36%) in early ages. Few differences and specifications related to food triggers were reported according to the geographic areas of the manuscripts. Asthma was the main co-factor/risk factor related to FIA admissions (60%), but personal history of anaphylaxis and food allergy (60%) were described in older children. Details regarding the specific types of treatment are limited to 20% of the publications. However, the rates of adrenaline use seemed to be variable between studies and age groups. Only 4 manuscripts (16%) mentioned the setting where the reaction occurred, all of them outside the health care system.

As observed in Table 2, studies covered an average of 7 years of data from national or institutional databases. Morbidity records, covering ED admissions and hospitalizations, were collected using the World Health Organization's (WHO) International Classification of Diseases (ICD)-9, ICD-10 or national adaptations in 84% of studies. Data from the 4 remaining studies were extracted using anaphylaxis registries. No other classification, such as Systemized Nomenclature of Medical Clinical Terms (SNOMED-CT), was used. There was no description of which severity score was applied in the selected reports. There are significant differences in global FIA admission rates, but trends based on the selected publications indicated increasing numbers of hospitalizations due to FIA, with a peak in the childhood (Table 1).

DISCUSSION:

The data presented was able to capture the global trends of FIA and to identify possible at-risk phenotypes. We could also identify unmet needs and propose strategies to prevent FIA.

GLOBAL TRENDS OF FOOD-INDUCED ANAPHYLAXIS MORBIDITY

Most of the data analysed were generated at the country level; thus, our data was able to provide a big picture of the global trends of FIA and support public health strategies.

The data presented was able to demonstrate that the FIA ED and hospital admissions are increasing in many countries. However, published data have demonstrated that the rate of fatalities due to FIA is not following the same trends, with mortality rates decreasing in some world regions.

Recognized difficulties in obtaining accurate anaphylaxis data are the variations in definitions of anaphylaxis across different world regions, across different time periods when the studies were done, logistical and coding issues related to collection of large health data sets, and the inherent difficulties in collecting data for a disease states that frequently occurs in the community, not within a hospital, captive region or health resources (3,4).

188 Due to country-to-country differences of food intake and disease prevalence, trends should be better
189 analyzed using longitudinal data or repeating cross-sectional studies in the same country with the same
190 methodology. Registries are also a good source of information, in which more detail would be available
191 although they introduce a selection bias and do not reflect the country level epidemiological data.
192 Although the trends of hospitalizations of FIA seem to be increasing worldwide, most of the population-
193 based studies do not address the possibility of recurrence of episodes, and, therefore, of cumulative
194 incidence. For this reason, most epidemiological studies using incidence as the main variable may
195 overestimate the number of anaphylactic episodes (4). Conversely, the true frequency of anaphylaxis is
196 possibly underestimated due to under-recognition of early manifestations and hence under-diagnosis by
197 health care professionals (3,4).
198 Although morbidity studies are key for clinical and epidemiological utility, most documents are based on
199 ED admissions and hospitalizations, which may imply in the identification of only more severe cases of
200 anaphylaxis. Mild reactions may not be captured in these studies, particularly those managed before the
201 ED admission and without presentation at health care facilities. Although the severity scoring systems for
202 anaphylaxis should be interpreted as a dynamic progression of anaphylaxis, mild manifestations can be
203 underrecognized and under-reported.
204 One of recognized difficulties in gathering accurate anaphylaxis data in population-based studies both for
205 morbidity (13) and for mortality (14) is the misclassification of this condition under the WHO ICD. The ICD
206 is the broadest classification and coding system used to monitor the incidence and prevalence of diseases
207 and other health problems, reflecting the general situation in countries and populations (15). In other
208 words, if a condition or a group of diseases are badly represented in this international health
209 classification, it hampers the visibility of these conditions and prevent public health actions and
210 investments.
211 Despite limitations of population-based studies, the reported increases of FIA probably reflect a true
212 increment in the prevalence of allergic conditions, but are also confounded by cumulative incidence of
213 anaphylaxis, better awareness and recognition of anaphylaxis, and changes in anaphylaxis coding, in part
214 due to modifications in the ICD, and further improvement in the definition of the anaphylaxis overtime
215 (16).

216

217 **SCOPE OF THE PROBLEM: FOOD-INDUCED ANAPHYLAXIS MORBIDITY**

218 The data presented was able to identify potential phenotypes at-risk of FIA. We could provide evidence-
219 based data. For example, we observed a change in the prevalence of anaphylaxis rates associated with
220 gender. Hormonal status and the X-chromosome coded factors are deeply involved in the regulation of T-

cell and B-cell responses, which may influence the gender differences noticed in allergic diseases (17). Although the influence of hormones is not fully understood in anaphylaxis, the possible role of sex hormones is indirectly suggested through the rare phenotype of catamenial and breastfeeding anaphylaxis (18). Estrogen and progesterone affect mast cells *in vitro* but *in vivo* effects are still unknown (18,19). Animal models have demonstrated that anaphylaxis is more severe in female than male mice and that estrogens upregulate endothelial nitric oxide synthase and mast cell degranulation, resulting in increased vascular permeability and systemic manifestations (20).

