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Drug-Induced Anaphylaxis: An Update on Epidemiology and Risk Factors

Frederico S. Regateiro[a–c] Maria Luís Marques[d] Eva Rebelo Gomes[d]

[a]Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; [b]Institute of Immunology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [c]Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal; [d]Allergy and Clinical Immunology Department, Centro Hospitalar e Universitário do Porto, Porto, Portugal

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Abstract
Drug hypersensitivity is one of the most frequent causes of anaphylaxis, particularly in adults and in hospitalized patients. Drug-induced anaphylaxis (DIA) is also associated with more severe outcomes than other anaphylaxis triggers, and drugs are responsible for the majority of deaths due to anaphylaxis. We here review the current knowledge on the incidence, prevalence, drugs involved, mortality, and mortality risk factors for DIA. The incidence of both anaphylaxis and DIA seems to be increasing worldwide. Antibiotics and analgesics are the most frequently reported triggers of DIA. However, the importance of other drug groups should be taken into account, especially in particular settings (e.g., peri-operative and oncology). The identification of risk factors, geographical variables, and drugs associated with higher risk for DIA may improve the outcomes of this entity.

Introduction

Anaphylaxis is an acute, potentially life-threatening, generalized, or systemic allergic reaction that is mediated by the degranulation of mast cells and basophils. The clinical diagnosis of anaphylaxis is somewhat intricate [1], and it is generally agreed that the condition is underrecognized and underreported [2]. The World Health Organization's International Classification of Diseases (ICD) code 9 and ICD-10 incompletely cover anaphylaxis, therefore impairing the registration of anaphylaxis episodes and the identification of anaphylaxis triggers [2]. When analysing data from medical records, it is important to take into consideration whether the reported changes represent a real variation in disease frequencies or variations in reporting and coding practices. The difficulties in identifying and correctly reporting anaphylaxis and its causes have been carefully discussed elsewhere [3]. Importantly, the coding for anaphylaxis has changed across the different ICD versions. Together with other factors, these changes may have influenced the trends of electronically reported frequencies across time. The new ICD-11 coding system, which will come into effect on January 1, 2022, again modifies anaphylaxis reg-

karger@karger.com
www.karger.com/iaa

Prof. Frederico S. Regateiro
Allergy and Clinical Immunology Department
Centro Hospitalar e Universitário de Coimbra
PT–3000-075 Coimbra (Portugal)
regateiro@gmail.com

istration, and it was shown to further increase the accuracy and sensitivity of anaphylaxis identification [4]. The adoption of ICD-11 will improve the number of anaphylaxis episodes correctly identified and coded [4], and it is therefore expected to influence the epidemiological measures identified by coding methods.

A wealth of studies identifies hypersensitivity to drugs as one of the most frequent causes of anaphylaxis, particularly in the adult age [2, 5–8]. Drug-induced anaphylaxis (DIA) is also unique in respect to the location where anaphylaxis occurs, as it is the most frequent cause of anaphylaxis in hospitalized patients (approximately 1 in 3,000 hospitalized patients suffers DIA) [9, 10]. Drugs may cause both IgE-mediated and non-IgE-mediated anaphylaxis [11].

Incidence and Prevalence

A wide range of incidences and prevalences have been reported for all-cause anaphylaxis and for DIA in many countries [11, 12], with different study methodologies producing variable results. In Europe, a systematic meta-analysis published in 2013 found incidence rates for all-cause anaphylaxis between 1.5 and 7.9 per 100,000 person-years [8] and estimated that 0.3% of the population will develop anaphylaxis at some point in their lives [8], while American studies estimated lifetime prevalences between 0.5 and 2% [6, 13] or even more [10].

The relative importance of different anaphylaxis triggers varies according to age, geography, industrialization, access to healthcare, etc. While foods are mostly implicated as triggers of anaphylaxis in young children, drugs are consistently found to be the most frequent cause of anaphylaxis in adolescents and adults [2, 5–8]. A large study in the USA showed that about 35% of anaphylaxis cases were caused by medications [10], whereas another study in the UK found that drugs were responsible for 42% of all identified causes of anaphylaxis [14]. In the pilot phase of the first European Anaphylaxis Registry (EAR) (published in 2014 [15], including 3,333 cases of anaphylaxis from 10 countries), drugs were the second most frequent cause of anaphylaxis in adults, after insect venom, accounting for 22.4% of the anaphylaxis episodes, whereas in children (<18 years old) drugs were responsible for only 4.8% of the cases [15].

