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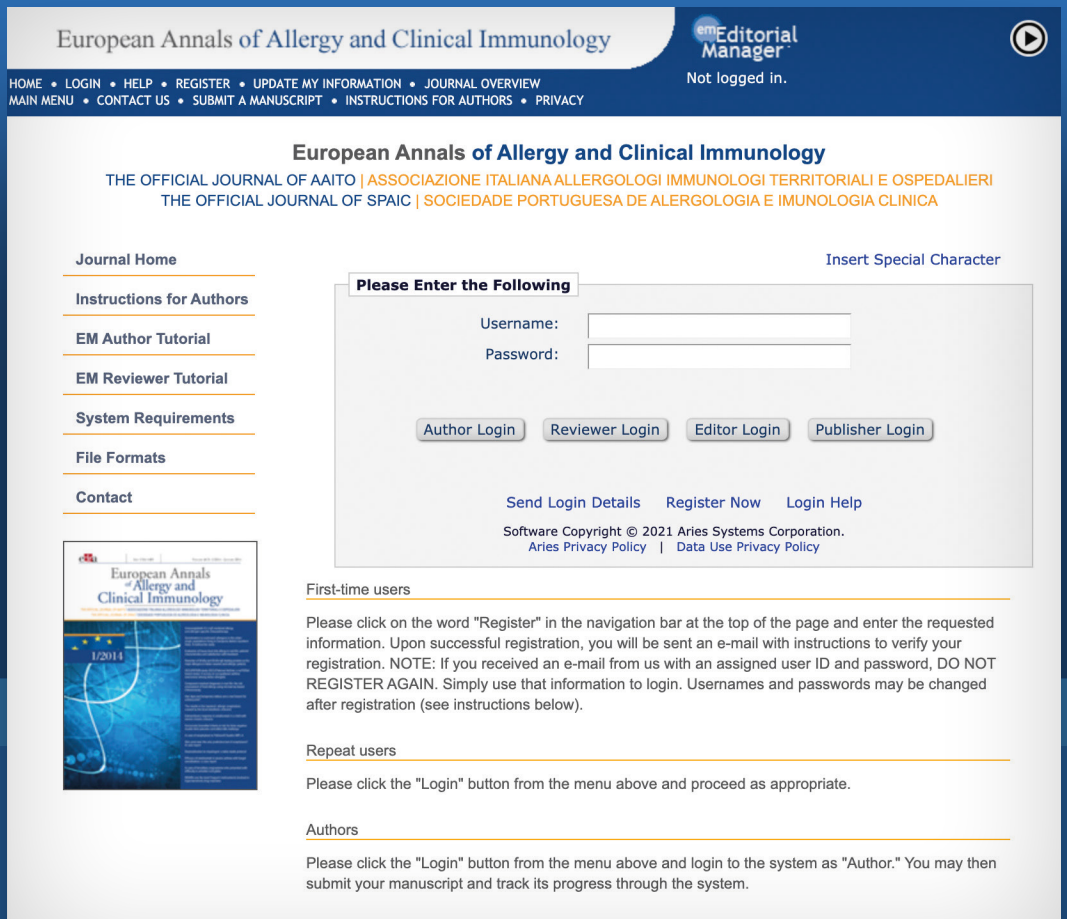
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Maria Bernadette Cilona[1], Giuseppe Alvise Ramirez[1], Chiara Asperti[1], Arianna Ferlito[1], Giovanni Benanti[1], Serena Nannipieri[1], Rawad Mansour Abdul Hadi[2], Carlo Capellini[2], Lorenzo Dagna[1,2], Marcello Cottini[3], Mona-Rita Yacoub[1]

Impact of asthma on severe food-induced allergic reactions: a systematic review and meta-analysis

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Key words

Asthma; anaphylaxis; food allergy; risk factor; severe allergic reactions.

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Impact statement

Patients with asthma and food allergy have an increased risk of severe, potentially fatal reactions. Optimizing management and prevention strategies is essential to reduce life-threatening events in this high-risk population.

Summary

Background. *Food allergy can range from mild to severe, life-threatening reactions with various symptoms and organ involvement. The impact of asthma on severe food-induced allergic reactions is not completely understood. In the hypothesis that asthma increases the risk of severe food-induced allergic reactions, the aim of this study is to compare the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.* ***Methods.*** *We performed a systematic research on electronic databases, including PubMed, Scopus and Web of Science. Observational studies, studies reporting medical characteristics of patients diagnosed with food allergy and studies reporting medical history of patients with allergic reactions were included. The primary outcome was the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.* ***Results.*** *Eight studies with a total of 90,367 patients met the inclusion criteria and were included, with a total population of 28,166 of patients with food allergy. The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma was increased (OR 1.28; 95%CI 1.03-1.59; p = 0.03; I^2 = 59%).* ***Conclusions.*** *Individuals with both food allergy and asthma are at high risk of severe, potentially fatal allergic reactions. Healthcare professionals should prioritize prevention and management strategies for these subjects. Patients with asthma and food allergy are at increased risk of potentially fatal food-induced allergic reactions. Optimal management of both diseases is necessary to prevent potentially life-threatening events.* ***Study registration.*** *The protocol of this review was registered in PROSPERO (CRD42023448293).*

Introduction

Food allergy is responsible for a variety of symptoms and disorders which can vary widely in severity ranging from mild to severe, potentially life-threatening reactions with multiple organ involvement (1). The prevalence of food allergy in the general population ranges from approximately 1% to 10% and can vary depending on the specific geographical location or age group (2). Asthma is even more common, with approximately 262 million people worldwide suffering from this condition (3).

Despite the increasing prevalence of asthma and food allergy in general population, little is known about the coexistence of these

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two diseases. In addition, there appears to be a significant rise in the incidence of asthma among individuals with severe food-induced allergic reactions (4). Understanding the potential link between asthma and food allergy is of paramount importance for several reasons. Indeed, there is growing evidence that asthma can potentially worsen severe food-induced allergic reactions through various immunoinflammatory mechanisms which can lead to more pronounced respiratory and systemic symptoms contributing to a high risk of life-threatening complications, including anaphylaxis (5). It is therefore necessary for clinicians to thoroughly investigate the simultaneous presence of both conditions in order to provide patients with the correct dietary indications and treatments for potentially life-threatening events.

In the hypothesis that asthma increased the risk of severe food-induced allergic reactions, the aim of this study is to compare the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma in studies that investigate the characteristics of patients with severe food-induced allergic reactions.

Materials and methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (6). The review question was developed using the Population, Intervention or exposure, Comparison, Outcome framework (7): among patients with food allergy (P), those with history asthma (E), compared with patients without asthma (C), is increased the incidence severity reaction (O)? The protocol of this review was registered in PROSPERO (CRD42023448293).

Literature search

A systematic review of the literature was conducted to identify observational studies reporting medical characteristics of patients with food allergy. Electronic databases, including PubMed, Scopus and Web of Science were comprehensively searched to identify relevant studies up to July 2023. The search strategy involved using relevant keywords, Medical Subject Headings, and Boolean operators to capture relevant articles. The search string follows below:

((food[tiab]) OR (peanut [tiab]) OR (milk [tiab]) OR (wheat[tiab]) OR (seafood [tiab]) OR (crustac* [tiab]) OR (nut [tiab]) OR (fish [tiab])) AND ((allergic reaction [tiab]) OR (hypersensitivity [tiab]) OR (anaphyl* [tiab]))

No restrictions were applied regarding the publication date or languages.

Study selection

Two independent reviewers screened the titles and abstracts of the identified studies to assess their eligibility for inclusion. The full texts of potentially relevant studies were then retrieved and further evaluated. Inclusion criteria for study selection were as follows: 1) observational studies (cohort studies, case-control studies, or cross-sectional studies); 2) studies reporting medical characteristics of patients diagnosed with food allergy; and 3) studies reporting medical history of patients with allergic reaction. Disagreements between the reviewers were resolved through discussion or consultation with a third reviewer.

Data extraction and synthesis

Data extraction was performed using a standardized data extraction form. Relevant information from each selected study was extracted, including study characteristics (*e.g.*, study design, sample size, and follow-up duration), participant characteristics (*e.g.*, age, gender, and food allergy diagnosis criteria), and outcomes of interest (*e.g.*, incidence of asthma in food allergy patients). Characteristics and reason for exclusion of major excluded studies were reported in **table IS**.

Data analysis

Data of the incidence of severe allergic reactions to food in patients with history of asthma was compared with patients without history of asthma in the entire cohort of selected studies. A qualitative analysis was also conducted to provide a comprehensive overview and synthesis of the findings from the included studies.

Ethical approval

As this study is a systematic review based on published literature, ethical approval was not required. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed during the conduct and reporting of this systematic review (6).

Outcomes

The primary outcome was the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.

Statistical analysis

Computations were performed with Review manager version 5.4.1. This meta-analysis was performed in compliance with PRISMA (8). We calculated pooled odds ratio (OR) for the primary and secondary outcomes and 95% confidence intervals (CI) using the Mantel-Haenszel method for dichotomous outcomes (9). The statistical heterogeneity hypothesis was evaluated with statistical significance set at the two-tailed 0.05 levels, whereas the extent of statistical consistency was quantified with Higgins and Thompson's I^2. I^2 values around 25, 50, and 75% were considered respectively low, moderate, and severe statistical inconsistency (I^2 > 50% was used as a threshold indicating significant heterogeneity for individual studies) (10). Pooled data were analyzed using the inverse variance method with a fixed-effect model in case of low-moderate (I^2 < 50%) statistical inconsistency or with a ran-

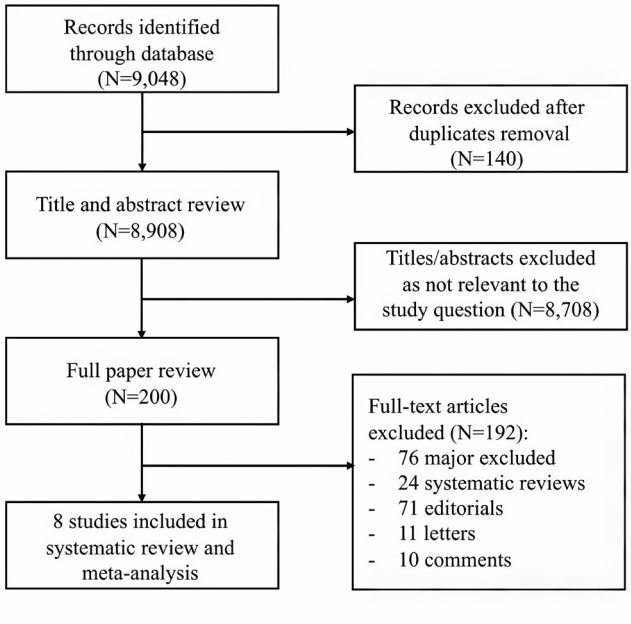
dom-effect model when the I^2 was above 50% (11). A P-value < 0.05 was considered statistically significant. The risk of bias was assessed by the tool Risk Of Bias In Nonrandomized Studies-of Interventions (ROBINS-I) (12). Results of pooled analyses were presented with forest plots. A sensitivity analysis was performed including only the studies that report unpooled data in the results.

Results

Characteristics of the studies

The research strategy of electronic databases detected 9,048 potentially relevant articles (**figure 1**).

Figure 1 *- PRISMA flow diagram showing literature search results.*



Eight studies with a total of 90,367 patients met the inclusion criteria and were included, with a total population of 28,166 of patients with food allergy (13-17). All studies were conducted between February 2005 and January 2022, including data of patients from 1990 and 2020. Five studies were conducted in Europe (13, 15, 18-20), three in United States (14, 16, 17). Six studies were retrospective observational studies (14, 15, 17, 18-20), two were prospective (13, 16). Five studies were multicentric (13, 15, 16, 18, 20). Three studies included only children (13, 17, 19), the other studies both adults and children (14-16, 18, 20). Five studies included only patients with food allergy (13, 15-17, 19), while three studies included patients with history of anaphylactic reactions also to other agents (14, 18, 20). Two studies defined severity of food-induced reaction according to Ring and Messmer grading scale for anaphylactic reactions (18, 20). One study used Sampson's grading system to identify the level of severity of food-induced allergic reactions (13). One study used Mueller's scale to identify the severity of anaphylaxis (19). One study defined severe anaphylaxis as an index event requiring hospitalization and identified severity of anaphylaxis as an index event resulting into cardiorespiratory failure or the need of cardiorespiratory/resuscitative intervention (14). Three studies defined the degree of severity of allergic reactions according to level of multisystem organ involvement (15-17) (**table IIS**). Majority of studies had a low risk of bias (**figure 1S**). Characteristics of the studies are reported in **table I**.

Outcome

The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma was increased (OR 1.28; 95%CI 1.03-1.59; p = 0.03; I^2 = 59%, **figure 2**).

We performed a sensitivity analysis including only the studies that report unpooled data in the results (706/4,427 [15.9%] *vs* 2,558/18,589 [13.8%]; OR 1.26; 95%CI 0.98-1.63; p = 0.07; I^2 = 66%, **figure 3**).

Figure 2 *- The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.*

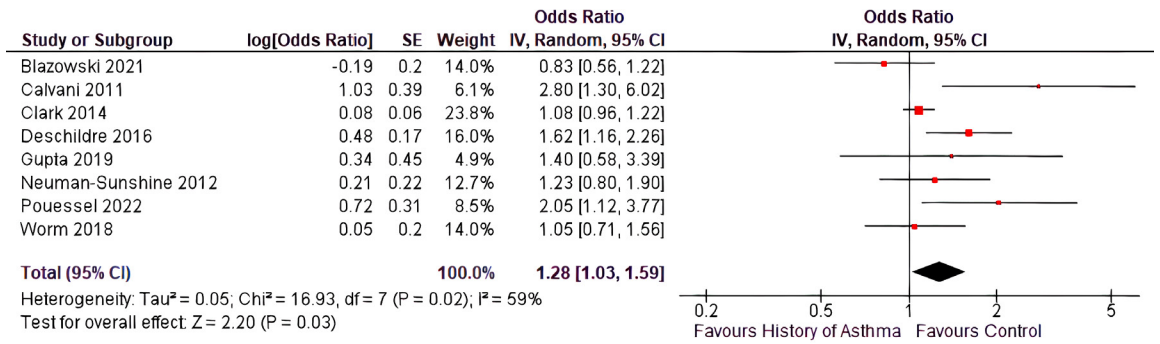


Table I *- Characteristics of included studies.*

Study	Country	Population	n of patients	Number of patients with food allergy (%)	Number of severe food-induced allergic reactions (%)	Number of patients with asthma (%)	Number of patients without asthma (%)
Calvani *et al.* (2011) (13)	Italy	Children with food allergy, 0-18 years	163	163 (100%)	36 (22%)	59 (36%)	104 (64%)
Clark *et al.* (2014) (14)	United States	Adults requiring hospitalization for anaphylaxis, no age limitation	36,943	11,972 (32%)	2,622 (7%)	1,822 (5%)	10,150 (27%)
Deschildre *et al.* (2015) (15)	France	Peanut-allergic children ≤ 6 years; school age children 6-12 years; teenagers, 12-16 years; adults ≥ 16 years	669	669 (100%)	202 (30%)	381 (57%)	288 (43%)
Gupta *et al.* (2019) (16)	United States	Adults with suspected food allergy ≥18 years	40,443	4,368 (11%)	2,228 (51%)	NR	NR
Neuman-Sunshine *et al.* (2011) (17)	United States	Children with peanut allergy, 0-16 years	782	782 (100%)	443 (57%)	436 (56%)	346 (44%)
Worm *et al.* (2018) (18)	Germany	Individuals with immediate hypersensitivity reactions, 0-93 years	7,316	7,316 (100%)	187 (3%)	1,125 (15%)	6,191 (85%)
Blazowski *et al.* (2021) (19)	Poland	Children with food-induced acute allergic reaction, 0-18 years	541	421 (78%)	175 (32%)	223 (41%)	198 (37%)
Pouessel *et al.* (2022) (20)	France	Children and adults patients with anaphylactic reactions	3,510	2,475 (71%)	42 (1.7%)	817 (33%)	1,658 (77%)

Funnel plot show less heterogeneity in both analyses in terms of size and effect estimates of included studies (**figures 4, 5**).