The highest rates of non-fatal FIA occur in young children, but the greatest risk appears to be in adolescence and young adulthood (8,9). Recently, a study suggested a distinct FIA phenotype when infants (≤ 12 months) were compared with pre-school children (1-6 years). Infants presented with their first anaphylaxis episode triggered by cow's milk, and manifested a higher frequency of hives, hypotonia and hypotension (21). Adolescent and young adult patients are at higher risk due to specific challenges associated with this age group where transition to adulthood requires an added multidisciplinary involvement for training, enhancing knowledge and skills to guide and empower them to self-manage their health condition (22).

The most frequent food allergens involved in FIA at any age are peanut and tree nuts, accounting for 55% to 87% of deaths (8,9,11,12). However, food triggers can vary with country-specific or world region-specific consumption patterns. In some countries, such as in UK and in France, milk has been identified as the main food implicated in FIA (22,23). Goat and sheep milk are responsible for 13% of anaphylaxis deaths in France (23). Meanwhile, seafood and fish are relevant FIA inducers in Australia and Portugal (Table 1). Currently, peanut allergy affects 2% of the general population, and is associated with higher rates of accidental exposure, severe reactions and potentially fatal cases of FIA (23,24). It is estimated that approximately 7-14% of patients with peanut allergy experience accidental exposure annually, and one-third to one-half experience anaphylaxis (24,25). There is no doubt that preventing new episodes of FIA is able to decrease avoidable deaths.

Both asthma and anaphylaxis are recognized noncommunicable hypersensitivity conditions, which can coexist, mimic or worsen each other (26). As shown in most selected publications within our study, an history of asthma is a known risk factor for FIA admissions and fatal FIA, primarily from bronchospasm and laryngeal angioedema, with cardiovascular collapse generally occurring secondary to hypoxia and respiratory arrest (26,27). Limited data in population-based studies are available regarding the association with mast cell disorders.

252 Although ED and hospitalization data have been included in our study, limited number of documents
253 addressed specific treatments. Delayed administration or incorrect use of adrenaline or AAI are known
254 risk factors for FIA worst outcomes.

255 In summary, we could identify 2 populations at-risk to develop severe FIA: (i) male pre-school children,
256 with uncontrolled asthma or frequent episodes of bronchospasm, with FIA due to milk or egg; (ii) female
257 with more than 15 years, with personal history of food allergy or anaphylaxis and uncontrolled asthma,
258 with FIA due to peanuts. In both cases, FIA is initiated outside the healthcare settings.

259

260 **GENERAL STRATEGIES TO REDUCE FOOD-INDUCED ANAPHYLAXIS**

261 *Implementing awareness, policies and collaboration between specialties*

262 Populations at-risk should be the main starting targets of preventive measures. Most cases of anaphylaxis,
263 including FIA, are often first seen by general practitioners (GPs), pediatricians or emergency room doctors.
264 However, only approximately 50% of patients are referred to allergists for further investigation and/or
265 treatment and risk stratification (28,29). Recommendations for follow-up and trigger avoidance at the time of
266 discharge from the ED are provided infrequently putting the patient in danger. In order to strengthen the
267 health care pathways and optimize the patients' time across the health system, the EAACI Logogram task force
268 together with the Montpellier WHO Collaborating Centre leadership are moving efforts at national and
269 international levels in order to implement actions and collaboration among specialists (30).

270 With the aim of trying to standardize management of anaphylaxis and promote quality care, the allergy
271 academies have been moving efforts to provide guidance (6,23,31-36). The WAO anaphylaxis committee has
272 just provided a great piece of work to support a better management of anaphylaxis in different world regions
273 (37). Meanwhile, many initiatives have been produced in order to promote awareness among health
274 professionals and the lay population, such as the World Allergy Week and the EAACI Food Allergy and
275 Anaphylaxis Campaigns (37,38).

276 Most of FIA cases happen outside of the healthcare systems and may be due to accidental exposure.
277 Increasing the awareness and training the patients and carriers to read food labels is key to prevent
278 accidental FIA. Recent changes in European legislation (enshrined the European Food Information to
279 Consumers Regulation 1169/2011) now requires allergen information to be made available with respect
280 to 14 food allergens on all foods irrespective of whether the food is pre-packed or sold from a catering
281 establishment. These allergens include the most common ones implicated in fatal FIA (peanuts, nuts,
282 milks, fish and shellfish) (39). However, while allergen disclosure is regulated under the legislation in
283 terms of font size and language, more flexibility is allowed in catering establishments and for "loose" non-
284 prepacked foods. This has also allowed for wide variations in the provision of allergen information to

285 consumers across the EU. The Regulation also requires that “may contain” or “precautionary” warnings
286 are only used where justified and with limited regards to cross-contamination. These regulations should
287 be extended in all non-European countries.