In Latin America, drugs were responsible for 31% of all anaphylaxis cases [5]. A study in the Boston area, USA, used electronic health records of 1,756,481 patients and identified 622,152 (35.4%) with at least one reported drug allergy and 19,836 cases of DIA (corresponding to 1.1% of the population having at least one episode of DIA) [6].

While DIA can occur in all ages, its frequency tends to increase with age [5, 7, 15–17]. This is probably related to the higher consumption of medications in elderly ages, while other factors, such as co-morbidities or co-medications, may account for the increased severity of hypersensitivity reactions. Age as a risk factor for more severe reactions is discussed below. Females seem to be more prone to developing DIA [5, 6, 16, 18], and some studies report that females are twice as likely to have DIA than males (e.g., female/male odds ratio [OR] 2.20 [6]). The reasons for this sex discrepancy are still incompletely understood [19].

The incidences of both all-cause anaphylaxis and DIA are reported to be stable or increasing in most studies. In the USA, a recent report using the US National Inpatient Sample reported stable rates of admissions for non-food-related anaphylaxis from 2001 to 2014 [20], whereas others found a slight increase in DIA electronic health reports between 1995 and 2013 in the same country [6]. In the UK, hospital admissions for all-cause anaphylaxis increased by 615% in 20 years (1992–2012), and hospital admissions for DIA increased significantly from an age-standardized rate of 0.78 to 1.4 per 100,000 population per annum, an increase of 82% [7]. This steep increase occurred mostly in the higher age groups: while patients aged 0–14 years had stable rates, the groups aged 15–60 years and >60 years had increases in age-standardized rates of 71% (rate ratio 1.04, 95% confidence interval [CI] 1.03–1.04) and 85% (rate ratio 1.05, 95% CI 1.04–1.05), respectively [7].

In Australia, the rate of hospital admissions for all-cause anaphylaxis increased 8.8% per year between 1993–1994 and 2004–2005 (from around 4 to 10 hospitalizations due to anaphylaxis per 100,000 population per annum) [21]. Admissions for anaphylaxis caused by food had the biggest average annual increase (13.2%), particularly in children aged 0–4 years, but also non-food-caused anaphylaxis (here included DIA) increased steeply in 10 years (average annual increase of 8.5%), particularly in adults aged >35 years [21].

Although anaphylaxis is a severe systemic reaction, deaths due to anaphylaxis are rare, with 0.33–3 fatalities per 1,000,000 population per annum [7, 17, 22]. Death occurs in 1% of hospitalizations and 0.1% of emergency department attendances for anaphylaxis [23]. Drugs as elicitors of anaphylaxis are associated with the severity of the reaction [17] and also with fatal anaphylaxis [17, 22, 24, 25]. In the USA, drugs were the most common cause of fatal anaphylaxis, accounting for 58.8% of all anaphylaxis-related deaths [25]. Risk factors for DIA and for fatal