Discussion

The main finding of this study is that there is a significant association between history of asthma and the incidence of severe food-induced allergic reactions. However, the results of the sensitivity analysis did not reach statistical significance. Individuals with asthma have an increased risk of 28% to experience severe food-induced allergic reactions compared to those without a history of asthma. The results of the sensitivity analysis, which included only studies reporting unpooled data, confirm the direction and the magnitude of the primary analysis, although they

Figure 3 *- The incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma, including only the studies reporting unpooled data.*

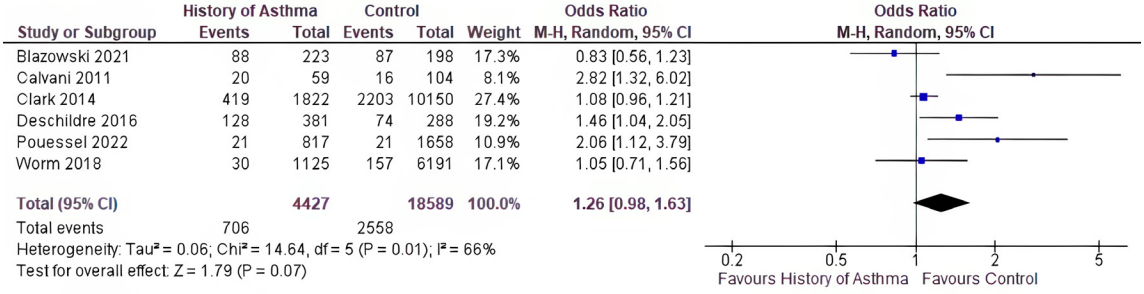


Figure 4 *- Funnel plot of the primary outcome measure: incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma.*

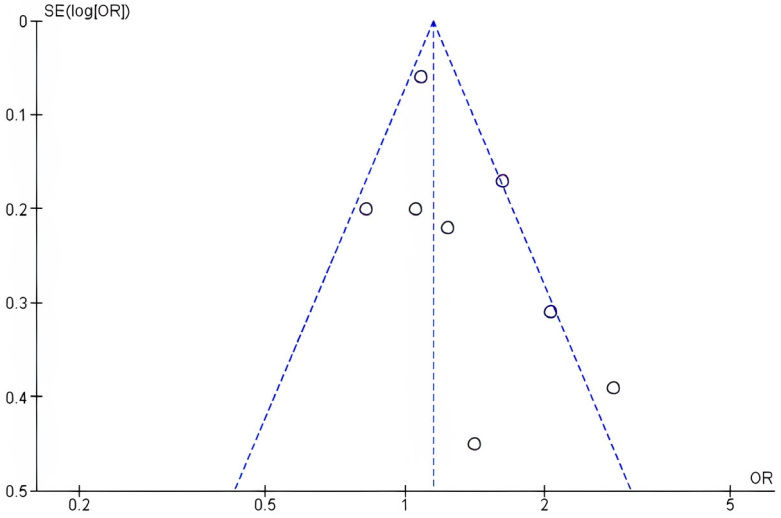
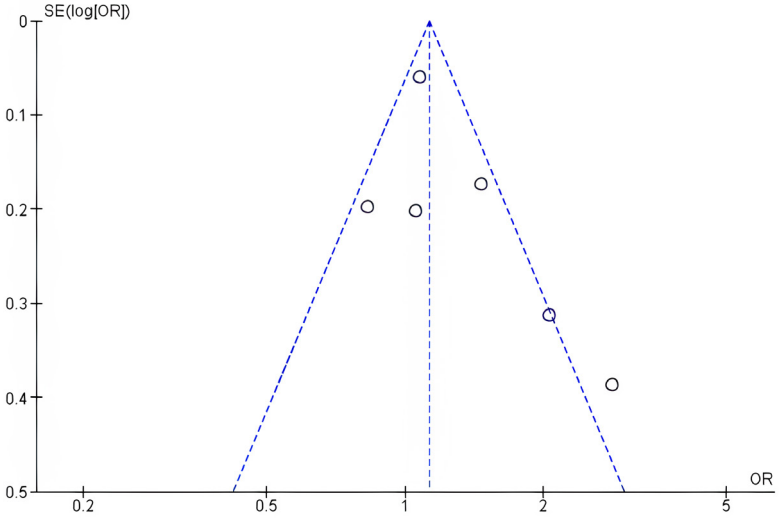


Figure 5 *- Funnel plot of the sensitivity analysis: incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma, including only the studies reporting unpooled data.*



report only a trend consistent with the initial finding. One of the main reasons for the mismatch between the main analysis and the sensitivity analysis is likely the inclusion of a heterogeneous population in terms of asthma control and severity. Included studies did not distinguish between controlled and uncontrolled asthma, resulting in a heterogeneous population. Although it is not possible to confirm this from our analysis results, it is plausible that uncontrolled asthma makes individuals more susceptible to severe reactions compared to controlled asthma. Another reason was the reduction in sample size, which decreased the statistical power and led to non-significant results in the sensitivity analysis. The funnel plot analysis indicates less heterogeneity in terms of study size and effect estimates among studies included, providing additional support for the validity of the results.

Turner *et al*. in their meta-analysis reported that asthma increases the risk of severe allergic reactions to food, consistent with our analysis (21). However, they included studies that did not clearly report data specifically related to the population of interest. In-

deed, Motosue *et al*. did not report specific data on exclusively food-induced allergic reactions in asthmatic population (22). The same was observed for Olabarri and colleagues who considered history of asthma as a risk factor for all the anaphylactic events and not specifically food-induced reactions (23). Furthermore, Versluis *et al.* in their prospective cohort study did not include subjects with a clinically defined diagnosis of asthma (24). Finally, Gabrielli *et al*. did not report data on the prevalence of asthma in subjects with severe allergic reactions, but exclusively in individuals with mild and moderate reactions (25). In addition, Turner and colleagues did not report which of these individuals developed severe allergic reactions (21). We included these studies as major excluded studies, despite they could have empowered our message. A particularly impactful finding is that among a cohort of 32 children who died due to food-induced allergic reactions, 24 of them had a definitive diagnosis of asthma (26). Similarly, in a separate cohort of 12 children with fatal reactions, all of them had a history of asthma (27).

The present findings have important clinical implications. They highlight the need for increased awareness and vigilance among healthcare professionals in managing individuals with both asthma and food allergies. Patients with asthma should be closely monitored and educated about the potential risks of severe food-induced allergic reactions. Although not addressed in our review, the association between asthma and severe food-induced allergic reactions could be mediated by reduced respiratory reserve in asthmatic individuals. It can be assumed that patients with uncontrolled asthma may be more susceptible to experience severe allergic reactions to food. Indeed, the latest updated GA2LEN guideline 2022 on management and treatment of food allergy report that it is good practice to optimize asthma control in people with food allergy as this reduces morbidity and mortality due to asthma (28). However, they report that the evidence on optimizing asthma control to reduce the risk of severe food-induced allergic reactions is unclear with low level of evidence for all good practice statements. In addition, they did not address that all asthmatic patients have an increased risk of severe allergic reactions, but they only hypothesized that uncontrolled asthma could be related to severe allergic reactions. EAACI guidelines emphasize that asthma is a risk factor for experiencing anaphylaxis in the context of food allergy and that reactions in individuals with severe asthma are a factor to consider for prolonged observation following anaphylaxis (29). These recommendations may act as a confounding factor in observational studies, leading to increased vigilance among clinicians and patients. This heightened awareness could potentially result in a lower prevalence of severe allergic reactions in asthmatic individuals, masking their heightened susceptibility. The underlying mechanisms linking asthma and increased susceptibility to severe food-induced allergic reactions need further investigations. It is possible that chronic airway inflammation and bronchial hyperresponsiveness in asthma contribute to the exaggerated immune response seen in food allergies (30). Understanding these mechanisms could potentially lead to the development of targeted interventions to mitigate the risk of severe reactions in individuals with both diseases. Targeting this specific population to prevent asthmatic exacerbations may have dual benefits by addressing the underlying mechanisms of both food reactions and asthma, given the bidirectional relationship between these two conditions (4). Indeed, pharmacological interventions, such as omalizumab, which have a dual impact on both food allergy and asthma, may elicit a synergistic effect in the treatment of these two conditions (30). Moreover, strategies for prevention, early recognition, and prompt treatment of allergic reactions should be emphasized in this high-risk population. One of the major clinical implication of our study is to emphasize the significance of ensuring that asthmatic patients with food allergies receive adequate chronic asthma treatment to effectively prevent severe allergic reactions. The current indications for oral immunotherapy for food allergy do not specifically mention individuals with asthma, indicating that the association between asthma and the high risk of severe food-induced allergic reactions is not yet fully understood (31). Further research and investigation are needed to better understand the potential benefits in terms of prevention for individuals with coexisting asthma. Moreover, the current algorithm for the administration of self-injectable adrenaline in patients with food allergies does not include individuals with concomitant diagnosis of asthma (32). These individuals may represent the ideal population for desensitization strategies and for the prescription of adrenaline auto-injectors in out-of-hospital setting, as these interventions play a crucial role in reducing the risk of life-threatening allergic reactions and improving their overall quality of life.

To the best of our knowledge, our review includes the latest available evidence regarding the impact of asthma on significant patient-centered outcomes. Notably, it includes recent and significant data that may contribute to a more precise estimation and interpretation of treatment effects. A notable strength of our study lies in its focused examination of a single outcome, the incidence of severe food-induced allergic reactions in patients with history of asthma compared with patients without history of asthma in studies that investigate the characteristics of patients with severe food-induced allergic reactions. This approach reinforces and emphasizes the crucial role and impact of asthma on the level of severity of these reactions. In this way, our study provides a clear and robust understanding of the association between asthma and the risk of potentially fatal food-induced allergic reactions. The methodological strengths of this review are attributed to its clear research question, specific population, defined interventions, and comparators. In addition, we performed a sensitivity analysis that exclusively considered studies with unpooled data, further enhancing the reliability of our findings.

However, it is important to acknowledge certain limitations associated with this review. First, the included studies used different classification systems to define the level of severity of food-induced allergic reactions, which could potentially influence the overall results. One important limitation is the lack of distinction between various levels of asthma severity in relation to the primary outcome. However, the data available in the included manuscripts did not allow for a distinction between patients with controlled and uncontrolled asthma. It is plausible that patients with uncontrolled asthma are more susceptible to severe allergic reactions; further research are needed to address this topic. Additionally, factors such as age, concomitant allergies, and specific food allergens were not considered in subgroup analysis, as the included manuscripts did not provide the necessary data. Further studies with larger sample sizes, different populations, and comprehensive patient characteristics would provide better understanding of the relationship between asthma and severe food-induced allergic reactions.

Conclusions

This study provides strong evidence that individuals with both food allergy and asthma might be at high risk of severe, potentially life-threating food-induced allergic reactions. Healthcare professionals should be aware of this association and take appropriate measures to prevent and manage these potentially fatal reactions. Further studies are needed to investigate the underlying mechanisms and empower management and treatment strategies for individuals with both asthma and food allergy.

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Contributions

MBC: conceptualization, writing – original draft, data curation, methodology, formal analysis, validation. GAR: writing – review & editing, visualization, validation. CA, AF, GB, SN, RMAH, CC: writing – review & editing, data extraction, validation. LD, MC, MRY: conceptualization, writing – review & editing, supervision, methodology, validation.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Relevance of the diagnosis of hypersensitivity reactions to antineoplastic and biological agents: experience with drug provocation test

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Key words

Chemotherapy hypersensitivity reactions; drug provocation test; rapid desensitization; regular supervised administration; restart protocol.

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Impact statement

This work highlights the safety and effectiveness of DPT in the assessment of HSRs to antineoplastics.

Summary

Background. *Evidence regarding drug provocation test (DPT) with chemotherapeutic agents is scarce. The aim of our study is to describe the experience of DPT in patients with a history of hypersensitivity reactions (HSRs) to antineoplastic and biological agents.* ***Methods.*** *Eight-year retrospective, observational, descriptive study of patients with a history of HSRs to chemotherapy who were submitted to DPT. Anamnesis, skin tests (ST) and DPT were analyzed. Patients with a negative DPT were submitted to at least one regular supervised administration (RSA). Patients with positive DPT or HSR during RSA were offered rapid drug desensitization (RDD).* ***Results.*** *A total of 54 patients were submitted to DPT. The most common suspected drugs were platins (n = 36), followed by taxanes (n = 11). Most of the initial reactions were classified as grade II (n = 39) according to Brown's grading system. ST with platinum (n = 35), taxanes (n = 10) and biological agents (n = 4) were negative, except for one intradermal test with paclitaxel, which was positive. A total of 64 DPTs were performed. Eleven percent of all DPTs were positive [platins (n = 6), doxorubicin (n = 1)]. Of the 57 RSA with the culprit drugs, 2 were positive (platins). The diagnosis of hypersensitivity was confirmed by DPT/RSA in 9 patients. All patients with positive DPT/RSA presented HSRs of equal or less severity than the initial one.* ***Conclusions.*** *DPT followed by RSA allowed to exclude HSRs in 45 patients (55 culprit drugs). DPT before desensitization prevents non-hypersensitivity patients from undergoing RDD. In our study DPT was safe, all reactions were managed by an allergist.*

Introduction

The diagnosis of neoplastic and inflammatory diseases has increased over the last years, leading to a larger number of patients exposed to antineoplastic and biological agents and to a rise in the incidence of hypersensitivity reactions (HSRs) (1-3).
These HSRs may be severe and life-threatening, jeopardizing first-choice treatments and leading to less effective and tolerated treatments which affect patient's survival and prognosis (4).
Rapid drug desensitization (RDD) is a cost-effective technique that enables hypersensitive patients to receive their first-choice treatments (5, 6). RDD temporarily modifies the patient's immune response to drug antigens, allowing the full dose to be achieved in a few hours without major side effects (5, 7-10).
In a recent study, it has been reported that a percentage of patients with suspected HSRs to antineoplastic and biologic agents may not be allergic and will not need RDD, making drug provocation testing important in de-labeling and economizing resources (1, 2).
Drug Provocation Test (DPT) is a diagnostic technique that involves administering a drug to a patient who carries a label of an unconfirmed allergy to that drug, and it is the gold standard to confirm or rule out an allergy (4, 11).