288

289 *Strengthen the care of food-induced anaphylaxis*

290 Recently, EAACI updated the guidelines on food allergy prevention and some suggested measures are
291 aligned with the identified phenotypes. It appears that the most effective age to introduce peanut and
292 well-cooked egg as complementary feeding is from four to 6 months of life. Also, supplementation with
293 regular cow’s milk formula should be avoided in the first week of life (40).

294 Uncontrolled asthma was an identified associated factor for increased rates of ED and hospital admissions
295 due to FIA. Although the definitive diagnosis of asthma is difficult in infants, respiratory manifestations
296 should be well controlled in this population. Since uncontrolled asthma is a known risk factor for
297 developing respiratory symptoms during anaphylaxis episodes and increases the risk of fatalities.
298 Therefore, all children suffering from FIA, should have early diagnosis of asthma and receive the
299 treatment accordingly (26).

300 Most of our reports mentioned FIA in patients with personal history of anaphylaxis and food allergy,
301 accidentally triggered outside the health system, probably at home or at school. For this reason, all
302 patients with proven food allergy and anaphylaxis should receive a personalized written guidance,
303 recommendations of use of AAI when indicated and personal identification. It is crucial to strengthen the
304 communication with patients and their carriers in order to avoid accidental exposure and initiate prompt
305 treatment in case of recurrence.

306 Since FIA can occur virtually in any setting increasing the rates of admissions at the EDs and hospitals, in
307 some countries, such as France, UK, USA and Canada, Individual Healthcare Plans have been proposed to
308 be used in the school settings to communicate food allergies and their emergency action plan to staff (41-
309 44). A number of countries now require schools to have specific policies and procedures to help keep
310 food-allergic children safe. In addition, the USA, UK, France and Australia now have legislation which
311 allows for schools to source their own AAI devices (rather than an individual patient’s) for emergency use
312 (41,42). Schools need adequate support and training in order to maintain a safe environment, as
313 exemplified by the government-funded drive in New South Wales and Australia to mandate anaphylaxis
314 training in state schools (41). The availability of care action plans, policies and emergency protocols for
315 families and in schools, approved by academics and available to all physicians and healthcare
316 professionals, are intended to harmonize procedures and support ongoing dialog with governmental
317 regulators.

318

319 *Perspectives of better definition, classification and coding*

320 Recently, the definition of anaphylaxis was reviewed by the WAO in order to capture not only severe
321 cases but also align with the anaphylaxis definition proposed in the WHO ICD-11: “Anaphylaxis is a severe,
322 life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially
323 life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated
324 with skin and mucosal changes or circulatory shock.” (30,45,46). This can support for instance the
325 appropriate treatment of FIA manifested by skin and gastrointestinal symptoms, which would not be
326 termed anaphylaxis if we applied the previous definition.

327 FIA morbidity data, as well as all allergic and hypersensitivity conditions, will gain greater accuracy thanks
328 to the ICD-11 implementation. Taking the ICD-11 revision as a key window of opportunity, a detailed
329 academic and evidence-based action plan was put in place under the ALLERGY in ICD-11 initiative, led by
330 Luciana Kase Tanno and Pascal Demoly, with the aim of creating a more appropriate classification for
331 allergic and hypersensitivity conditions in the new edition of ICD. This work was a strategic international
332 academic actions acknowledged by the Joint Allergy Academies (comprising the American Academy of
333 Allergy Asthma and Immunology (AAAAI), the European Academy of Allergy and Clinical Immunology
334 (EAACI), the World Allergy Organization (WAO), the American College of Allergy Asthma and Immunology
335 (ACAAI), the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI), and the Latin
336 American Society of Allergy, Asthma and Immunology (SLAAI) and the WHO ICD representatives (46).
337 These efforts have been documented by peer-reviewed publications (4,5,13,14,16,47-55) and resulted in
338 the creation of a new “Allergic and hypersensitivity conditions” section in the chapter on “Disorders of the
339 Immune system” (46,49). We were also able to introduce changes in the WHO mortality coding rules to
340 include anaphylaxis as an underlying cause of death in official death certificates. In recognition of the
341 work done and with the aim of formalizing collaboration with the WHO Family on International
342 Classifications (WHO-FIC), a WHO Collaborating Center (WHO CC) for the Scientific Classification of
343 Allergic and Hypersensitivity Diseases was established in June 2018 at the University Hospital of
344 Montpellier, with Luciana Kase Tanno being appointed to the 20-member Medical and Scientific Advisory
345 Board to support the WHO ICD and other international classifications. ICD-11 was presented and fully
346 endorsed during the last World Health Assembly (May 2019) and this new classification is currently being
347 introduced worldwide, with full global implementation anticipated by 2022. The creation of a new
348 classification of allergic and hypersensitivity disorders in ICD-11 is considered a timely and much-needed
349 milestone in the history of the allergy specialty (16). More reliable, accurate, comprehensive and
350 comparable FIA epidemiological data will provide a far clearer global picture of these conditions and will