Table 1. Major groups of drugs implicated in DIA

Group of drugs	Percentage of all cases of DIA (variable, depending on age, local prescription patterns, regional genetic susceptibilities, reporting systems, etc.)
Antibiotics	35.5–66.6% of all cases of DIA [Ref. 4, 12, and 14]
	β-Lactams: penicillins 13.1–40.7% (most frequently amoxicillin), cephalosporins 5.4–9.5% [Ref. 4 and 12]
	Non-β-lactams: sulphonamides 13.4%, macrolides 3.3%, fluoroquinolones 3.2–5.9%, tetracyclines 1.8% [Ref. 4 and 12]
NSAIDs and other analgesics	21.5–28.5% of all cases of DIA [Ref. 4 and 12]
	NSAIDs 11.5%
	Opiates 8.7%
	Local anaesthetics 1.3%
	In Latin America, NSAIDs were the first cause of DIA, accounting for 57.8–72% of all cases of DIA [Ref. 3 and 27], and also in Portugal, Europe (47.9% of the cases) [Ref. 14]
Particular settings Peri-operative	Neuromuscular blocking agents 60.6% (2012, [Ref. 29]) (out of which suxamethonium 68.2%, atracurium 13.9%, rocuronium 10.6%)
	Antibiotics 18.2% (2012, [Ref. 29]) (out of which cephalosporins 53%, penicillins 35%, vancomycin 7.7%)
	Surgical dyes 5.4% (2012, [Ref. 29]) (out of which Patent blue 89%, methylene blue 11%)
	Latex 5.2% (2012, [Ref. 29])
	Chlorhexidine from 1% (2012, [Ref. 29]) to 9% [Ref. 30], 3rd or 4th cause of peri-operative anaphylaxis in some series [Ref. 29]
Children/adolescents	Analgesics 40%, cephalosporins 16.4%, penicillins 12.8% [Ref. 33]
Regional specificities	In Beijing, China, traditional Chinese medicines 11.9% (2nd most frequent cause) [Ref. 16]

DIA, drug-induced anaphylaxis; NSAID, nonsteroidal anti-inflammatory drug.

DIA are discussed below. Fatal anaphylaxis increased in the USA between 1999 and 2010 [25]: using the National Mortality Database and the ICD-10 coding of US death certificates, it was found that the incidence of fatal anaphylaxis increased from 0.27 per million in 1999–2001 to 0.51 per million in 2008–2010 [25]. In the UK, despite sharp increases in hospital admissions for all-cause anaphylaxis and for DIA, the annual fatality rates for both remained stable at around 0.047 and 0.024 cases per 100,000 population, respectively [7].

Drugs Involved in DIA

Antibiotics and analgesics are the drug classes most commonly implicated in drug allergy and also in DIA (Table 1). However, striking geographical differences do exist. These differences are likely caused by local prescription patterns but may also be influenced by other less characterized factors, such as genetic differences. The genetics of immediate hypersensitivity reactions to drugs have been reviewed elsewhere [26].

In the USA, a study with one of the largest populations assessed to date (19,836 DIA patients) showed that antibiotics were, by far, the most frequent culprit drugs, accounting for about two-thirds of all cases reported from 1995 to 2013 [6]: penicillins were implicated in 40.7% of the reported DIA cases (amoxicillin was the most common causative drug), sulphonamides in 13.4%, cephalosporins in 5.4%, macrolides in 3.3%, fluoroquinolones in 3.2%, and tetracyclines in 1.8%. The second largest group of drugs in this study was the analgesics (21.5% of the total cases, with NSAID, nonsteroidal anti-inflammatory drugs (NSAIDs) accounting for 11.5%, opiates for 8.7%,

and local anaesthetics for 1.3%) [6]. Interestingly, the relative importance of penicillins seems to be consistently decreasing in frequency from 1995 to 2013 (from about 50% to about 30% of all DIA cases) [6]. All drug classes were more frequently implicated in ethnically White patients except for angiotensin-converting enzyme inhibitors that were more frequent in Black patients (2.7/10,000 in Black patients vs. 1.4/10,000 in White patients, and even lower frequencies in other ethnicities) [6].

In Europe, the pilot study of the EAR (published in 2014 [15]) recorded 340 cases of DIA, and the most frequently involved drugs were antibiotics (penicillins in 13.1% of all DIA cases, cephalosporins in 9.5%, and quinolones in 5.9%) and analgesics (metamizole in 10.2%, diclofenac in 9.3%, and ibuprofen in 9.0%). Also, in the UK, antibiotics were the most implicated drugs, followed by NSAIDs and antihypertensive medications [14]. Amoxicillin was the most prevalent cause of antibiotic-related anaphylaxis [14]. Recently, it was reported that clavulanic acid (as a component of amoxicillin-clavulanic acid) may itself trigger DIA [27].