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DPT is helpful to avoid unnecessary RDDs, to study patients who received more than one drug simultaneously and to find alternative drugs in hypersensitive patients (6).
Despite these invaluable benefits, DPT is a high-risk technique, especially when dealing with highly sensitizing intravenous drugs such as chemotherapy or biologics agents (1, 3, 4, 12). Therefore, careful patient selection and optimal risk-management plans are critical to ensure patient safety during intravenous DPT (11, 13, 14). Despite the European Academy of Allergy and Clinical Immunology (EAACI) international consensus recommendations on performing diagnostic DPTs (4), whenever feasible, prior to drug desensitization, the financial and staffing expenditure linked to the high-risk technique of DPT with chemotherapy can explain why real-life data are still scarce (6).
The aim of this study was to describe the experience of DPTs in patients with a history of HSRs to antineoplastic and biological agents in an Allergy Department of a Tertiary Hospital in Portugal.

Materials and methods

Study design and population

The authors performed a retrospective, observational, descriptive and inferential review of patients with a history of HSRs to antineoplastic and biological agents who were submitted to DPT, during an eight-year period (between 2014 and 2022) in our Allergy and Clinical Immunology Department. Patients were also required to be older than 18 years of age and able to provide written informed consent before each DPT.

Informed consent statement

This study was conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946 (15). The institutional ethics committee approved the study, and informed consents were signed by patients and allergists.

Initial reaction classification

Initial reactions were classified as immediate (occurring during drug infusion or within 1 hour after treatment) and non-immediate (> 1 hour after completion of the infusion). The latter were excluded. Immediate reactions were graded according to both the Brown's grading system (BGS) (grade I, II and III corresponding to mild, moderate and severe reactions, respectively) (16) and the Ramon y Cajal University Hospital (RCUH) classification (grade I-IV, corresponding to mild, moderate, severe and anaphylactic shock, respectively) (1, 17) (**table I**).

Table I *- Brown and RCUH classification for grading system for hypersensitivity reactions.*

Brown Classification (14)		
I. Mild Reaction	**II. Moderate reaction**	**III. Severe Reaction**
Skin and subcutaneous tissues only: • Generalized erythema • Urticaria • Periorbital edema • Angioedema	Features suggesting respiratory, cardiovascular, or gastrointestinal involvement: • Dyspnea, stridor, wheeze, chest or throat tightness. • Nausea, vomiting, abdominal pain • Dizziness (presyncope), diaphoresis	Hypoxia, hypotension, or neurologic compromise: • Cyanosis or $SpO_2 \leq 92\%$ at any stage • Hypotension (SBP < 90mmHg in adults) • Confusion, collapse, loss of consciousness or incontinence

RCUH classification (15)			
I. Mild Reaction	**II. Moderate reaction**	**III. Severe Reaction**	**IV. Anaphylactic shock**
• Erythema • Pruritus • Local urticaria/angioedema • Fever/chills (< 38 °C) • Mild back pain	Slow onset (> 15 min): • Generalized urticaria/angioedema • Coryzal symptoms • Irritative cough • Dyspnea ($SpO_2 > 92\%$) • Nausea • Abdominal pain • Severe back pain • Fever (> 38 °C)	Rapid onset (< 15 min): • Generalized urticaria/angioedema • Coryzal symptoms • Irritative cough And/or manifestation of: • Throat tightness with dysphagia and/or dysphonia and/or stridor • Wheezing • Chest tightness • Vomiting • $SpO_2 < 92\%$ • Diaphoresis • Dizziness • Hypertension	Immediate onset (or rapid progression) of any of the latter and manifestation of any of the following: • Hypotension • Cyanosis • Sense of impending doom • Faintness • Loss of sphincters control • Cardiovascular and/or respiratory arrest

Diagnostic protocol

Patients were evaluated by detailed clinical history: characterized according to demographic data, histological subtypes of cancer, staging, therapeutic cycle involved in HSR and severity of reaction. Patients were eligible for an allergic diagnostic work-up if the oncologist confirmed the absolute need to maintain the treatment. Patients were then classified in two groups depending on their risk assessment: favorable or non-favorable risk for DPT.

Risk-assessment outcomes included a combination of several factors, namely, patient-related factors (any reason for frailty or comorbidities that would lower the possibilities of anaphylaxis survival, as uncontrolled asthma or lung diseases with FEV1 < 70%, unavoidable use of beta-blocker drugs and mastocytosis), HSR-related factors (severity of the initial reaction) and endophenotyping (results of the allergy work-up such as skin testing (ST) or biomarkers such as tryptase and IL-6) (1, 14).

Whenever appropriate, ST, including skin prick testing (SPT) and intradermal testing (IDT), were performed according to concentrations and safety measures for cytostatic drugs by European Network on Drug Allergy of the EAACI (18).

Patients with negative or equivocal ST results, favorable risk assessment and who signed the informed consent (after an explanation of their individual risk–benefit assessment) were submitted to DPT.

DPTs were performed on patient's scheduled treatment, in which the desired full dose of the culprit drug was administered according to the manufacturer's instructions, respecting infusion rates of the standard regimes and with no additional premedication rather than the standards according to manufacturer/ institutional protocols (4, 13). Beta-blockers and ACE inhibitors were held prior to the procedure (2).

In order to keep standard regimens, any additional required medication, as other antineoplastics, were also administered after DPT following oncologist prescription. As appropriate, provocations with other drugs involved in the initial reaction were performed before DPT with the culprit drug (2, 4).

DPT was considered positive when it reproduced the original symptoms or showed an objective HSR. In the case of a positive DPT, the infusion was stopped and the HSRs were treated according to severity (1, 2, 4, 19). Whenever possible, once symptoms were controlled, the infusion was immediately restarted at an adjusted desensitization protocol until all the medication was administered ("restart protocol") (1, 2, 4, 12, 17).

Patients with a negative DPT were submitted to at least one regular supervised administration (RSA). RSA consists of drug administration at standard time, without additional premedication, under the supervision of an allergist in our Allergy/Oncology Day Care Unit (2).

Patients with negative DPT and RSA were considered non-allergic and continued with their regular chemotherapy sessions in the Oncology Unit.

Patients with positive ST, positive DPT, HSRs during RSA and/ or non-favorable risk assessment were offered RDD, for which we used a modified, 12 step-protocol, described by Castells *et al.* (8, 9, 20-22).

Trained personnel performed ST, DPT, RSA and RDD. ST were performed in our Allergy Day Care Unit and DPT, RSA and RDD in a special area of Allergy/Oncology Day Care Unit, with a 1:2 nurse-to-patient ratio, allergist at the bedside, hazardous drugs handling resources, all the necessary equipment to address severe anaphylaxis and rapid access to the intensive care unit.

Statistical analysis

Statistical analysis was performed using the software IBM SPSS Statistics for Windows, version 26. A descriptive statistical analysis was performed. For variables with normal distribution, we present mean and standard deviation, and for variables without normal distribution, median and interquartile range (IQR).

Results

Demographic and clinical characteristics

A total of 54 patients (34 female and 20 male) with suspected HSRs to chemotherapy agents were submitted to DPT during an eight-year period, from January 2014 to august 2022. The mean age of the study population at the time of the DPT was 62 ± 13 years (ranging from 19 to 83 years). The most common malignancies were colon, ovarian and breast adenocarcinoma, followed by lymphoma. Eight patients had more than one drug implicated in the initial reaction (6 patients had 2 and 2 patients had 3), bringing the total number of DPT to 64. Platins (n = 36) were the most common suspected drugs, followed by taxanes (n = 11), biological agents (n = 8) and others antineoplastic agents in 9 patients. A total of 24 patients (44% of the 54 patients) were under curative treatment. Patients' characteristics are summarized in **table II** and **table III**.

Characteristics of initial HSRs

Clinical manifestations and severity of the 54 suspected HSRs (total 64 culprit drugs) are illustrated in **figure 1**. All initial reactions were immediate. According to BGS (16) and RCUH classification (17), respectively, HSRs were characterized as grade I in 25% (n = 16) *vs* 15.6% (n = 10), grade II in 60.9% (n = 39) *vs* 59.5% (n = 38), grade III in 14.1% (n = 9) *vs* 25% (n = 16) and no patients were classified in grade IV according to RCUH. The most frequent clinical manifestations were cutaneous in 57.8% (n = 37) and respiratory in 48.4% (n = 31). In 54.7% (n = 35), the initial reaction was classified as anaphylaxis.

The median number of cycles until the first episode of HSR occurred was 3 cycles (minimum 1, maximum 20; IQR 7). The first episode of HSR to platins occurred at a median 8 cycles (minimum 1, maximum 20; IQR 7) and lower for other drugs:

Table II *- Patient characteristics.*

Patient	Gender	Age	Cancer	Suspected culprit drug	Skin Test	HSR cycle	Severity (Brown)	Severity RCUH)	Tryptase reaction	DPT	RSA	Positive DPT/RSA		Treatment session completed	RDD	Final diagnosis
												Brown	RCUH			
1	F	59	Colon	Oxaliplatin	-	3	II	III	3.00	-	-				N/A	-
2	F	69	Lymphatic	Cyclophosphamide	N/A	2	II	II		-	-				N/A	-
				Etoposide	N/A	2	II	II		-	-				N/A	-
				Bleomycin	N/A	2	II	II		-	-				N/A	-
3	F	72	Colon	Oxaliplatin	-	2	II	II		-	-				N/A	-
				Docetaxel	-	2	II	II		-	-				N/A	-
4	F	65	Colon	Bevacizumab	-	2	III	III		-	-				N/A	-
				Oxaliplatin	-	2	III	III		+	N/A	II	II	Yes	Yes	+
5	F	51	Ovarian	Paclitaxel	-	3	II	II		-	-				N/A	-
				Carboplatin	-	3	II	II		+	N/A	I	I	Yes	Yes	+
6	M	69	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
				Cetuximab	-	3	II	II		-	-				N/A	-
7	F	19	Lymphatic	Bleomycin	N/A	1	I	II		-	-				N/A	-
				Doxorubicine	N/A	1	I	II	6.00	-	-				N/A	-
				Vimblastine	N/A	1	I	II	6.00	-	-				N/A	-
8	M	72	Parotid	Docetaxel	-	2	II	II		-	-				N/A	-
				Trastuzumab	N/A	2	II	II		-	-				N/A	-
9	F	68	Colon	Panitumumab	N/A	9	I	I	4.40	-	-				N/A	-
				Oxaliplatin	-	9	I	I	4.40	-	-				N/A	-
10	M	59	Colon	Oxaliplatin	-	11	II	III		-	-				N/A	-
11	F	52	Colon	Oxaliplatin	-	2	II	III		+	N/A	II	II	No	No[b]	+
12	M	66	Colon	Oxaliplatin	-	12	II	III		-	-				N/A	-
13	F	65	Colon	Irinotecan	N/A	7	I	I		-	-				N/A	-
14	M	73	Lung	Nivolumab	-	5	II	III		-	-				N/A	-
15	M	83	Stomach	Oxaliplatin	-	5	I	II		-	-				N/A	-
16	F	57	Endometrial	Paclitaxel	-	1	II	II		-	-				N/A	-
17	F	79	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
18	F	74	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
19	F	63	Colon	Oxaliplatin	-	9	II	II		-	-				N/A	-
20	M	61	Pancreas	Oxaliplatin	-	8	I	I		-	-				N/A	-
21	F	71	Ovarian	Carboplatin	-	14	II	II		-	+	II	II	Yes	Yes	+
22	M	60	Colon	Oxaliplatin	-	19	II	III		-	-				N/A	-

Patient	Gender	Age	Cancer	Suspected culprit drug	Skin Test	HSR cycle	Severity (Brown)	Severity RCUH)	Tryptase reaction	DPT	RSA	Positive DPT/RSA		Treatment session completed	RDD	Final diagnosis
												Brown	RCUH			
23	F	62	Breast	Paclitaxel	+[a]	1	I	I		-	-				N/A	-
24	F	57	Colon	Oxaliplatin	-	4	II	II		-	-				N/A	-
25	F	65	Ovarian	Carboplatin	-	19	II	II		-	-				N/A	-
26	M	45	Colon	Oxaliplatin	-	9	II	II		-	-				N/A	-
27	F	66	Breast	Docetaxel	-	1	III	III		-	-				N/A	-
28	M	74	Breast	Docetaxel	-	8	III	III	3.70	-	-				N/A	-
29	F	73	Breast	Docetaxel	N/A	1	I	I	4.00	-	-				N/A	-
30	F	73	Ovarian	Carboplatin	-	12	II	II		-	-				N/A	-
31	F	65	Colon	Oxaliplatin	-	7	III	III		-	-				N/A	-
32	M	47	Hematologic	Rituximab	N/A	2	I	II		-	-				N/A	-
33	M	52	Colon	Oxaliplatin	-	7	II	II	8.70	-	+	I	I	Yes	Yes	+
34	F	55	Stomach	Oxaliplatin	-	1	II	II		-	-				N/A	-
35	F	48	Stomach	Oxaliplatin	-	3	II	II		-	-				N/A	-
36	M	70	Hematologic	Rituximab	N/A	1	II	II		-	-				N/A	-
37	M	60	Colon	Oxaliplatin	-	8	II	II		-	-				N/A	-
38	F	32	Colon	Oxaliplatin	-	12	II	II		+	N/A	I	I	Yes	Yes	+
39	F	60	Breast	Paclitaxel	-	18	II	III		-	-				N/A	-
40	F	46	Stomach	Cisplatin	-	1	II	II		-	-				N/A	-
41	M	69	Lung	Nivolumab	-	2	III	III		-	-				N/A	-
42	F	62	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
43	F	79	Ovarian	Placlitaxel	-	8	III	III		-	-				N/A	-
44	F	50	Pancreas	Oxaliplatin	-	8	II	II		-	-				N/A	-
45	F	57	Colon	Oxaliplatin	-	1	II	II		-	-				N/A	-
46	M	29	Skin	Doxorubicine	N/A	3	II	II		+	N/A	I	I	Yes	Yes	+
47	M	62	Colon	Oxaliplatin	-	10	I	I		-	-				N/A	-
48	F	72	Pancreas	Irinotecan	N/A	3	I	II		-	-				N/A	-
49	M	76	Colon	Oxaliplatina	-	20	I	I		-	-				N/A	-
50	F	81	Ovarian	Carboplatin	-	9	III	III		+	N/A	II	II	Yes	Yes	+
51	M	73	Colon	Oxaliplatin	-	18	II	II		-	-				N/A	-
52	F	55	Endometrial	Carboplatin	-	14	III	III	9.90	+	N/A	II	II	Yes	Yes	+
53	M	54	Ovarian	Carboplatin	-	15	I	I		-	-				N/A	-
54	F	63	Endometrial	Paclitaxel	-	2	II	II		-	-				N/A	-

DPT: drug provocation test; HSR: hypersensitivity reactions; ID: intradermal tests; N/A: not applicable; RDD: rapid drug desensitization; RCUH: Ramon y Cajal University Hospital classification; RSA: regular supervised administration; [a]positive ID at 10^{-1} (0.1mg/ml); [b]treatment was changed by patient oncologist due to oncologic disease progression.