strengthen improved management of allergic disorders worldwide. The ICD-11 will also provide the means of correctly label FA and FIA. As the only WHO CC for classification of allergic and hypersensitivity conditions, we are establishing close collaboration with national and international bodies in order to implement actions for better patients' care, monitoring and prevention, develop collaborative research, and to launch measures to reduce avoidable deaths. Extended international actions are supported by the WHO-FIC, academic and scientific networks, the Joint Allergy Academies, stakeholders, and patient's organizations. Our WHO CC provides the means though which governmental and nongovernmental collaborating parties can align their strengths to achieve focused objectives, such as putting in place the global initiative against anaphylaxis (30). Since the availability of AAls is limited to only 32% of world countries, our WHO CC is leading the initiative to achieve global availability of AAls (8).

This study however presents some limitations. As we selected populational-based studies, it was not possible to identify recurrences of FIA nor biphasic cases of anaphylaxis. We restrained our evaluation to main clinical patterns of FIA (Table 1) and the methodologies used in the publications (Table 2), we did not assess additional data since details such as dietary restrictions or quality of life are usually not available in populational-data studies. Mild reactions are usually not captured in these studies, mostly because the ICD-9 or ICD-10 are not able to capture mild degrees of anaphylaxis. However, the ICD-11 may provide new perspective by allowing to add the severity of the reactions. The limited number of publications selected is unlikely to be related to the search process. However, we prioritised the qualitative analysis of the data. A prospective step will take place to validate our findings.

CONCLUSION:

Anaphylaxis is a recognized public health issue. FIA is associated with increasing rates of ED admissions and hospitalizations and imply in risk of death. More than reviewing and critically interpreting the key patterns related to FIA morbidity published data, we proposed strategies in order to promote quality care of patients suffering from FIA. Our WHO Collaborative Center is deeply involved in this process and we believe that the proposed strategies will inform future healthcare policies on anaphylaxis. The long-term objective would be to improve clinical care and quality of life of patients and their families, and develop risk-stratified, cost-effective preventive measures.

ABBREVIATIONS:

AAAAI: American Academy of Allergy Asthma and Immunology

- 384 AAI: adrenaline auto-injectors
- 385 ACAAI: American College of Allergy Asthma and Immunology
- 386 APAAACI: Asia Pacific Association of Allergy, Asthma and Clinical Immunology
- 387 EAACI: European Academy of Allergy and Clinical Immunology
- 388 ED: Emergency department
- 389 FA: food allergy
- 390 FIA: food-induced anaphylaxis
- 391 ICD: International Classification of Diseases
- 392 SLAAI: Latin American Society of Allergy, Asthma and Immunology
- 393 WAO: World Allergy Organization
- 394 WHO: World Health Organization
- 395 WHO CC: WHO Collaborating Center
- 396 WHO-FIC: World Health Organization- Family of International Classifications
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575 The first and last authors contributed to the construction of the document (designed the study, including
576 the questionnaire, analysed and interpreted the data, and wrote the manuscript). All the authors critically
577 revised and approved the final version of the manuscript and agree to be accountable for all the aspects
578 of the work.

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Table 1: Clinical data of published food-induced anaphylaxis hospitalization and emergency admissions data

Author	Publication date	Population	Racial data	Age data	Sex data	Clinical profile	Setting of the reaction	Manifestation	Suspected food trigger	Severity	Co factor (atopy, asthma, other)	Treatment
Gaspar A et al (51)	2020	3 months old to 90 years 30% under 18 years 48% did food induced anaphylaxis	Molluscs allergy in Madeira island oral mites anaphylaxis in Arizona LTPs common cause of FIA in the Mediterranean area, main cause in Spain and Italy	30% <18 years	male gender 1:4 predominated in children, while in adult's female was predominant 1:9	LTP sensitisation > rosacea fruit allergy++> main elicitor of FDEIA Latex-fruit syndrome (51%)	NA	Mucocutaneous symptoms (96%) Respiratory symptoms (78%) CV signs, laryngeal oedema, loss of consciousness (57%) gastrointestinal signs (paediatrics>adults)	shellfish (Crustaceans -> shrimps++) 26,8% is the first cause, and occurred most commonly in adults 2nd cause: fruits (rosacea > peach and also kiwi) Milk is the third cause, however the leading cause in children	NA	44 of patients have asthma, 1 have systemic macrocytosis Exercise: 44 of patients did a FDEIA with cereals (wheat), tree nuts, rosacea fruits	only 43% of the patients received adrenaline
Poirot E. et al (61)	2020	>0					5 deaths, 4 occurred at home and 1 at school.	NA	Peanuts are the most common allergen implicated in hospitalizations (27,1%) and ED visits (20,2%)			