However, in Latin America, several studies identified NSAIDs as the most frequent drugs involved in DIA (57.8% in Jares et al. [28] and 72% in Sole et al. [5]), followed by antibiotics. Also in Portugal, Europe, NSAIDs were the most frequent culprit drugs in DIA (47.9% of cases), followed by antibiotics (35.5%) and anaesthetic agents (6.1%) [16]. NSAIDs and opiates can cause severe hypersensitivity reactions by their cyclooxygenase-inhibiting mechanism or by direct effects on mast cells, and it is possible that some of the reported cases in these groups are pseudoallergic or IgE-independent anaphylactic reactions, rather than IgE-mediated anaphylactic reactions.

In Beijing, China, traditional Chinese medicines were the second most frequently implicated cause of DIA (accounting for 11.9% of the cases), only after antibiotics (39.3%, out of which cephalosporins accounted for 34.5% and fluoroquinolones 29.6%), whereas NSAIDs were less frequent than radiocontrast agents (11.9%) or antineoplastic agents (10.3%) [18].

The peri-operative anaphylaxis presents some particularities. The most frequent peri-operative elicitors have changed over time [29, 30]. For decades, and to this day, neuromuscular blocking agents – in particular suxamethonium, atracurium, and rocuronium – have been the most frequently implicated agents (in France, the large study by the Groupe d'Études des Réactions Anaphylactoïdes Peranesthésiques, GERAP [29], from 1989 to 2012, found that neuromuscular blocking agents corresponded to 48–80% of the identified elicitors). Latex was, for some decades, the second most commonly involved agent but it is becoming less prevalent [29] as latex-free products become generalized. On the contrary, the number of peri-operative anaphylaxis episodes attributed to antibiotics has steadily increased and this group is now the second most frequent cause in most studies (with cephalosporins most involved) [29, 30]. Also, surgical dyes are becoming increasingly recognized as a cause of peri-operative anaphylaxis [31], and the latest GERAP study found dyes were the third most common cause [29].

During the diagnostic workup of the peri-operative anaphylaxis, it should be borne in mind that any drug or substance used may be a cause of the hypersensitivity reaction. Anaphylaxis to chlorhexidine, a ubiquitous antiseptic in healthcare and the community, has been described after contact to chlorhexidine gels, chlorhexidine-impregnated devices, chlorhexidine preparations used on wounds and broken skin, and cases after dental procedures [32], and some studies report chlorhexidine as the top 3 or 4 most commonly diagnosed cause of peri-operative anaphylaxis [31, 32].

Other relevant causes of DIA in specific clinical settings are iodinated contrast media (with the particularity that as many as 34.6% of the anaphylaxis cases develop on the first exposure to the contrast media [33]) and antineoplastics (frequently requiring laborious desensitization protocols to allow first-line treatment of cancer [34]).

In children and adolescents, drugs are less frequent triggers of anaphylaxis than other elicitors. For instance, in the EAR 2016 analysis [35], which included 1970 anaphylaxis patients in these age groups (1865 with known elicitors), drugs were known or suspected elicitors in only 101 cases (5.4% vs. 69.2% for foods and 20.4% for *Hymenoptera* stings). Drugs accounted for only 3.1% of the anaphylaxis in pre-schoolers aged <6 years, 4.1% in children aged 6–12 years, and 12.1% in adolescents aged 13–17 years. Analgesics were the most frequently implicated drugs [35].

Mortality and Risk Factors

Anaphylaxis and anaphylactic shock are the most severe presentations of type I hypersensitivity reactions to drugs. The mechanistic reasons why some patients develop only mild type I reactions to drugs while others go on to develop severe manifestations are still ill-defined. However, several risk factors have been identified that may contribute to the development of anaphylaxis or to the severity of the anaphylaxis manifestations. These can

be divided into intrinsic factors (patient-related) and extrinsic factors. A good knowledge of the conditions that may contribute to severity may allow prophylactic or treatment interventions to prevent ominous outcomes. These conditions include several (1) risk factors determined by association, (2) co-factors (patient-related or external circumstances that increase the risk of an allergic reaction occurring or its severity), and (3) co-morbid diseases or medications that affect prognosis. Most of these conditions are common to anaphylaxis of all causes, and not specific for DIA, as most studies do not provide subanalysis with the DIA patients only.