Table III *- Characteristics of the patients referred to our department that were submitted to a Drug Provocation Testing.*

Characteristics	Number of patients, n(%)
Primary diagnosis	
Colorectal adenocarcinoma	24 (44.4%)
Breast adenocarcinoma	5 (9.3%)
Serous ovarian	5 (9.3%)
Endometrial	
Endometrioid	2 (3.7%)
Clear cell	1 (1.9%)
Serous	2 (3.7%)
Stomach adenocarcinoma	4 (7.4%)
Pancreatic adenocarcinoma	3 (5.6%)
Squamous cell lung	2 (3.7%)
Chronic lymphocytic leukemia	2 (3.7%)
Non-Hodgkin lymphoma	2 (3.7%)
Parotid adenocarcinoma	1 (1.9%)
Kaposi Sarcoma	1 (1.9%)
Treatment	
Curative	24 (44.1%)
Paliative	30 (55.6%)
History of atopy	5 (9.3%)
Culprit-drug	**Number of culprit-drugs, n (%)**
Platins	36 (56.3%)
Oxaliplatin	28 (43.8%)
Carboplatin	7 (10.9%)
Cisplatin	1 (1.6%)
Taxanes	11 (17.2%)
Paclitaxel	6 (9.4%)
Docetaxel	5 (7.8%)
Biological agents	8 (12.5%)
Rituximab	2 (3.1%)
Nivolumab	2 (3.1%)
Cetuximab	1 (1.6%)
Bevacizumab	1 (1.6%)
Panitumumab	1 (1.6%)
Transtuzumab	1 (1.6%)
Other drugs	9 (14.1%)
Liposomal Doxorubicine	2 (3.1%)
Irinotecan	2 (3.1%)
Bleomycin	2 (3.1%)
Etoposid	1 (1.6%)
Cyclophosphamide	1 (1.6%)
Vinblastine	1 (1.6%)

2 (1,18; IQR7) for taxanes and 2 (1, 9; IQR3) for biologics. Thirty-nine percent (25 out of 64) of the HSRs occurred after the sixth cycle.

Skin tests

SPT and IDT were performed with 50 culprit drugs, platinum compounds in 36 patients, taxanes in 10 and biological agents in 4. All tests were negative, except one positive IDT with paclitaxel 0.1 mg/ml. Interestingly, the patient with the positive ST had a negative DPT/RSA and experienced no reactions in the following cycles.

Drug Provocation Test outcomes

Results are shown in further detail in **figure 2** and **table IV**.

A total of 64 DPTs were performed with the culprit drug: 89.1% (n = 57) were negative and 10.9% (n = 7) were positive, all mild or moderate reactions according to BGS and RCUH classification. No patient had a positive DPT to more than one drug.

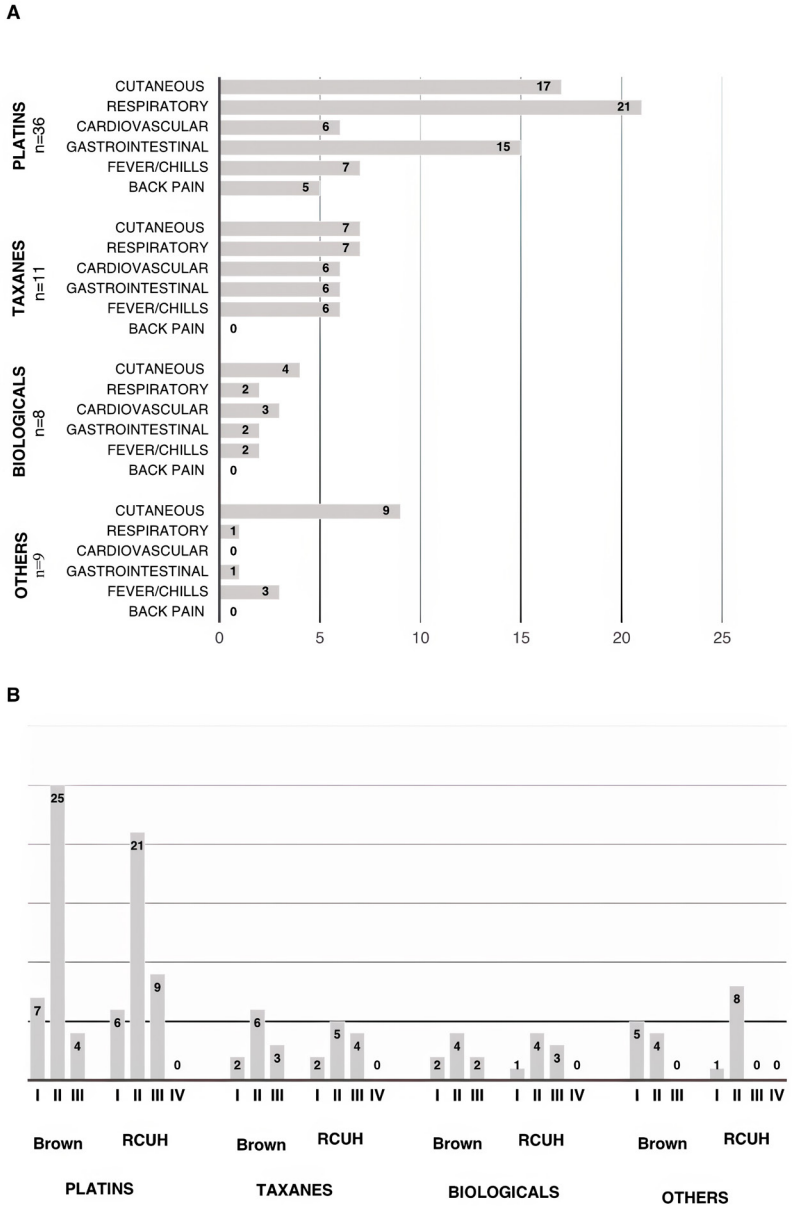
Six of these 7 patients (85.7%) had a positive DPT with platins: 3 patients with oxaliplatin and the other 3 with carboplatin. In patients with HSR to oxaliplatin, the reactions were: facial erythema, nausea and back pain; nausea and chills (T < 38 °C); local urticaria on the abdomen. In patients with HSR to carboplatin: facial erythema and pruritus; palmoplantar pruritus and nausea in two patients. One patient had a positive DPT with doxorubicin: erythema and itching on the abdomen and legs. All of them were treated with intravenous clemastine and intravenous methylprednisolone. All patients with positive DPT to carboplatin had a previous chemotherapy cycle and the median time interval between the HSR and previous chemotherapy cycle was 16.7 months (minimum 4 months, maximum 36 months).

Patients with a negative DPT were submitted to at least one RSA. Two of the 57 patients with a negative DPT (3.5%), suffered a reaction with platins during RSA: one patient with oxaliplatin [generalized erythema and chills (T < 38 °C)] and other with carboplatin (facial erythema, irritative cough and abdominal pain). These patients were treated with intravenous clemastine, methylprednisolone and inhaled beta 2 agonists in those with respiratory symptoms.

All DPT/RSA-reactive patients presented HSRs of equal or less severity than the initial one and 8 out of the 9 DPT/RSA-reactive patients tolerated a full dose of the culprit drug on the same day of the DPT/RSA ("restart protocol").

RDD was performed in 8 of the 9 (88.9%) patients with confirmed HSRs (positive DPT or RSA with the respective drug involved in the HSR). All patients completed the proposed chemotherapy desensitization protocol. One patient (RSA positive to carboplatin) discontinued treatment, due to progression of the oncological disease, so he did not undergo desensitization.

Figure 1 - (A) *Clinical manifestations of the 54 suspected HSRs with chemotherapeutic agents (total 64 culprit-drugs) referred during an eight-year period for DPTs;* ***(B)*** *Severity of HSRs according BGS and RCUH classification.*

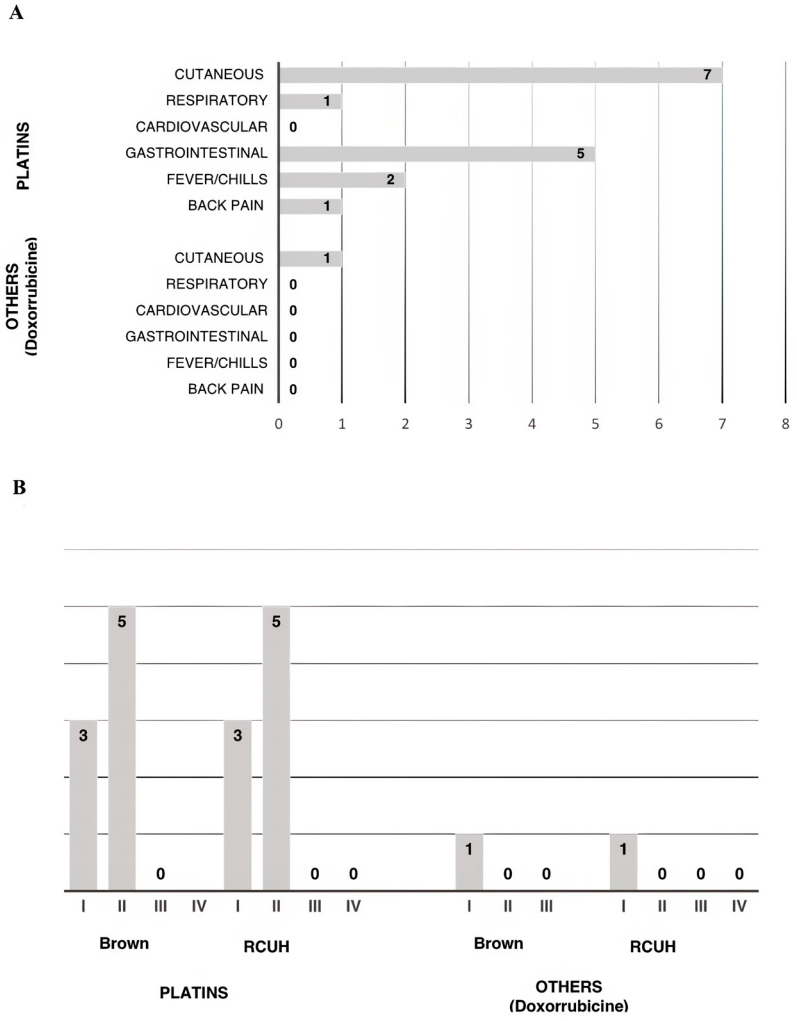


Discussion and conclusions

DPT is a gold standard diagnostic technique used in the study of drugs HSRs (23). More recently, the application of DPT has extended to address chemotherapy and monoclonal antibodies (1, 2). As with other drugs, the diagnostic assessment of HSRs to chemotherapeutics is essential. For patients with malignancies, changing to a second line agent after a HSR may negatively impact quality of life and life expectancy (3, 12).

In this study we report our experience with DPTs with antineoplastic and biological agents. We performed 64 DPTs with platinum compounds, taxanes, biological agents and others antineoplastic agents, in 54 patients who experienced immediate HSRs. Eighty-nine percent (57/64) of DPTs were negative. All

Figure 2 - (A) *Clinical features of HSR in the DPT (n = 7) and RSA (n = 2) of the 9 patients;* ***(B)*** *Severity of HSRs in the DPT and RSA according BGS and RCUH classification.*



patients with negative DPTs were followed during subsequent standard drug administration (RSA), which was positive in 2 (3.5%) patients (carboplatin and oxaliplatin). This approach (DPT/ RSA) allowed the exclusion of hypersensitivity in 85.9% (55/64) of the suspected culprit drugs, de-labeling 83.3% (45/54) of patients. If we had not performed DPT or RSA, this would have caused an unnecessary estimate increase of 85.9% in RDDs. This approach avoided the need for desensitization or switching to second-line therapy and allowing them to normally continue their treatment (6). It is important to emphasize the role of the RSA, if it was not performed with allergology surveillance, we would have misdiagnosed 2 patients.

In our population, 8 out of the 9 patients with positive DPT/ RSA achieved a full dose of the culprit drug on the same day of the DPT/RSA (1, 2, 14, 17, 24). Once symptoms were stabilized and the patient was asymptomatic, the infusion was restarted with 1 bag desensitization protocol (1/1,000 of the original infusion, 2-fold dose increments, along with increasing infusion rate each 15 minutes until the remaining medication was administered) – "restart protocol".

Patients with negative study (DPT and RSA) had no further reactions after follow-up with their oncologists.

In our study 8 patients had more than one culprit drug implicated in reaction (2 patients had 3 drugs and 6 patients had 2). DPT seems to be a safe and cost-effective technique to establish diagnosis in patients who received more than one drug simultaneously (1, 6, 25).

In our sample, most patients were undergoing palliative care, which requires treatment maintenance for long periods (26-28).

Table IV - *Outcomes of 64 DPT and 57 RSA with antineoplastic agents in 54 patients.*

	Positive, n(%)	Negative, n(%)	Total, n(%)
DPT (n = 64)	7 (10.9%)	57 (89.1%)	64 (100%)
Platins (n = 36)	6 (9.4%)	30 (46.9%)	36 (56.3%)
Taxanes (n = 11)	0	11 (17.2%)	11 (17.2%)
Biological (n = 8)	0	8 (12.5%)	8 (12.5%)
Other (n = 9)	1 (1.6%)	8 (12.5%)	9 (14.1%)
RSA (n = 57)	2 (3.5%)	55 (96.5%)	57 (100%)
Platins (n = 30)	2 (3.5%)	28 (49.1%)	30 (52.6%)
Taxanes (n = 11)	0	11 (19.3%)	11 (19.3%)
Biological (n = 8)	0	8 (14%)	8 (14%)
Other (n = 8)	0	8 (14%)	8 (14%)

Forty-four percent (24/54) were undergoing curative treatment, with a high percentage of recurrence described in some neoplasms. A percentage of these patients may be submitted again to the initial treatment scheme; therefore, it is important to confirm or exclude hypersensitivity to antineoplastic agents (26-28).