Cheng BT et al (62)	2020	<18		higher risk of readmission with FIA associated with ages 13 to 17 years			NA	NA	higher risk of readmission with seeds and tree nuts			
Pouessel G et al (67)	2020	preschool children (<7 years) focusing on infants (<12 months)					school 28% and home 22%	mucocutaneous 79% >gastrointestinal 49%> respiratory 48%	cow's milk 59%> hen's egg 30%>wheat 6%> peanut 3%		atopic dermatitis 31% (infants)	
Ko J et al (68)	2020	<4					NA	skin and mucocutaneous symptoms	eggs in infants whereas peanuts in toddlers and pre-schooler		pre-schooler were significantly more likely to have asthma, allergic rhinitis and previous ED visits for FA compared with infants and toddlers - eczema was common across all ages	prehospital treatment: older children were more likely to receive antihistamines - greater use of epinephrine in older children pre-schoolers 12,5%, tofflers 12,4%

												and infants 4,3%
Okubo Y.et al (63)	2019	<20	rates among Asian and Pacific Islanders and black children are greater than those among white and Hispanic children		hospitalization rates in boys is higher than those in girl		NA	NA	peanuts > tree nuts and seeds > milk products with increasing trends// hospitalization rates associated with egg allergy showed a significantly decreasing	milk products, crustaceans were significantly associated with severe condition		
Österlund J et al (69)	2019	0-18	Sweden paediatric population	NA	58% boys	NA	NA	skin 70%> gastrointestinal 43%> oral 29%	milk 32%> peanuts 21% > unidentified foods 16%> eggs 14%	NA	NA	adrenalin 75%; 70% received it first at the hospital, 6% at home Bronchodilators 33%
Corrigan J et al (74)	2019	0-88	NA	NA	NA	NA	NA	lower respiratory tract symptoms if asthma gastrointestinal manifestations	peanuts, nuts, hen's eggs, cow's milk, shellfish	Grade ≥3 (45,8%) Ring & Messmer	asthma/ cardiovascular disease/ alcohol/ drugs (BB- NSAID	adrenaline: 32,4% in majority by IV injection and in children

											ACEI PPI)	
Yao T.C et al (57)	2018	>0	Asian population	NA	male gender in all-cases anaphylaxis	NA	NA	NA	NA	NA	NA	ICU (12%) in all-cases anaphylaxis
Jeong K. et al (58)	2018	>0	Korean population	NA	number of male patients was higher in children and adolescences, whereas the number of female patients was higher in young adults in their twenties and old age groups of 70 or older	NA	NA	NA	NA	NA	NA	epinephrine administratio n 35,8% in all cases of anaphylaxis during the five- year study period

Speakman S. et al (59)	2018	1 to 14	Rates highest among asian children and Pacific children, lowest among Maori children	rates highest among children aged less than 2 years	rate of FIA among males 1,5 times that female, the difference was most apparent in children aged 2-4 years	NA	NA	NA	Peanut 25,8% > cow's milk 21,3% - wheat/gluten is the least common 2,6% - cow's milk is the most prevalent in children aged less than 2	Anaphylactic shock - Grade III	NA	NA
Motosue M.S et al (60)	2018	<18	rates of FIA related ED visits were highest among those in the Northeast US census region	paediatric population < 18 years	60% of males	NA	NA	NA	Peanut >tree nuts/seeds - greatest increase for tree nuts/seeds (373% increase over the study period)- rates of milk and eff FIA related ED visits increased significantly in younger paediatric patients 0-2 years, and did not significantly change in older paediatric patients	NA	NA	NA
Wang Y. et al (65)	2018	<18	Asian paediatric population	increase in food related anaphylaxis was most pronounced in children under 15	Boys also tended to have a higher incidence rate of food-related anaphylaxis,		NA	NA	peanuts>seafood>eggs>milk products >tree nuts > seeds - eggs only reported in children under 4 years of age, crustaceans only in the 15-18 year age group			

				years	but this difference was not statistically significant.							
Jeppesen A.N et al (53)	2016	>0	NA	median age in the study: 44,2 for men and 45,6 for women	male gender 49,5% female gender 50,5%	In children, AS caused by adverse food reactions comprised 34% of cases	NA	anaphylactic shock (AS)	NA	Anaphylactic shock ("severe, potentially lethal allergic reaction characterized by an acute generalized hypersensitivity reaction and critical organ hypoperfusion after exposure to a previously encountered antigen")	Based on the Charlson Comorbidity Index score	ICU (14,5%) mechanical ventilation (2,1%) continuous infusion of inotropes or vasopressors (2,7%)