An US study analysed 38,695 emergency department visits for anaphylaxis and found that severe anaphylaxis (defined by hospital or intensive care unit admission, endotracheal intubation, or meeting criteria for a near-fatal reaction) accounted for 11.6% of all anaphylaxis episodes [36]. Another US database including 11,972 individuals with anaphylaxis found that 22% had a severe anaphylactic reaction (defined as an index event requiring hospitalization), 10% required admission to the intensive care unit, and 6% were hospitalized and had cardiorespiratory failure or required cardiorespiratory/resuscitative interventions [17]. The most important risk factors for severe anaphylaxis and mortality are drugs as elicitors, age, mastocytosis, cardiovascular diseases, respiratory disease, and concomitant medications (each factor is separately described below) [7, 17, 25, 36–38]. A combination of several of these risk factors may be a stronger predictor for severe reactions and fatality, even in otherwise unsuspected eliciting situations (e.g., skin testing with drugs [39]).

As mentioned previously, anaphylaxis caused by drugs has, in itself, a higher risk of severe anaphylaxis than other elicitors [17, 22, 24, 25, 37]. Drugs as a trigger are associated with hospitalizations and cardiorespiratory arrest/failure or cardiorespiratory/resuscitative interventions, with an OR of 1.80 and 2.25, respectively [17]. In a large-scale study in the USA including 2458 anaphylaxis-related deaths, medications accounted for 58.8% of all anaphylaxis-related deaths [25]. The most common drugs involved in fatal anaphylaxis were antibiotics (40.5%, mostly penicillins and cephalosporins), followed by radiocontrast agents and other diagnostic agents (30.4%) and antineoplastics (12%) [25]. Radiocontrast agents may entail a higher fatality risk "per injection" than antibiotics [38]. General anaesthesia and neuromuscular blocking agents are also associated with fatal drug anaphylaxis [38].

Age is consistently associated with severity and fatal anaphylaxis in many studies [7, 17, 25, 36, 37]. A recent publication that used the EAR (including 8055 anaphylaxis patients, in 122 centres, in 11 European countries) found that the most important risk factors for severe anaphylaxis (all causes) were higher age (each year increased the odds of experiencing a severe anaphylactic event 1.6%, 95% CI 1.4–1.9%) and mastocytosis (OR 3.1, 95% CI 2.6–3.7). Hospitalization due to DIA is associated with an increased age (and with female sex) [17]. The rates of fatal DIA significantly increase with age [25]: the rate per million US population were 0.05 in the 0–19 years of age group, 0.18 in the 20–39 years, 0.51 in the 40–59 years, 1.23 in the 60–79 years, and 1.28 in the >80 years [25]. Most DIA deaths occur between 55 and 85 years [22] with median ages around 58–60 years [7, 26]. The increased risk with ageing may be attributed to concomitant comorbidities (such as cardiovascular or respiratory diseases) or co-medications (such as β-blockers), as these are independent risk factors for anaphylaxis severity [36] (see below).

Females are more likely to have DIA, but female sex does not seem to influence the severity of anaphylaxis [7, 17], while others found increased severity in males [37]. In the USA and Australia, DIA deaths showed equal sex distribution [22, 25]. In the USA, DIA is more frequent in White ethnicity patients than in other ethnicities (OR 2.38) [6], but ethnically Black patients were more likely to have fatal anaphylaxis [25].

Systemic mastocytosis is a clonal disorder in which increased release of mast cell mediators leads to frequent and more severe immediate hypersensitivity reactions. A study in mastocytosis patients found that as many as 43% of the patients had had at least one episode of anaphylaxis [40], and about 30% had more than one episode of anaphylaxis. The most frequent triggers were *Hymenoptera* stings, while drugs accounted for less than 10% of the cases [40]. Nevertheless, patients with systemic mastocytosis were found to have increased odds of reporting drug anaphylaxis (OR 4.60) [6]. Also, in patients with drug sensitization, mastocytosis may contribute to the severity of the reaction, in particular in hypersensitivity to NSAIDs [41, 42]. Importantly, a recent study [43] showed that NSAIDs are safe for most patients with mastocytosis (only 1 in 50 patients tested positive in double-blind, placebo-controlled acetylsalicylic acid challenge up to 520 mg), while a retrospective chart review of 191 patients found that only 4.1% of the patients had a history of NSAID-related hypersensitivity reaction(s) [43].