Prior to DPT, appropriate selection of patients should be carried out, assessing risk by severity scales (BGS and RCUH classification) and ST (1, 16-18). SPT and IDT performed to detect drug specific IgE are only useful for some chemotherapeutic drugs (6). Platinum ST are recommended and validated (8, 29). In our study, despite all 35 patients had negative STs for platinum salts, 8 of those patients had positive DPT/RSA, 4 with oxaliplatin (3 positive DPTs and 1 reaction during the RSA) and 4 patients with carboplatin (3 DPTs and 1 RSA). STs with paclitaxel and docetaxel predictive value has not yet been demonstrated, although some authors recommend its use in the allergological workup (30, 31). In our study, ST for taxanes were negative in 90% (9/10) of the patients. One patient presented positive IDT with paclitaxel in 10^{-1} concentration (0.1 mg/ml). In this case, the suspected HSR was mild (grade I), so the DPT followed by RSA were performed with no reactions experienced.

DPTs is a high-risk procedure that should be performed in specialized centers equipped with specific resources and expert professionals (1, 3, 4, 12). When DPT is performed under these conditions it has a good safety profile (2, 23, 32).

In our population, all patients with positive DPT/RSA presented HSRs of equal or less severity than the initial one. Mild reactions were found in 44.4% and moderate reactions in 55.6% of DPTs/RSA and no severe reactions or deaths were reported. In the group of patients with positive DPT/RSA, all reactions were managed by an allergist and no patient needed medical emergency activation or intensive care hospitalization.

Our results are in accordance with other studies published in the last years, namely in the RCUH studies, 64% (2) and 67% (1) of all performed DPTs were negative, and only 11% (2) and 15% (1) of all performed DPTs showed a severe reaction, according to Brown's classification (16).

General limitations

Our study has a number of limitations, as it is a single-center study, with a wide spectrum of drugs studied (platins, taxanes, biologics and other chemotherapeutic agents), and the groups of patients labeled as allergic are very heterogeneous. Further investigations with different populations, standardization of DPTs protocols and selection of candidates are needed.

Tryptase and IL-6 levels were not measured in all initial reactions, and the lack of these data can lead to an incorrect interpretation of some reactions.

In conclusion, our study demonstrated the safety and effectiveness of DPTs in the assessment of immediate reactions to chemotherapeutic drugs. In our sample, DPT followed by RSA allowed us to exclude HSRs in 45 patients (55 culprit drugs). Without RSA we would have missed the diagnosis in 2 patients, who could have had a potentially more severe reaction without the support of the allergy specialist.

All DPT/RSA-reactive patients presented HSRs of equal or less severity than the initial one, there were no severe reactions and only one did not complete the full dose.

DPT before desensitization prevents non-hypersensitivity patients from undergoing unnecessary desensitization. Our approach (DPT followed by RSA) enabled de-labeling of 83.3% of patients with suspected HSR to one or more chemotherapy agents, corresponding to a total of 85.9% suspected drugs that were excluded and, therefore, desensitization was avoided.

Access to a multidisciplinary team led by experts in drug allergy was very helpful to the optimal management of these patients.

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Contributions

JQG, LPPD: conceptualization, investigation, formal analysis, writing - original draft. PB, JBL, MJS, SC, DM: writing - review & editing. DM: resources.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Evaluation of the origin and educational quality of YouTube videos on adrenaline auto-injectors

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Key words

Adrenaline; epinephrine; anaphylaxis; auto-injector; YouTube.

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Impact statement

The adrenaline auto-injector is a potentially life-saving device in the treatment of anaphylaxis, but it has been shown that only a small percentage of patients can use it correctly. It is important to evaluate videos on YouTube from this perspective.

Summary

Background. *Guidelines highlight the pivotal role of adrenaline auto-injector (AAI) training. However, the standards of visual training platforms have not been determined. Our aim was to evaluate the reliability and quality of the AAI related videos on YouTube.* ***Methods.*** *After a search on YouTube about AAI, all videos were categorized into groups based on their origin and the aim of the content. The quality, reliability, understandibility, and actionability of the videos were evaluated using the Global Quality Scale (GQS), Patient Education Materials Assessment Tool Audovisiual (PEMAT-A/V), Quality Criteria for Consumer Health Information (DISCERN), and a modified DISCERN. In each video, the application steps of AAI were evaluated according to a scale of correct usage.* ***Results.*** *107 YouTube videos in English were included. No significant difference in terms of views, likes, duration and uploading time was observed between the health and non-health groups whereas the GQS ($p = 0.001$), DISCERN total ($p = 0.02$) and modified DISCERN ($p = 0.001$) scores were higher in the health group. It was found that scores tended to be higher in educational videos. AAI use was mentioned in 85% videos. The median number of mentioned steps was 6.* ***Conclusions.*** *YouTube is an effective platform for visual learning for the use of AAIs. Although the visibility of the videos is equal independent of the origin, the ones recorded by medical professionals seem to provide the most qualified and reliable information.*

Introduction

Anaphylaxis is a potentially life-threatening allergic reaction characterized by acute onset of symptoms affecting multiple organ systems, necessitating immediate intervention (1, 2) and adrenaline remains as the cornerstone of acute treatment (3). International guidelines recommend prompt self-administration of adrenaline auto-injector (AAI) as an initial step of treatment (2, 4). Accordingly, AAIs should be prescribed to individuals with a history of anaphylactic reactions triggered by food, latex or aeroallergens, exercise-induced anaphylaxis, idiopathic anaphylaxis, co-existing unstable or moderate to severe persistent asthma and food allergy, Hymenoptera venom allergy, or an underlying systemic mastocytosis in adults with any previous systemic reaction (2, 4). Prompt prehospital injection of adrenaline during anaphylaxis has been associated with a lower risk of hospitalization and mortality (5-8). Administering adrenaline has been also found to lower the risk of biphasic reactions (2,6,9-11). On the other hand, the patients during an acute attack can be reluctant to use the AAI. A study by Goldberg *et al.* showed that only 22% of venom allergy

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patients who were prescribed an AAI were able to use and among them, 44% demonstrated proper usage (12). Similarly, Gold *et al.* stated that parental knowledge regarding the usage of AAI was insufficient and in recurrent anaphylaxis, with only 29% demonstrating the ability to use an AAI (13).

The international guidelines emphasize the pivotal role of AAI training in people at risk of anaphylaxis (2, 4). However, the standards of the educational content on visual platforms have not yet been determined (2). Recently, where the internet provides easily accessible information, numerous videos on YouTube (https://www.youtube.com/) discussing the use of AAI can be found. These YouTube videos serve as an uncontrolled source of information regarding the utilization of AAIs and can potentially prove to be helpful. Therefore, we aimed to evaluate the characteristics of the YouTube videos for the use of AAIs.

Materials and methods

Study design

A search on YouTube (https://www.youtube.com/) was conducted using the terms of "adrenaline auto-injector", "epinephrine auto-injector" and the marketing names for AAI. The most relevant 157 videos in English were initially screened. The flowchart in **figure 1** shows the reasons and numbers for excluding videos.

Statement of ethics

This study protocol was reviewed and approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee, Istanbul University, approval number 1815210, 2159248.

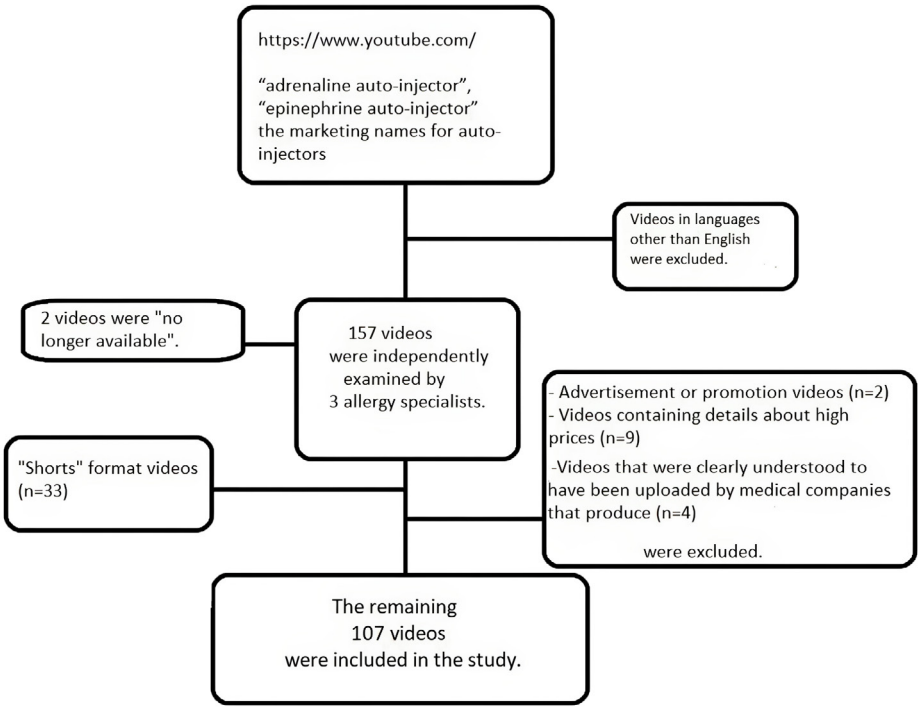
Evaluation of the videos

Data on views, likes, time of upload (in months), and duration (in minutes) were collected. Views and likes were also recorded by calculating the average views per month, likes per month, and likes/views ratio. The content of two identical videos were evaluated as two separate videos when the number of views, likes and links was different.

Categorization of the videos

The videos were categorized into two groups according to the presenter and/or the YouTube channel as the "health group" and the "non-health group". Accordingly, when the presenter was a medical doctor, a paramedic, a nurse or a pharmacist or an unspecified healthcare professional, the video was considered to belong to the health-group. Additionally, when the channel belonged to a medical doctor, a paramedic, a nurse or a pharmacist, a healthcare facility, training or education center/company, a non-profit medicial association or a governmental medical organization, the video was again considered within the health group. All other presenters and channels formed the non-health

Figure 1 *- Research methodology flowchart.*



group. All the videos were further classified into four subgroups based on their aim of content, as medical professional education (MPE), patient education (PE), patient experience, and awareness:

- MPE: The video's target audience is primarily healthcare professionals.
- PE: Patient education videos aim to educate the public.
- Patient experience: Patient experience videos focus on the experiences of patients or their relatives without educational purposes.
- Awareness: These videos aim only to raise awareness without any educational purpose or experience.

Content quality, reliability, understandibility and actionability of videos

The quality, reliability, understandability, and actionability of the videos were assessed using several tools: the Global Quality Scale (GQS), the Patient Education Materials Assessment Tool Audovisual (PEMAT-A/V), the Quality Criteria for Consumer Health Information (DISCERN), and a modified version of DISCERN. These tools were utilized to evaluate the videos (**table IS**). Video quality and streaming were assessed using a 5- question GQS score in which a higher GQS score indicated a greater content-quality and information (14-21). To evaluate the understandability and actionability of videos pertaining to the use of AAI the PEMAT-A/V score was applied (22-24).

For the evaluation of the quality, reliability, and detailed treatment options in the content of the videos, the DISCERN (25) and modified DISCERN (18, 26) scores were utilized. Each of these scoring systems was rated on a scale of 1-5, with higher scores indicating greater reliability.

In addition, an assessment was conducted to determine whether the videos contained any false information (17, 20, 21, 27-31). To ensure reliability and objectivity, the videos were reviewed by three allergists independently.

Scales used to evaluate the quality, reliability, understandibility and actionability of the video content are shown in detail in the supplementary **table I** (17, 18, 20-24, 26-31).

Evaluation of application steps of an adrenaline auto-injector presented in each video

The application steps of an AAI in each video were assessed according to a scale of correct usage as follows; step 1: checking the expiration date, step 2: removing the AAI from its container, step 3: removing the safety cap, step 4: displaying of the application area, step 5: stabbing of AAI, step 6: counting for 3-10 seconds, step 7: removing the AAI, step 8: massaging the application area and step 9: calling the first aid center (2, 4, 32-35).

Table I *- Comparison of quality reliability, understandability and actionability of the video content between the health and non-health groups.*

	Health (n = 96)	**Non-health (n = 11)**	**P-value**
Content, n (%)			< 0.001
Medical profession education	8 (8.3)	0	
Patient education	80 (83.3)	3 (27.3)	
Patient experience	3 (3.1)	7 (63.6)	
Awareness	5 (5.2)	1 (9.1)	
GQS, median (IQR)	3 (3-4)	2 (1-3)	0.001
PEMAT-A/V, median (IQR)			
PEMAT-A/V actionability	100 (100-100)	100 (0-100)	NS
PEMAT-A/V understandibility	78 (67-91)	67 (57-82)	NS
DISCERN, median (IQR)			
DISCERN total	31 (29-34.75)	30 (22-31)	0.02
DISCERN reliability	24 (22-25)	23 (15-24)	NS
DISCERN treatment	7 (7-9)	7 (7-7)	NS
DISCERN overall	4 (3-4)	3 (1-4)	NS
Modified DISCERN, median (IQR)	3 (3-4)	3 (0-3)	0.001

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences. Additionally, Microsoft PowerPoint was utilized to generate the figures.

The distribution pattern of the quantitative data was assessed using the Kolmogorov-Smirnov test.

Baseline characteristics were evaluated by descriptive analysis, and the interquartile range was presented as median percentages with 25-75 percent (IQR 25-75) according to the distribution of data. Continuous variables were compared between the two groups using either the independent t-test or the Mann-Whitney U test. Statistically significant differences were defined as p-values less than 0.05.

Videos were examined independently by three physicians working in the allergy and immunology unit. The two results that were closest to each other were selected for further analysis, and the Correlation Coefficient (ICC) was calculated as an average measure.

Results

General analysis of the data

A total of 9 hours and 21 minutes of video streaming was observed in 107 videos. Additionally, these videos received a total of 16,631,161 views and 193,050 likes. The median length of the videos was 2 (1-5) minutes; the median loading time was 55 (25-92) months; the median number of views was 4,362 (360-26,005) and the median number of likes was 18 (3-190). The views/months rate, the likes/months rate and likes/views rate were calculated as 68.50 (10.97-686.20), 0.37 (0.08-3.22) and 0.005 (0.002-0.012), respectively. The distribution of the videos depending on the presenter and channel are shown in **figure 2**. The majority was presented by a health advocate with unknown profession. The training or education center/company was the leading YouTube channels.

Comparison of general characteristics of the videos in health and non-health groups

No significant differences were found between the health and non-health groups in terms of views, likes, duration (in minutes), upload time, views/months rate, likes/months rate and likes/views rate ($p = 0.943$, $p = 0.833$, $p = 0.276$, $p = 0.186$, $p = 0.601$, $p = 0.482$, $p = 0.663$, respectively) (**table IIS**).