Kivisto J.E. et al (66)	2016	0-19	Finland and Sweden paediatric populations	Finnish boys had a median age of 6 and 9 years in girls, respectively. In Sweden, the median ages were 8 years in boys and 12 years in girls.	The incidence increased for both boys and girls in the two countries	NA	NA	NA	NA	Anaphylactic shock grade III	NA	The prevalence of EAI prescriptions among Finnish children increased by fourfold during 1999– 2011. In Sweden, an increase in prescriptions was not identified
Turner P.J et al (52)	2015	>0	NA	highest rate in children and adults less than 24 years old mean age of fatal FIA: 25 years	<15 years: male gender > female gender >1 years: female > male gender	NA	27% fatalities in the patient's own home, and (20%) occurred in restaurant s.	laryngopharyngeal and/or respiratory compromise	peanuts or tree nuts (73%) cow's milk (21%)	NA	Asthma (78%)	NA

Mullins R.J et al (55)	2015	>0	NA	More in two age groups: 5 to 14 years and 15to 29 years	NA	NA	NA	NA	NA	peanut, treenut allergy	NA	Risk factors: "include city living, higher maternal education, infant feeding practices, higher socioeconomic status and income (perhaps surrogate markers of a westernized lifestyle),6,33, 34 use of acid- suppressive medication, altered exposure to gut microbiota in early life (eg, childcare and exposure to pets or farm animals),35 family	NA
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											history, ²⁹ and filaggrin loss- of-function gene mutations and early-onset atopic eczema, ³⁶ perhaps increasing food sensitization risk through nonintact skin"	
Tejedor- Alonso M.A et al (56)	2015		African American race	Food anaphylaxis is more prevalent during the first and second decades of life	Anaphylaxis is more frequent in males until age 10-15, women experienced more episodes after age 15	NA	NA	NA	eggs, milk, peanuts, and tree nut or seeds but milk, eggs, and fish accounted for 50% of admissions due to food anaphylaxis	NA	NA	NA
Nocerino R. et al (64)	2015	<14	hospital admissions for FIA	mean age: 15,5 years	males 56,5%	NA	NA	NA	milk>eggs>tree nuts and seeds> fruits and vegetables	Anaphylaxis grade II	role for vitamin D insufficiency	NA

			occurred mainly in the North of Italy									
Dyer AA et al (70)	2015	0-19	hispanic children less frequently visited the hospital for food induced anaphylaxis, however they also experienced the greatest annual percent increase in ED visits and hospitalizatio n/ visits were most frequent for Asian children	annual percent increase most pronounced among children aged 5 to 9 years/ visits were most frequent for children aged 0 to 4 years			NA		the annual percent increase was most pronounced for children with tree nut induced anaphylaxis- visits were most frequent for children with peanut induced anaphylaxis > tree nut > fin fish > milk allergy/ hospitalization were significantly more frequent for children with milk induced anaphylaxis			

Vetander M et al (72)	2012	0-18	paediatric population	anaphylaxis' occurrence: 28% in the group 0–3 years old 40% in the group > 4 years old	no differences	NA	NA	cutaneous manifestation 74% lower airways: 49% without underlying asthma VS 72% with underlying asthma	peanut and tree nuts 39% - in 26% no specific trigger food could be identified- milk and egg common in infants <i>Reactions to peanut and tree nuts are as common as reactions to milk and egg in early life</i>	asthma - allergy related disease	73% of children had a history of allergic disease, 60% a history of known food allergy - children allergic to pollen, admission due to anaphylaxis tended to be more common during the deciduous tree pollen season Marc May	71% were administered adrenaline before arrival at the hospital or at the ed
Moro Moro M et al (73)	2011	>0	Spanish population	<20 years ++ : 0-4 years	NA	NA	NA	Mucocutaneous and lower respiratory signs or symptoms	0 to 4 y.o: cow's milk > hen egg > fruit > fish 5 to 29 y.o : complex foods (foods manufactured or meal cooked) , fish, fruit, and shellfish 30 to 69 y.o : fish >fruit >tree nuts	NA	NA	NA

Patel DA et al (75)	2011	>0	USA population	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rudders SA et al (71)	2010	0-18	Black> White> Asian>Hispanic	median age 8,5 years	predominant male gender	NA	More than two thirds at Home	NA	peanuts, tree nuts, milk products, shellfish, eggs, fruits, seeds, fish, wheat	NA	asthma> eczema> hay fever	percentage of anaphylaxis patients receiving epinephrine (pre ED or ED) increased over time (40 to 59%), however epinephrine treatment specifically in the ED did not change significantly
Liew W.K et al (54)	2009	>0		2 age peaks: one in the 0 to 4 year age group and one in the 15 to 29 year	equal numbers of male and female subjects - male subjects	NA		NA	Peanut is the most common 23% food allergen, followed by fish 18%, crustaceans 16%, tree nuts 16%, eggs 9% and milk 8%	NA	Food anaphylaxis risk factors: age 10 to 35 years, active asthma,	adrenaline 75%; 70% received it first at the hospital, 6% at home

				age groups - hospitalizati on rate were highest in the 0 to 4 years age group	outnumbered female subjects 1,5:1 less than 15 years of age whereas female subjects outnumbered male subjects 1,4:1 older than 15 years					peanut allergy, ingestion of food prepared outside of the subject's residence, and delayed administration of adrenaline	
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ED : emergency department, FIA : food-induced anaphylaxis, ICD: International Classification of Diseases, NA: not available