Respiratory and cardiovascular diseases have been associated with poorer prognosis as they may lead to insufficient compensatory mechanisms to endure anaphylaxis

complications, such as hypotension or hypoxia [36, 44]. Severe or uncontrolled asthma has been considered a risk factor for anaphylaxis [6] and also to poor prognosis, and this has been included in some guidelines [2]. A cohort study in the UK found that the incidence rate of all-cause anaphylaxis in asthmatics is more than double of the rate in non-asthmatics (50.45 vs. 21.28 per 100,000 person-years), and this frequency increased with the severity of asthma (from 43.01 in non-severe asthmatics to 65.35 cases per 100,000 person-years in individuals with severe asthma) [14]. Anaphylactic shock is also associated with asthma and asthma severity, with incidence rates in non-asthmatics of 2.48 per 100,000 person-years versus 5.61 in non-severe asthmatics and 14.24 in severe asthmatics [14]. However, some studies did not find associations between asthma and the severity of anaphylaxis [17, 37], or even found that a history of asthma reduced the likelihood of hospital admission, ICU admission, and endotracheal intubation [36]. Chronic obstructive pulmonary disease has also been found to be a risk factor for anaphylaxis [6] and for anaphylaxis severity [17].

Concomitant medications may potentiate anaphylaxis manifestations or thwart anaphylaxis treatment. Both angiotensin-converting enzyme inhibitors and β-blockers – but not aspirin or angiotensin-receptor antagonists – have been associated with severity [17, 37]. Using multivariable logistic regression to evaluate independent predictors of severe anaphylaxis, Clark et al. [17] found that the concomitant use of angiotensin-converting enzyme inhibitors is strongly associated with hospitalization (OR 1.50, 95% CI 1.33–1.68) and cardiorespiratory arrest/failure or cardiorespiratory/resuscitative interventions (OR 1.68, 95% CI 1.40–2.02). Furthermore, these drugs are usually taken in the setting of cardiovascular diseases that are, themselves, risk factors for poor prognosis (adjusted OR 1.44, 95% CI 1.18–1.76, for cardiorespiratory arrest/failure or cardiorespiratory/resuscitative interventions) [17]. β-Blockers impair the efficacy of adrenaline treatment and were found to be associated with the severity of anaphylaxis (OR 1.857, 95% CI 1.47–2.25) [37]. Clark et al. [17] did not find an association between β-blockers and severe anaphylaxis after adjusted analysis.

Anaphylaxis or the severity of the reaction has also been associated with hypertension, the use of antidepressants, vigorous exercise, psychological burden [17, 37], and less consensual risk factors, such as Sjögren syndrome [6] or atopic eczema/dermatitis. Atopic dermatitis was found to be strongly associated with anaphylaxis in both asthmatics (adjusted OR 1.69 vs. control population) and non-asthmatics (adjusted OR 2.83) in one study [14], whereas others failed to observe any association between eczema (or atopic disease) and severe anaphylaxis to drugs [16, 36].

Conclusion

The overall incidence and prevalence of allergic diseases is clearly on the rise over the past decades. However, the interpretation of epidemiological data concerning DIA is still a challenge. This is mainly due to variations in the definition of anaphylaxis, to under/overdiagnosis, and to methodological differences between the available studies. Altogether, it seems likely that the incidence of DIA is increasing worldwide. Drugs most frequently involved in DIA are antibiotics and analgesics, but some regional variations are observed. Also, in particular settings (e.g., oncology, peri-operative, and radiology/imaging), specific drugs/substances need to be taken into account. When compared to other anaphylaxis triggers, drugs are associated with severe outcomes, including fatal anaphylaxis. The main risk factors for DIA (i.e., older age, female sex, systemic mastocytosis, and concomitant respiratory and cardiovascular diseases) do not appear to differ from other causes of anaphylaxis.

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Author Contributions

F.S.R., M.L.M., and E.R.G. all participated in the literature search and in the article planning and writing.