Comparison of quality, reliability, understandibility and actionability of the video content between the health and non-health groups

In terms of video content categories, there was a significant difference between the health and non-health groups. PE videos were found to be significantly more prevalent in the health group ($p < 0.001$). Furthermore, when evaluating video quality, the GQS score was significantly higher in the health group compared to the non-health group ($p = 0.001$).

However, there was no statistically significant difference between the health and non-health groups in terms of neither PEMAT-A/V

Figura 2 *- The distribution of the videos.*

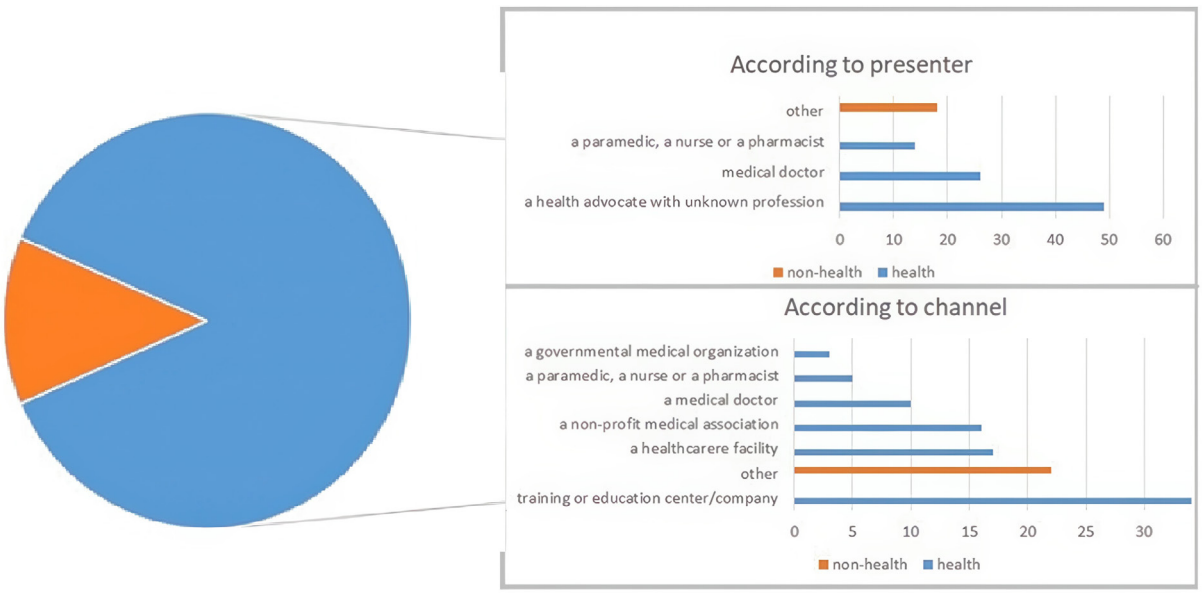


Table II *- Comparison of the video quality, reliability, understandability and actionability depending on the aim of the content.*

	Medical profession education (n = 8)	Patient education (n = 83)	Patient experience (n = 10)	Awareness (n = 6)	P-value
GQS, median (IQR)	4 (3-4)	3 (3-4)	1.5 (1-3)	2 (1-3)	< 0.001
PEMAT-A/V, median (IQR)					
Actionability	67 (8.25-91.75)	100 (100-100)	33.5 (0-100)	16.5 (0-75.25)	< 0.001
Understandability	73 (47-91)	78 (67-91)	67 (55-82.25)	65 (45-82.75)	NS
DISCERN, median (IQR)					
Total	31.50 (30-42.75)	32 (30-34)	27 (20-31)	26 (25-31.25)	0.006
Reliability	22.5 (21.25-24.75)	24 (22-26)	19 (13-24)	19 (18-20.75)	0.001
Treatment	7.5 (7-16.25)	7 (7-8)	7 (7-7.5)	7 (7-10.5)	NS
Overall	3 (3-3.75)	4 (3-4)	2 (1-4)	2.5 (2-3.25)	< 0.001
Modified DISCERN, median (IQR)	4 (3-4)	3 (3-4)	1.5 (0-3)	1.5 (0-3)	< 0.001

actionability nor PEMAT-A/V understandability (p = 0.141, p = 0.122, respectively).

The health group demonstrated statistically significant higher score in DISCERN total (p = 0.02). However, there was no significant difference in DISCERN reliability, DISCERN treatment and DISCERN overall scores between the health and non-health groups (p = 0.057, p = 0.165, p = 0.094, respectively). It is worth noting that the median value for DISCERN treatment was 7 which was the lowest score in both groups. The modified DISCERN score was found to be significantly higher in the health group compared to the non-health group (p = 0.001) (**table I**). One (1%) video in the health group had the potential to be harmful, while 4 (4.1%) contained misleading information. In the non-health group, 2 (18.18%) videos had the potential to be harmful, and 1 (0.9%) video had misleading information.

Comparison of the general characteristics of the videos depending on their content

Among the four subgroups determined depending on different aims of the video content, there were no significant differences observed in terms of views, likes, views/months, likes/months, likes/views (p = 0.603, p = 0.956, p = 0.920, p = 0.929, p = 0.095, respectively). However, there were statistically significant differences in video duration (in minutes) and the time of upload (in months) (p = 0.002, p = 0.005, respectively) (**table IIIS**). Among the four subgroups, the patient experience videos were found to be the oldest, while the MPE videos were the newest (p = 0.005). Additionally, the MPE videos had the longest duration, whereas patient experience videos were the shortest (p = 0.002).

Comparison of quality, reliability, understandibility and actionability assessment of the videos depending on their content

When comparing video quality assessment according to GQS, the GQS score was significantly higher in the MPE subgroup (p < 0.001). The PEMAT-A/V actionability score was statistically higher in the PE subgroup (p < 0.001). However, there was no statistically significant difference in PEMAT-A/V understandability among four subgroups (p = 0.114).

The DISCERN total, reliability and overall scores were significantly higher in the PE subgroup (p = 0.006, p = 0.001 and < 0.001, respectively) whereas there was no difference in the DISCERN treatment (p = 0.348). On the other hand, the modified DISCERN score was significantly higher in the MPE subgroup (p < 0.001) (**table II**). In the PE group, four videos (4.8%) contained misleading information, and one video (1.2%) had the potential to provide harmful information. In the patient experience group, two videos (20%) had the potential to be harmful, while one video (10%) contained misleading information.

Analysis of the reliability between two reviewers for assessment of the videos

The intraclass correlation average measure for the following variables was determined: 0.959 for GQS; 1 for content; 0.949 for PEMAT-A/V actionability, 0.895 for PEMAT-A/V understandability, 0.872 for DISCERN reliability; 0.839 for DISCERN overall, 0.782 for DISCERN treatment, and 0.834 for modified DISCERN.

Table III - *Evaluation of adrenaline auto-injector application in a stepwise manner.*

Auto injector usage step	Presented n (%)
Step 1. Checking the expiration date	22 (20.6)
Step 2. Removing the autoinjector from its container	44 (41.1)
Step 3. Removing the safety cap	85 (79.4)
Step 4. Display of the application area	77 (72)
Step 5. Stab of autoinjector	84 (78.5)
Step 6. Counting 3-10 seconds	83 (77.6)
Step 7. Removing the autoinjector	76 (71)
Step 8. Massaging the application area	38 (35.5)
Step 9. Calling for first aid center	58 (54.2)

Evaluation of application steps for the correct use of adrenaline auto injectors

AAI use was mentioned in 91 (85%) videos. Each of the nine AAI application steps was evaluated independently by three allergists**.** The two closest results to each other were selected for the evaluation, and intraclass correlation average measure was determined as 1 among the two results.

The presence of each step in the videos are presented in rates in **table III**. All the steps were shown in only three videos. The median number of mentioned steps was 6 (5-7). The steps of AAI application were shown in similar numbers in health and non-health groups.

Discussion and conclusions

The AAI is a potentially life-saving device in the treatment of anaphylaxis. However, as shown in previous studies, only a small percentage of patients can correctly administer an AAI during anaphylaxis in daily practice (12, 13)**.** In line with this, the World Allergy Organization (WAO) 2020 guidelines recommend that patients should carry a written anaphylaxis emergency action plan with instructions on how to quickly inject AAI (4). It should be noted that the recent European Academy of Allergy and Clinical Immunology (EAACI) guideline has clearly stated that the issue of how patient education will be carried out has not yet been clarified (2). Therefore, an educational video on YouTube that describes the use of AAI can be life-saving, especially for patients and their relatives who have been prescribed an AAI but have never used it before. Our study provides a good evidence by evaluating the AAI videos found on YouTube.

One of the main strengths of our work was that it reflects real-life practical scenarios. When we conducted a search YouTube, we observed that patients or their relatives frequently watch the videos demonstrating the usage of AAI. We found a total of 9 hours and 21 minutes of video streaming and 16,631,161 views of these videos. This may serve as evidence have a need for visual instruction on how to use an AAI.

The quality of these videos, the adequacy of the narration regarding AAI usage, and the presence of any false information are all crucial factors to consider. Many studies have been conducted on informative and educational YouTube videos in the field of health (20, 36, 37). Alataş *et al.* found the videos useful in terms of training by evaluating the videos on YouTube between 2006 and 2015 (38). It is obvious that an up-to-date evaluation is necessary with the increasing use of social media.

Our study highlighted that the videos on patient experience were the oldest, while the MPE group contained the recently recorded videos. This finding provides clear evidence that there has been an increase in the uploading of educational videos on this subject in recent years. The predominance of PE videos indicates the availability of various choices for patients seeking information on the use of AAI. Our study demonstrated that YouTube videos concerning AAI, uploaded by professional healthcare workers were valuable sources for obtaining accurate and reliable information on the use of AAI. This conclusion is derived from multiple analyses we conducted, using GQS, DISCERN and PEMAT scores. We evaluated DISCERN in both its original and modified forms.

In previous studies examining the quality and reliability of YouTube videos in the field of health, it was found that the health-related videos had higher GQS and DISCERN scores (39). A similar outcome was observed in a study with anakinra, a medication administered by self-injection like AAI (40). Furthermore, a study focusing on urticaria, within the field of allergy, concluded that the videos uploaded by physicians demonstrated higher quality and reliability, as indicated by DISCERN and GQS scores (37). Similarly, in our study DISCERN-total, modified DISCERN and

GQS scores of the videos in the health group were statistically significantly higher than the non-health group. Another important result from these data is that DISCERN total and modified DISCERN yielded similar results. Consequently, we believe that in future studies assessing video reliability, it may be adequate to utilize the modified DISCERN tool without necessarily employing the original DISCERN tool.

In their study on the use of social media, Benetoli *et al.* stated that YouTube was particularly utilized for medical procedures (41). The PEMAT score has been commonly employed in literature, especially in YouTube evaluation studies on medical procedures (42-45). We believe that when evaluating the videos pertaining to medical devices that requires self-administration, it is important to determine the understandability and actionability. Therefore, we also evaluated the PEMAT score in the videos to enhance its validity and examine the videos' understandability and actionability separately. In this context, according to PEMAT-A/V, the median understandability and actionability scores were similar in both study groups. In fact, it was observed that the health-related group had higher rates of understandability, although the difference did not reach statistical significance (**table I**). Interestingly, Vural Solak *et al.*'s study about YouTube videos on epinephrine autoinjectors, found that understandability was lower in health-related videos (46). This difference may be attributed to the video grouping. They categorised the video sources in two major groups as health worker sources and other sources including organization/administrations, independent users and drug companies. In our study, we evaluated both the sources and presenter(s) separately and categorized them as either health or non-health related since we also consider the possibility of the presence of a health worker in a non-health video source. Therefore, in our categorization the rate of health-related videos was higher when compared to their study (46).

In the current study, the majority of the videos in the health group were intended for PE. Conversely, most of the videos in the non-health group focused on patient experience. The quality of the videos in the health group ranged from moderate and excellent. Since the videos exhibited higher GQS and DISCERN scores and are primarily aimed at PE, they represent a suitable choice for patients seeking information about the use of AAI.

In a previous study YouTube on rehabilitation, educational physician videos were found to have significantly higher GQS and DISCERN scores (47). Similarly, in our study, the GQS score, PEMAT actionability, DISCERN total, DISCERN reliability, DISCERN overall and modified DISCERN were found to be higher in the educational videos (MPE and PE group). Based on these findings in GQS, PEMAT-A/V and DISCERN, we can conclude that videos presented by healthcare professionals or volunteers, particularly for educational purposes, tend to offer better quality. However, we found no significant difference in terms of DISCERN-treatment scoring. This suggests that videos lacked sufficient information regarding how each treatment works, the associated benefits and risks, the consequences of not using the treatment, the impact on overall quality of life, and presenting multiple treatment options for shared decision-making.

In Peters-Geven *et al.*'s previous study on the use of intranasal spray, the application method was evaluated step by step (36). They concluded that only few instructional videos on YouTube provided correct instructions for the administration of nasal sprays to patients (36). In our study, while 85% of the videos mentioned the AAI usage steps, only 3 videos included all the steps. When we focused on the crucial steps of AAI application such as removing the safety cap, displaying the application area, activating the autoinjector, and counting 3-10 seconds for proper drug delivery, we found that more than 70% of the videos correctly mentioned these crucial steps for transferring the drug to the patient's body.

Our study had several limitations. Firstly, it was conducted exclusively in English. While English is a widely spoken language, conducting a more comprehensive analysis would involve examining videos of patients recorded in other languages as well. To achieve this, multicenter studies are necessary. Secondly, as the videos continue to be uploaded day by day, auto-injectors may struggle to keep up with the evolving designs. Thirdly, since the videos, clearly understood to have been uploaded by medical companies that produce AAI, were excluded, the videos with high scores and completely accurate application content may have been excluded.

In conclusion, YouTube is an effective platform for visual learning for the use of AAIs. Patients can conveniently access instructional videos by searching on YouTube in their daily lives. However, the uploaded videos should be of higher quality, regularly updated, should contain feature completely accurate narration and be approved by international association working groups. Therefore, healthcare professionals should be encouraged to provide educational videos for patients, and patients should be informed to exclusively watch professional training that have been approved videos approved by their doctors.

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Contributions

IDT, PK, ZK, DU, AG, SD: data curation, investigation, methodology. IDT, DU, AG, SD: project administration, formal analysis. IDT, PK, ZK: resources, software. IDT, DU, AG, PK, ZK, SD: supervision, validation, visualization. DU, AG, IDT, SD: writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Allergic emergencies in the prehospital setting: a 5-year retrospective study

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Impact statement

This pioneer study of allergic emergencies in the prehospital context highlights the main features of hypersensitivity reactions in this setting, particularly of anaphylaxis, which appears to be underdiagnosed on-site.