Table 2: Characteristics of published food-induced anaphylaxis hospitalization and emergency admissions data

Author	Publication date	World Region	Country	Period of data extraction	Rate of FIA (95%CI)	Method	Database used	Population	Number of hospital admissions/ED visits for food-induced anaphylaxis (FIA)	Trends
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Gaspar A et al (51)	2020	Europe	Portugal	2007-2017	NA	Anaphylaxis was diagnosed according to the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria	nationwide notification system implemented by the Portuguese Society of Allergology and Clinical Immunology	3months old to 90 years 30% under 18years	1426 - 80% (ED visit)/ 357 - 20% (hospitalization) 48% for FIA	0
Poirot E. et al (61)	2020	Nothern America	United States	2000-2014	Age-adjusted rates for hospitalizations 26.2/1 000 000 person-years (95% CI = 25.4-27.0) and 50.9/1 000 000 person-years (95% CI = 49.5-52.3) for ED visits	ICD9 CM, based on the World Allergy Organization anaphylaxis guidelines	New york state Statewide Planning and research Cooperative System	>0	3049 hospitalizations, and 4013 ED visits not resulting in hospitalization age adjusted rates for hospitalisation 26.1/ 1 000 000 person-years and 50.9/ 1 000 000 person-years for ED visits	Rates of hospitalizations increased from 16.5/1 000 000 person-years during 2000 to 2003 to 34.0/1 000 000 during 2011 to 2014.
Cheng BT et al (62)	2020	Nothern America	United States	2012-2016	30-day readmission rate for FIA 0.3%	ICD	National readmission database	<18	5872/ 62 re-admissions Re-admission after FIA hospitalization is rare 1.1% of children were readmitted	
Pouessel G et al (67)	2020	Europe	France	2002-2018	NA	Definition outlined by Sampson et al	Allergy Vigilance Network	preschool children (<7 years) focusing on infants (<12 months)	386 in preschool children food induced anaphylaxis reactions, and 61 in infants	

Ko J et al (68)	2020	Northern America	United States	2006-2018	Pas accès article	ICD-10, definition for anaphylaxis: second symposium on the Definition and Management of Anaphylaxis	Kaiser Permanente Northern California	<4	1518 food allergy ED, 538 anaphylaxis (35,4%)	
Okubo Y. et al (63)	2019	Northern America	United States	2006,2009,2012	annual hospitalization rates 1.2 per 100,000 children in 2006/1.5 per 100,000 children in 2012	ICD 9 CM	Kid's Inpatient Database	<20	988 hospitalizations with FIA in 2006, 1113 in 2009 and 1326 in 2012	increase
Österlund J et al (69)	2019	Europe	Sweden	2006-2015	30 per 100 000 person-years	ICD-10	visit with an emergency reaction to food in the Umea Universite hospital	0-18	99 : 71 led to hospitalization, one needed intensive care/ incidence of food triggered anaphylaxis during the 10 year period 30 per 100 000 person years	increase
Corrigan J et al (74)	2019	Europe	French	2015	incidence estimated at 34 per 100 000 person-years	ICD-10	data from 7 Eds in institutions from the University of the Lorraine	0-88	137 – 42.4% of the cases of anaphylaxis: 77.4% of anaphylaxis for children; 25.3% for adults	
Yao T.C et al (57)	2018	Asia	Taiwan	2001-2013	incidence rates of all cases anaphylaxis 1.06	ICD9 CM, based on the World Allergy Organization anaphylaxis guidelines	Longitudinal health insurance database composed of medical claims data from the national health insurance	>0	anaphylaxis: 1178 ED (47%), 495 20% hospitalization 32%, 305 intensive care unit (12%)	the proportion of patients requiring hospitalizations increased with age

							research database in Taiwan			
Jeong K. et al (58)	2018	Asia	Korea	2010-2014	NA	Korean classification of diseases 6th edition (equivalent to the ICD 10)	Korean National Health Insurance	>0		increase (the increase in the prevalence of emergent anaphylaxis was greater in young children)
Speakman S. et al (59)	2018	Oceania	New Zealand	2006-2015	16.2 per 100 000 children	ICD 10	Ministry of Health's National Minimum Dataset	1 14	1441 hospital ED presentations FIA: 1381 were coded as FIA and 60 (4%) unspecified anaphylaxis with an accompanying doof indced text description	Increase: almost tripled 2,8 times, greatest increase seen among 0-4 year olds (2,5 times)
Motosue M.S et al (60)	2018	Nothern America	United States	2005-2014	Emergency department visit rates 2014 20.05	ICD9 ICD9 CM	OptumLabs Data Warehouse	<18	7310 ED visits for FIA 78.8% were discharged home directly - observation for 15,8%	increased nu 214% suring the studding - highest rates for 0-2year olds group - ICU admission decreased over the study period - 45,3 %
Wang Y. et al (65)	2018	Asia	China		1.43 (1.19-1.71)					
Jeppesen A.N et al (53)	2016	Europe	Denmark	1995-2012	NA	ICD 10	Danish National Patient Registry	>0	926	Increasing (largest increase in diagnostic codes for AS hospitalization was seen in the codes for adverse food reaction)