References

1 Simons FE, Ardusso LR, Bilò MB, Dimov V, Ebisawa M, El-Gamal YM, et al. 2012 Update: world allergy organization guidelines for the assessment and management of anaphylaxis. Curr Opin Allergy Clin Immunol. 2011;12(4):389–99.

2 Muraro A, Roberts G, Worm M, Bilò MB, Brockow K, Fernández Rivas M, et al. Anaphylaxis: guidelines from the European academy of allergy and clinical immunology. Allergy. 2014;69(8):1026–45.

3 Tuttle KL, Wickner P. Capturing anaphylaxis through medical records: are ICD and CPT codes sufficient? Ann Allergy Asthma Immunol. 2020;124(2):150–5.
4 Tanno LK, Chalmers R, Bierrenbach AL, Simons FER, Martin B, Molinari N, et al. Changing the history of anaphylaxis mortality statistics through the World Health Organization's International Classification of Diseases–11. J Allergy Clin Immunol. 2019;144(3):627–33.
5 Sole D, Ivancevich JC, Borges MS, Coelho MA, Rosario NA, Ardusso LRF, et al. Anaphylaxis in Latin America: a report of the online Latin American survey on anaphylaxis (OLASA). Clinics. 2011;66(6):943–7.
6 Dhopeshwarkar N, Sheikh A, Doan R, Topaz M, Bates DW, Blumenthal KG, et al. Drug-induced anaphylaxis documented in electronic health records. J Allergy Clin Immunol Pract. 2019;7(1):103–11.
7 Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: An analysis of United Kingdom national anaphylaxis data, 1992–2012. J Allergy Clin Immunol. 2015;Apr;135(4):956–e1.
8 Panesar SS, Javad S, De Silva D, Nwaru BI, Hickstein L, Muraro A, et al. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy. 2013;68(11):1353–61.
9 Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med. 2001;161(1):15–21.
10 Wood RA, Camargo CA, Lieberman P, Sampson HA, Schwartz LB, Zitt M, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. J Allergy Clin Immunol. 2014;133(2):461–7.
11 Montañez MI, Mayorga C, Bogas G, Barrionuevo E, Fernandez-Santamaria R, Martin-Serrano A, et al. Epidemiology, mechanisms, and diagnosis of drug-induced anaphylaxis. Front Immunol. 2017;8(8):614.
12 Simons FE, Ardusso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J. 2014;7(1):9.
13 Lieberman P, Camargo CA, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol. 2006;97(5):596–602.
14 González-Pérez A, Aponte Z, Vidaurre CF, Rodríguez LA. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. J Allergy Clin Immunol. 2010;125(5):1098–e1.
15 Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernandez-Rivas M, Cardona V, et al. First European data from the network of severe allergic reactions (NORA). Allergy. 2014;69(10):1397–404.
16 Faria E, Rodrigues-Cernadas J, Gaspar A, Botelho C, Castro E, Lopes A, et al. Drug-induced anaphylaxis survey in Portuguese allergy departments. J Investig Allergol Clin Immunol. 2014;24(1):40–8.
17 Clark S, Wei W, Rudders SA, Camargo CA. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. J Allergy Clin Immunol. 2014;134(5):1125–30.
18 Zhao Y, Sun S, Li X, Ma X, Tang H, Sun L, et al. Drug-induced anaphylaxis in China: a 10 year retrospective analysis of the Beijing Pharmacovigilance Database. Int J Clin Pharm. 2018;40(5):1349–58.
19 Castells MC. Capturing drug-induced anaphylaxis through electronic health records: a step forward. J Allergy Clin Immunol Pract. 2019;7(1):112–3.
20 Shrestha P, Dhital R, Poudel D, Donato A, Karmacharya P, Craig T. Trends in hospitalizations related to anaphylaxis, angioedema, and urticaria in the United States. Ann Allergy Asthma Immunol. 2018;122(4):401–e2.
21 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(4):878–84.
22 Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol. 2009;123(2):434–42.
23 Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. J Allergy Clin Immunol. 2014;133(4):1075–83.