Summary

Background. *Patients with severe allergic conditions often request support from the prehospital emergency services given the rapid, unexpected and potentially life-threatening nature of the reactions, such as anaphylaxis. Studies regarding prehospital incidents for allergic conditions are scarce. This study aimed to characterize prehospital medical requesting assistance due to suspected hypersensitivity reactions (HSR).* ***Methods.*** *Retrospective study of allergic-related requesting assistances between 2017 and 2022 of a Portuguese emergency dispatch center – Emergency and Resuscitation Medical Vehicle (VMER) – in Coimbra University Hospital. Demographic and clinical variables were analyzed, including clinical manifestations, anaphylaxis severity grading, therapeutic interventions, and post-incident allergic work-up. Regarding anaphylactic events, three diagnosis timings were compared: on-site, hospital emergency department and investigator-diagnosis based on data reviewed.* ***Results.*** *Out of 12,689 VMER requesting assistances, 210 (1.7%) were classified as suspected HSR reactions. After on-site medical evaluation, 127 (60.5%) cases maintained the HSR classification (median age 53 years; 56% males) and the main diagnoses included HSR to Hymenoptera venom (29.9%), food allergy (29.1%), and pharmaceutical drugs (25.5%). Anaphylaxis was assumed on-site in 44 (34.7%) cases, in the hospital emergency department in 53 cases (41.7%) and by investigators in 76 (59.8%) cases. Regarding management, epinephrine was administered on-site in 50 cases (39.4%).* ***Conclusions.*** *The main reason for prehospital requesting assistance was HSR to Hymenoptera venom. A high proportion of incidents met the criteria for anaphylaxis and despite the inherent difficulties of the prehospital setting, many of the on-site diagnoses agreed with the criteria. Regarding management, epinephrine was underused in this setting. After pre-hospital events, a proper referral to a specialized consultation is crucial for a full diagnostic work-up and disease management.*

Introduction

The National Institute of Medical Emergency (INEM) is responsible, in Portugal, for ensuring the proper functioning of an Integrated System of Medical Emergency and guaranteeing, whenever justified, immediate and appropriate healthcare assistance. Through on-site medical care, assisted victim transport and articulation between the various elements involved in the System, INEM asserts itself as a regulatory entity in medical emergency situations (1).

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The Urgent Patient Orientation Centres (CODU), an integral part of the INEM, through the European Emergency Number (EEN) 112, analyze the multiple requests for emergency assistance aiming towards the optimal triage by applying medical algorithms, and if justified, the selection and activation of the proper means of medical emergency, including the Emergency and Resuscitation Medical Vehicle (VMER). By using these fluxograms, a priority grade is assigned according to the severity of the episode and its potential evolution.

CODU functioning is ensured continuously 24 hours a day by a team of qualified professionals (doctors, prehospital emergency technicians and psychologists), trained to provide care, triage, counselling, proper selection, activation, and management of the necessary emergency resources. In addition, they are also responsible for contacting the respective healthcare units, preparing hospital reception, and promoting an integrated approach to the urgent/emergent patient situations (1).

Hypersensitivity reactions (HSR) are characterized by an excessive or inappropriate immune response to a particular stimulus, with variable clinical presentation and severity. The World Allergy Organization (WAO) estimates that HSR affect about 30 to 40% of the world's population, emphasizing that both the severity and complexity of these reactions are increasing exponentially (2). In Portugal, it is estimated that more than 2 million people (~20%) will experience at least one HSR during their lifetime (3).

Anaphylactic reactions, globally considered the most severe, sudden, and potentially fatal form of HSR manifestation, are a rising concern worldwide (4-6). Mortality can occur within minutes, without being possible to predict the rate of progression or its ultimate severity. Thus, the proper diagnosis of an anaphylactic reaction is essential to determine the most suitable treatment, namely the early administration of epinephrine, associated with improved prognosis and reduced mortality (7, 8). Despite clinical consensus establishing diagnostic criteria and guidelines for therapeutic approaches, national and international data consistently demonstrate that anaphylaxis remains underdiagnosed, underreported and undertreated (9, 10).

The estimated incidence of anaphylaxis in Europe is 1.5-7.9 per 100,000 person per year (4). However, it is considered to be underestimated, given the high rate of underdiagnosis and underreported situations. Factors such as demographic heterogeneity, usage of different diagnostic and classification criteria, varying degrees of differentiation of the health care services where patients with anaphylaxis are assessed and the lack of a national mandatory notification registry contribute to the heterogeneous nature of the published data.

In Portugal, during a 10-year period, a national anaphylaxis reporting system was implemented depending on voluntary reports by Clinical Allergists. Based on analysis of the collected data, it was observed that food allergens were the most frequent cause of anaphylaxis (48%) in pediatric age, while drugs were the main triggers in adulthood (37%) (3).

Allergic reactions, and anaphylaxis (given its sudden onset and unpredictability) are a frequent motive for the EEN requesting assistances, with an increase in referrals in recent years. According to the Portuguese CODU annual report for the year 2021, 7,303 of the overall occurrences were encoded as "Allergy-ALR", representing a 21% increase from the 2020 report (1).

Even though emergency departments (ED) often encounter severe allergic reactions, there is a lack of national studies exploring the management of allergic emergencies in the prehospital setting (11-13).

The present study aims to characterize the VMER requesting assistances of a tertiary hospital for suspected HSR, describing their frequency, severity and outcomes, as well as their on-site therapeutic approach.

Materials and methods

Study design and patient recruitment

A descriptive retrospective study was conducted analyzing data from all VMER requesting assistances that were referred to a tertiary hospital center in the Central Region of Portugal, during a 5-year period, from June 2017 to June 2022.

Records (both digital and on paper) that lacked patient identification or clinical data or that had imperceptible handwriting were immediately excluded. Of the remaining requesting assistances, those coded by the CODU as "Allergy-ALR" (suspected HSR) were selected. Patients that, despite being initially coded as "Allergy-ALR", were given an alternative diagnosis by the physician on-site, and thus not suspected of having an allergic reaction, were subsequently excluded from this study.

Each requesting assistance episode corresponded to a single patient.

Data collection

Data regarding demographic characteristics, clinical manifestations described on-site, atopic and cardiovascular background, therapeutic approach (*i.e.* use of anti-histamines, corticosteroids, epinephrine, bronchodilators, supplementary oxygen) on-site and in the ED, suspected culprit allergens, referral to an Allergy Clinic and prescription of epinephrine auto-injector was collected through the analysis of the VMER episode files (both in physical and digital format using iTeams® software), as well as the hospital system database (SClinico®). Severity of reactions described on-site was graded using the adapted WAO severity reaction classification published in 2017 (14).

In order to assess potential differences in the interpretation of anaphylactic events, three diagnosis timings were used:

1. VMER-classified anaphylaxis (VCA) − VMER episodes were classified by the on-site physician as "anaphylactic events".
2. Hospital-classified anaphylaxis (HCA) − VMER episodes were assessed in the ED by an observing physician and/or subse-

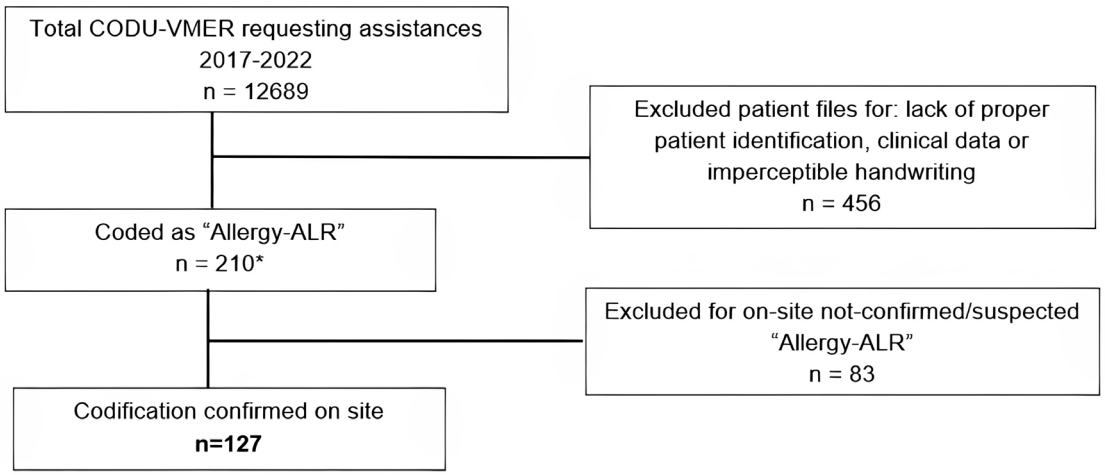
quently in an Allergy Clinic by an Allergist and registered as "anaphylactic events" after additional investigation or assumed in the absence of a more probable alternative.

3. Investigator-classified anaphylaxis (ICA) – on-site clinical data was reviewed by the authors and classified according to the 2021 European Academy of Allergy & Clinical Immunology (EAACI) anaphylaxis guidelines (9).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics® 27. Frequencies were calculated for nominal variables, medians and interquartile ranges for continuous variables. The normality of the distribution of continuous variables was analyzed using the Kolmogorov-Smirnov test. Chi-square (χ^2) and Mann-Whitney U tests were used for determining differences in the distribution

Figure 1 *- Study population selection.*



*Excluded all occurrences not coded as "Allergy-ALR".

Table I *- Characterization of the clinical presentation of events (n, %)*

Clinical manifestations	Suspected HSR (n = 127)	ICA (n = 76)	Epinephrine administration (n = 50)
Mucocutaneous	112, 88.2	70, 92.1	46, 92.0
Respiratory	59, 46.5	48, 63.1	29, 58.0
Cardiovascular	34, 26.8	27, 35.5	19, 38.0
Neurological	19, 15.0	12, 15.8	8, 16.0
Gastrointestinal	11, 8.7	9, 11.8	7, 14.0
Modified WAO Systemic Allergic Reaction Grading System			
1	16, 12.6	0, 0.0	2, 4.0
2	34, 26.8	14, 18.4	8, 16.0
3	46, 36.2	36, 47.4	20, 40.0
4	13, 10.2	9, 11.8	8, 16.0
5	18, 14.2	17, 22.4	12, 24.0

HSR: Hypersensitivity Reactions; ICA: Investigator-classified anaphylaxis; WAO: World Allergy Organization.

of nominal and continuous variables, respectively, between events with and without anaphylaxis criteria and events with and without epinephrine administration.
Statistical significance was considered for $p < 0.05$.

Results

An overview of suspected HSR events

Out of a total 12,689 VMER requesting assistances, 210 (1.7%) were coded by the CODU as "Allergy-ALR". After medical assessment on-site (mainly through anamnesis and objective examination plus information from relatives or individuals present at the scene), 83 episodes were excluded. In the remaining 127 occurrences, clinical suspicion of HSR was maintained, corresponding to 1.0% of the overall requesting assistances and to 60.5% of the episodes initially coded as "Allergy-ALR" (**figure 1**).
In our cohort of 127 episodes, affected patients were mainly adults (n = 111, 87.4%), males (n = 71, 56.0%), and with a median age of 54 (IQR 33-71) years.
Regarding clinical presentation of HSR, mucocutaneous symptoms were the most prevalent (88.2%) (mainly episodes of urticaria with or without angioedema), followed by respiratory symptoms (46.5%). By classifying the suspect HSR and the ICA through the modified WAO Severity Grading System, grade 3 was the most prevalent in our sample (mainly lower airway symptoms, such as dyspnea, associated with mucocutaneous symptoms such as urticaria and/or non-laryngeal angioedema). 18 patients had grade 5 reactions, the most severe, which progressed to respiratory failure and/or cardiovascular collapse and/or non-vasovagal loss of consciousness (**table I**).
The pattern of clinical manifestations in both anaphylactic events defined by EAACI criteria and episodes with epinephrine administration appeared to follow a similar trend.
The suspected allergic culprits are represented in **table II**. The main suspected diagnosis was HSR due to Hymenoptera venom, which corresponded to 29.9% of the episodes, mostly triggered by bee and wasp stings. Food allergy was the second most common suspicion, representing 29.1% of the cases, followed by drug allergy (25.2%). In the suspected food allergy cases, the most commonly identified triggers were seafood/fish, fresh fruits and peanut/tree nuts.
Regarding suspected episodes of drug-induced HSR, beta-lactam antibiotics and nonsteroidal anti-inflammatory drugs, particularly metamizole, were the main implicated pharmaceuticals.
In 15.8% (n = 21) of the occurrences, the etiology of the reaction could not be determined. In 9.4% (n = 12) of patients, diagnosis had already been confirmed at a Clinical Allergy consultation. After the presenting event, 47.2% (n = 60) of the patients were

Table II *- Characterization of suspected hypersensitivity reaction (HSR) agents (n, %)*

Suspected HSR etiology	Total Occurrences (n = 127)	Anaphylaxis Criteria (ICA) (n = 76)
Hymenoptera venom HSR	38, 29.9	22, 28.9
Bee	14, 11.0	10, 13.1
Velutine wasp	11, 8.7	5, 6.6
Common wasp	9, 7.1	4, 5.3
Unknown	4, 3.1	3, 3.9
Food HSR	37, 29.1	24, 31.6
Seafood/fish	10, 7.9	6, 7.9
Fresh fruits	7, 5.5	3, 3.9
Peanut/tree nuts	6, 4.7	5, 6.6
Unknown	14, 11.0	10, 13.2
Drugs HSR	31, 25.2	21, 27.6
Beta-Lactams	6, 4.9	6, 7.9
NSAIDs (including metamizole)	6, 4.9	5, 6.6
COVID-19 vaccine	4, 3.2	0, 0.0
Others	15, 12.2	10, 13.1
Unidentifiable agent	21, 15.8	9, 11.9

COVID-19: Coronavirus 19 disease; ICA: Investigator-classified anaphylaxis; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Table III - *Characterization of occurrences, anaphylaxis and diagnoses by the VMER (n, %).*

Occurrences	Total (n = 127)	ICA (n = 76)	HCA (n = 53)	VCA (n = 44)
ICA	76, 59.8	-	48, 90.6	40, 90.9
HCA	53, 41.7	48, 63.2	-	33, 75
VCA	44, 34.7	40, 52.6	33, 62.3	-
Epinephrine administration (on-site)	50, 39.4	41, 53.9	31, 58.5	39, 88.6

ICA: Investigator-classified Anaphylaxis; HCA: Hospital-classified Anaphylaxis; VCA: VMER-classified Anaphylaxis; VMER: Emergency and Resuscitation Medical Vehicle.

referred to a consultation, while 10.2% (n = 13) were already enrolled in an allergist consultation.