Kivisto J.E. et al (66)	2016	Europe	Nordic	1999-2011	Incidence of hospitalization fo allergic reaction per 100 000 person-years among Finnish children in 1999 and 2011 was 7.8 and 15.3, respectively. Incidence per 100 000 person-years among Swedish children was 13.7 in 1999 and 31.8 in 2011.	ICD 10	National hospital Discharge register in Finland, and the National Patient Register in Sweden	0-19	327 (Finnish) + 884 (Swedish)	increasing between 1999 to 2011
Turner P.J et al (52)	2015	Europe	UK	1992-2012	1.05 (95% CI, 1.05-1.06)	Extraction data relating to hospitalizations in which anaphylaxis was the primary diagnosis - ED visits that not result in a hospital admission were not included - Using ICD9 before 1998 and ICD 10 a	the hospital episodes statistics database and the patient episode database for Wales	>0	14675 hospital admissions for FIA	Highest rate in children and adults <24 years old - increasing between 1998 and 2012 from an Age-standardized rates of 1,.2 to 2.4 for 100,000 population per yearun (increasing of 106%) - increasing for paediatric admission by 137%
Mullins R.J et al (55)	2015	Oceania	Australia	1998-2012	5.6 in 2005-2006 and 8.2 in 2011-2012	ICD 10	Australian institute of health and Welfare	>0	14074	increase
Tejedor-Alonso M.A et al (56)	2015	Europe	Spain	2005-2015	0.82	ICD 10	Review of the epidemiology of anaphylaxis			number of studies on the epidemiology of anaphylaxis has increased by 100% in the last 10 years
Nocerino R. et al (64)	2015	Europe	Italy	2006-2011	incidence of hospital admission for FIA of about	ICD 9 CM	Italian Ministry of Health	<14	2252 FIA related admission of 1785	Increased incidence of hospital admission for FIA, more

					4.4 episodes per 100,000 children/year				patients, 1.2% of subjects required multiple hospital admission for FIA	pronounced in children aged 5 to 14 years than in those younger than 4 (+ 128% vs +44.2%)
Dyer AA et al (70)	2015	Nothern America	United States	2008-2012	10.9 ED visits and hospitalizations per 100,000 children 1.2 hospitalizations per 100,000 children	ICD 9 CM	Illinois hospital discharge data COMPdata	0-19	1893 ED visits and hospital admissions due to food induced anaphylaxis among children: annual rate of 10.9 ED visits and hospitalizations per 100 000 children - 10,7% were hospitalized: annual rate of 1.2 hospitalizations per 100 000 children	Increase in the rate of ED visits and hospitalization: increase of 29,3% for ED visits and 18,8% for hospitalization
Vetander M et al (72)	2012	Europe	Sweden	2007	29 per 100 000 persons years	ICD 10	children admitted to Sachs' Children's Hospital	0-18	128 incidence 29 per 100 000 person years	
Moro Moro M et al (73)	2011	Europe	Spain	2004-2005	incidence rates of all cases anaphylaxis 1,1	definition established by the NIAID-FAAN Symposium	electronic clinical records of emergency department	>0	61: 28.6% of anaphylaxis	
Patel DA et al (75)	2011	Nothern America	United States	2006-2007	NA	ICD-9	Healthcare Cost and Utilization Project's Nationwide Inpatient Sample	>0	Food induced anaphylaxis cases reported for 44% of the hospitalized	

									patients, and 10.6 of ED patient.	
Rudders SA et al (71)	2010	Nothern America	United States	2001-2006	2001 14.9 anaphylaxis visits per 10,000 total ED visits	ICD-9	all children presenting to the Children's Hospital Boston ED with a food related acute allergic reaction	0-18	846 ED visits for food induced anaphylaxis	increase in the rate of ED visits: 14,9 anaphylaxis visits per 10 000 in 2001, 38 per 10 000 visits in 2006
Liew W.K et al (54)	2009	Oceania	Australia	1997-2005	NA	ICD 10 from 1998 onward and IC9-CM before	National hospital morbidity database + Australian Institute of Health and Welfare	>0 2 age peaks: one in the 0 to 4 year age group and one in the 15 to 29 year age groups	5007	increasing: multiplicative increase of the rate per year, was 1.12 / increase of 350% over the 11 years - rate of admission in the 0 to 4 year age group was estimated to increase 1,04 times more rapidly than in the older age groups

ED : emergency department, FIA : food-induced anaphylaxis, ICD: International Classification of Diseases, ICU: Intensive Care Unit