24 Pumphrey R. Anaphylaxis: can we tell who is at risk of a fatal reaction? Curr Opin Allergy Clin Immunol. 2004;4(4):285–90.
25 Jerschow E, Lin RY, Scaperotti MM, Mcginn AP. Fatal anaphylaxis in the United States, 1999–2010: temporal patterns and demographic associations. J Allergy Clin Immunol. 2014;134(6):1318–e7.
26 Oussalah A, Mayorga C, Blanca M, Barbaud A, Nakonechna A, Cernadas J, et al. Genetic variants associated with drugs-induced immediate hypersensitivity reactions: a PRISMA-compliant systematic review. Allergy. 2016;71(4):443–62.
27 Torres MJ, Ariza A, Mayorga C, Doña I, Blanca-Lopez N, Rondon C, et al. Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions. J Allergy Clin Immunol. 2010;125(2):502–e2.
28 Jares EJ, Baena-Cagnani CE, Sánchez-Borges M, Ensina LF, Arias-Cruz A, Gómez M, et al. Drug-induced anaphylaxis in Latin American countries. J Allergy Clin Immunol Pract. 2015;3(5):780–8.
29 Tacquard C, Collange O, Gomis P, Malinovsky JM, Petitpain N, Demoly P, et al. Anaesthetic hypersensitivity reactions in France between 2011 and 2012: the 10th GERAP epidemiologic survey. Acta Anaesthesiol Scand. 2017;61(3):290–9.
30 Mertes PM, Tajima K, Regnier-Kimmoun MA, Lambert M, Iohom G, Guéant-Rodriguez RM, et al. Perioperative anaphylaxis. Med Clin North Am. 2010;94(4):761–89.
31 Harper NJN, Cook TM, Garcez T, Farmer L, Floss K, Marinho S, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121(1):159–71.
32 Rose MA, Garcez T, Savic S, Garvey LH. Chlorhexidine allergy in the perioperative setting: a narrative review. Br J Anaesth. 2019;123(1):e95–e103.
33 Kim MH, Lee SY, Lee SE, Yang MS, Jung JW, Park CM, et al. Anaphylaxis to iodinated contrast media: Clinical characteristics related with development of anaphylactic shock. PLoS One. 2014;9(6):e100154.
34 Castells M. Drug hypersensitivity and anaphylaxis in cancer and chronic inflammatory diseases: the role of desensitizations. Front Immunol. 2017;8:1472.
35 Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: the European anaphylaxis registry. J Allergy Clin Immunol. 2016;137(4):1128–e1.
36 Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. Risk factors for severe anaphylaxis in the United States, Ann Allergy Asthma Immunol. 2017;119(4):356–e2.
37 Worm M, Francuzik W, Renaudin JM, Bilo MB, Cardona V, Scherer Hofmeier K, et al. Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from the European Anaphylaxis Registry. Allergy. 2018;73(6):1322–30.
38 Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal Anaphylaxis: mortality rate and risk factors. J Allergy Clin Immunol Pract. 2017;5(5):1169–78.
39 Fernandes RA, Regateiro FS, Pita J, Ribeiro C, Carrapatoso I, Todo-Bom A, et al. Severe anaphylaxis with cardiac arrest caused by prick test with cefuroxime. J Investig Allergol Clin Immunol. 2018;28(6):426–8.
40 Gülen T, Hägglund H, Dahlén B, Nilsson G. High prevalence of anaphylaxis in patients with systemic mastocytosis: a single-centre experience. Clin Exp Allergy. 2014;44(1):121–9.
41 Brockow K, Bonadonna P. Drug allergy in mast cell disease. Curr Opin Allergy Clin Immunol. 2012;12(4):354–60.
42 Bonadonna P, Pagani M, Aberer W, Bilò MB, Brockow K, Oude Elberink H, et al. Drug hypersensitivity in clonal mast cell disorders: ENDA/EAACI position paper. Allergy. 2015;70(7):755–63.
43 Hermans MAW, van der Vet SQA, van Hagen PM, van Wijk RG, van Daele PLA. Low frequency of acetyl salicylic acid hypersensitivity in mastocytosis: the results of a double-blind, placebo-controlled challenge study. Allergy. 2018;73(10):2055–62.
44 Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. Clin Exp Immunol. 2008;153(Suppl 1):7–11.