Suspected anaphylactic events

From the 127 included reactions, anaphylaxis was diagnosed by the VMER medical team (VCA) in 44 (34.7%). In the hospital setting (in the ED and/or in an Allergy Clinic follow-up), however, anaphylaxis (HCA) was diagnosed in 53 cases (41.7%). The proportions of VCA and HCA were much lower than the investigators' anaphylaxis classification using the EAACI guidelines (ICA), which identified 76 (59.8%) events. Despite identifying fewer severe HSR, the VCA classification appeared to accurately interpret a high proportion of episodes – 40 (90.9%) VCA events were also classified as ICA, whereas 33 (75.0%) were defined as HCA episodes (**table III**). In the ICA group, the most frequent etiologic factors included food (31.6%) – mostly shellfish and peanut/tree nuts –, Hymenoptera venom (28.9%), particularly bee stings, and drugs (27.6%), with special relevance for beta-lactam antibiotics and metamizole. In 11.9% of ICA cases, it was not possible to determine an etiologic factor (**table II**). At the ED, only 9 events had a measurement of acute-phase serum tryptase.

Management of episodes

Regarding HSR management, epinephrine was administered by VMER professionals in 50 cases (39.4%) and, particularly, in 39 of all VCA episodes (88.6%). Using both HCA and ICA classifications, however, epinephrine appeared to be underused, with roughly half of these patients receiving this medication on-site. In addition, systemic corticosteroids were administered on-site in 82.9% of all patients, while antihistamine therapy was given in 75.0%. Supplementary oxygen associated with bronchodilator therapy was required by 18.4% of patients. At the emergency department, 56.6% received corticotherapy, 40.8% antihistamine therapy and 25.0% supplementary oxygen associated with bronchodilators. Seventeen percent (n = 21) of patients carried an epinephrine auto-injector pen. However, even though most of them (n = 17, 81%) met criteria for anaphylaxis, only 23.8% (n = 5) performed epinephrine self-administration.

Regarding whether or not epinephrine was administered on-site during the acute episodes, a comparison was made between the ICA group (n = 76) and all other suspected HSR events that did not meet EAACI anaphylaxis criteria (n = 51). It was found that in 46.1% (n = 35) of the occurrences that met criteria for anaphylaxis, epinephrine was not administered. Conversely, epinephrine was administered in 17.6% (n = 9) of patients who did not meet anaphylaxis criteria (**table IV**).

Demographic characteristics, atopic and cardiovascular background, clinical manifestations, suspected etiology and Allergy Clinic referral of suspected HSR occurrences, ICA criteria *vs* no criteria and epinephrine administration *vs* no administration are displayed in **table V**.

A predominance of the male gender was observed (55.9%), with no statistically significant difference between those with ICA

Table IV - *Characterization of epinephrine administration in the groups that either fulfilled or not anaphylaxis criteria (n, %).*

EAACI anaphylaxis criteria (ICA)	Epinephrine administration		Total
	Yes	No	
Yes	41, 53.9	35, 46.1	76
No	9, 17.6	42, 82.4	51

ICA: Investigator-classified anaphylaxis.

Table V *- Demographic and clinical characteristics of suspected hypersensitivity reactions (HSR), Investigator-classified anaphylaxis (ICA) and of those treated with epinephrine (n, %).*

Variable	Total (n = 127)	ICA (n = 76)	P-value (anaphylaxis criteria *vs* no criteria)	Epinephrine administration (n = 50)	P-value (Epinephrine *vs* no epinephrine)
Median Age (IQR)	54 (33-71)	53 (32-71)	0.678	56 (36-70)	0.686
Male	71, 55.9	40, 52.6	0.364	33, 66.0	0.065
Female	56, 44.1	36, 47.4		17, 34.0	
Patient Background					
Cardiovascular disease	55, 43.3	32, 42.1	0.739	21, 42.0	0.811
Atopy	44, 34.6	32, 42.1	**0.031**	20, 40.0	0.307
Clinical Manifestation					
Mucocutaneous	112, 88.2	70, 92.1	0.095	46, 92.0	0.284
Respiratory	58, 45.7	48, 63.2	**< 0.001**	28, 56.0	0.060
Cardiovascular	33, 26.0	27, 35.5	**0.003**	18, 36.0	**0.038**
Gastrointestinal	10, 7.9	9, 11.8	**0.049**	6, 12.0	0.190
Neurological	19, 15.0	12, 15.8	0.749	8, 16.0	0.791
Etiologic Suspected Factor					
Hymenoptera Venom	38, 29.9	22, 28.9	0.770	15, 30.0	0.998
Food	37, 29.1	24, 31.6	0.459	12, 24.0	0.305
Drugs	32, 25.2	21, 27.6	0.440	14, 28.0	0.558
Adrenaline auto-injector Prescription	21, 16.5	17, 22.4	**0.028**	13, 26.0	**0.018**
Allergy Clinic referral	60, 47.2	41, 53.9	0.065	27, 54.0	0.219

ICA: investigator-classified anaphylaxis; IQR: interquartile range.

criteria or no criteria (p = 0.364), nor between those treated with or without epinephrine (p = 0.065).

No statistically significant difference in age was found between occurrences with ICA criteria and no criteria (p = 0.678), neither between occurrences with epinephrine administration and no administration (p = 0.686).

Forty-four events (34.6%) occurred in patients with a personal history of atopy. The prevalence of atopy was significantly higher among those with ICA criteria (42.1% *vs* 23.5%, p = 0.031).

Regarding clinical manifestations, respiratory, cardiovascular and gastrointestinal symptoms were significantly higher among those with ICA criteria, while only cardiovascular symptoms were significantly higher between patients treated with epinephrine.

There was no difference in suspected etiology between patients with ICA criteria or no criteria and between those treated with epinephrine or not.

There was a statistically significant difference in the epinephrine prescription at discharge between the proportion of patients that received epinephrine and those that did not (26 *vs* 10.4; p = 0.018). A similar trend was found between those with ICA criteria and those without criteria (22.4 *vs* 7.8, p = 0.028). Regarding subsequent orientation of ICA occurrences, the majority of patients (n = 41, 53.9%) were referred to external consultation for etiologic investigation and further guidance.

Discussion and conclusions

The present study characterized the HSR events that triggered requests for assistance to the EEN (112) in a 5-year period, based on the consultation of physical and electronic hospital records.

The incidence of HSR in our sample was 1.7% of the total number of VMER requesting assistances. When compared with single center studies of Australian and United Kingdom emergency departments, where the incidence was 1 in 439 episodes and 1 in 277 episodes, respectively (15, 16), our incidence was relatively higher and more in agreement with the values reported in a US study of emergency episodes for acute allergic reactions, where HSR accounted for 1% of all ED visits (17).

About 60% of the HSR observed (1% of all requesting assistances) by emergency medical teams met criteria for anaphylaxis, pre-

dominantly in suspected reactions to Hymenoptera stings and food allergy.

The etiology of the HSR was previously known in only 9% of patients, thus hinting that unexpected and sudden events of HSR in patients without previous episodes or etiological suspicions seems to predispose to the request assistance of the VMER.

Of the 17% of patients that carried an epinephrine auto-injector, only about a quarter who met EAACI anaphylaxis criteria self-administered the device. These findings alert the authors to an underuse of epinephrine, even in cases where patients are equipped with the necessary tools. Strategies need to be created in specialized Allergy consultations to optimize the use of this treatment, namely through education and proper instruction for action in an anaphylactic event. Anaphylaxis may present important quality of life and social repercussions, and inappropriate contact with the potential allergen may put the allergic patient's life at risk. After the occurrence, only 47% of patients were referred to a Clinical Allergy consultation, while just 10% were already undergoing follow-up. This insufficiency is even more apparent in severe situations, where only two-thirds of the occurrences that met the EAACI criteria for anaphylaxis (ICA) were referred to an external consultation. This highlights a need for referral increase.

Although intramuscular (IM) epinephrine is the first-line drug treatment in cases of anaphylaxis (18), it is still underused, particularly when compared to corticosteroids and antihistamines, which continue to be the most commonly used group of drugs in these situations, as is widely described in scientific literature (7, 8, 19). On the other hand, it should be noted that only in 9 cases was IM epinephrine used inappropriately, particularly in patients who did not meet criteria for anaphylaxis, with no reported severe adverse events. This highlights the need to implement and disseminate protocols that aim for a more accurate anaphylaxis diagnosis and a correct use of epinephrine.

The collected data should be analyzed taking into account the specificities of medical practice in the prehospital setting, since these may hinder the diagnosis and, consequently, the correct therapeutic approach. An accurate diagnosis of anaphylaxis can be difficult to assess, due to the wide spectrum of clinical presentations and the lack of laboratory markers to support the diagnosis, such as serum tryptase (20).

Although the applied clinical diagnostic criteria have demonstrated high sensitivity (21), the signs and symptoms of anaphylactic reactions may vary widely and mimic other urgent/emergent pathologies.

Differential diagnoses to consider in this context range from acute generalized urticaria with or without angioedema, acute asthma exacerbation, vasovagal syncope, panic attacks or foreign body aspiration, to cardiovascular events (acute myocardial infarction, pulmonary thromboembolism), among others (22).

Regarding the etiology of HSR in VMER requesting assistances, they appeared to be similar to those described in the few studies published on this topic, but with differences regarding the prevalence of each suspected culprit (13, 23).

In our study, the main suspected causes of HSR were Hymenoptera stings (29.9%), followed by food (29.1%) and drugs (25.2%). This is in agreement with a previously published Australian cohort by Blackhall *et al.*, which yielded a similar order of anaphylaxis diagnoses: Hymenoptera stings (42.4%), food (36.6%), and lastly drugs (16.8%) (23). It should be noted that in approximately 1/3 of our sample, according to the registered data, it was not possible to identify a suspected triggering factor.

Other published cohorts depict important differences in etiological distribution. For example, in a study conducted by Capps *et al.* on British patients who activated medical services through emergency calls, 28% of events were food-HSR, 52% drug-HSR (mainly antibiotics), and only 7% were secondary to Hymenoptera venom (13).

According to the Portuguese National Apiculture Program (2020-2022), the central region of Portugal, along with the northern region, is the area that gathers the largest number of beekeepers in the country (66% of the total), being the region with the largest number of collective apiculture associations, which may explain the high number of requesting assistances secondary to this etiologic factor in our study (24).

This is the first nationally-known case series to date, which aimed to characterize allergic emergencies in a prehospital setting, allowing for an understanding of the clinical characteristics and the management of these patients in such a particular setting.

There seem to be considerable differences in the approach to patients in the pre-hospital setting compared to the approach to patients in the emergency department (25).

The retrospective nature of our study, with data collection from medical records both in physical and digital files (computer system used by the VMER [iTeams®]), restricted the gathered data to the information recorded, thus making it susceptible to bias. The relative rarity and unpredictability of HSR hinders prospective data collection. Inadvertently, HSR that were not coded as "Allergy-ALR" may have been excluded. Since CODU coding is operator-dependent and the information is provided by other elements, via telephone, this may not allow for a correct classification *ad initium*.

Additionally, due to the small number of pediatric patients in our sample, we were not able to draw conclusions regarding this particular age group.

Therefore, we believe that further studies would be beneficial to improve knowledge and outline better strategies to address HSR in prehospital settings, including multicenter and/or national studies.

In conclusion, this study provided a characterization of the VMER requesting assistances due to suspected HSR in a cohort of a tertiary hospital in the central region of Portugal.

HSR to Hymenoptera venom was the most commonly identified trigger; nevertheless, food and drugs were also fre-

quently implicated. In one-third of cases, the trigger was not identified.
A high percentage of confirmed on-site HSR met EAACI criteria for anaphylaxis (ICA). However, although epinephrine is the first-line drug in these cases, underutilization was noted.
The different forms of clinical presentation of HSR render them an entity of growing importance, both due to the increasing number of cases and the demand for adequate etiologic study; however, referral to specialized consultation has proven to be insufficient in this cohort, and needs to be optimized.
The true epidemiological impact of HSR on national VMER requesting assistances still needs to be unveiled.

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Contributions

JCL: conceptualization, data curation, investigation, methodology, writing – original draft, writing – review & editing. JCC: conceptualization, methodology, writing – review & editing. HPP: writing – original draft, writing – review & editing. ICF: software, formal analysis, writing – review & editing. PBA: formal analysis, writing – review & editing. FCP: project administration, resources. CR, ATB: supervision, validation.

Conflict of interests

The authors declare that they have no conflict of interests.

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edra COMMENTARY | Eur Ann Allergy Clin Immunol | Vol 57, N.1, 41-42, 2025

Öner Özdemir

Adrenalin use in Kounis syndrome: a well-unknown entity

Comment on: Kounis syndrome: an underestimated emergency – doi: 10.23822/EurAnnACI.1764-1489.260

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Key words

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I have read the article titled "Kounis syndrome: an underestimated emergency – doi: 10.23822/EurAnnACI.1764-1489.260", by Zisa *et al.* with great interest (1). Nevertheless, there are a couple of concerns raised in my mind about their study. And clarification of these concerns of this study will help to understand better the study.

Kounis syndrome (KS) is known as an acute coronary syndrome associated with hypersensitivity reactions to an allergen such as a drug or bee venom and is a life-threatening medical emergency that is under-diagnosed and under-treated (2).

First – In this retrospective study including 9 KS cases, only two patients received intramuscular epinephrine (patient 1 and patient 2), and the authors claimed that this minimized the risk of cardiac side effects (1). I do not think this is entirely correct and caution is needed in the use of adrenaline during anaphylaxis, especially if KS is considered at risk (3-7).

The management of the acute phase of KS is a real challenge for the clinician. Because it requires a complex balance between peripheral vasodilation due to anaphylactic shock, which requires the use of vasopressors, and coronary vasospasm, which requires the use of vasodilator drugs. Furthermore, some drugs used to treat cardiac symptoms may worsen the allergic reaction and conversely, those used to treat the allergic reaction may worsen cardiac symptoms (3-8).

Therefore, according to some authors, the administration of adrenaline should be reserved for cases with anaphylactic shock and laryngospasm, because of the worsening of vasospasm that adrenaline administration in KS can cause (9).

Second – It is said in the article that Patient 1 is reported to have had KS type 1 and type 2 reactions (1). Although this has never been discussed, it must be a rare case. Does one predispose to the other? What is the frequency of this kind of situation? It would be useful for the readers if this was discussed a little.

Third – There are some typographical and misrepresentations in table I and table II. In table I, it is mentioned that the patients

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1, 3, 4 did not have atopy, whereas in the following lines, it is shown that they were allergic to bees and even received venom immunotherapy for this (1). This created a contradiction.
Also, as shown in table II, the tryptase of the 7th patient increased to 92.4 mcg/l during the acute setting. Moreover, the diagnosis of this patient was confirmed by neither skin tests nor specific IgE for ceftriaxone (1). This very high tryptase value and the lack of confirmation of the diagnosis are puzzling. Could there be an underlying predisposing cause, *e.g.* mast cell activation syndrome that could trigger these very high levels?
Minor points - Table I also shows that the first patient had a KS type II reaction. However, when patient 1 is described in the text, it is mentioned that this person had type I and type II KS reactions. Again, in table II, the abbreviation CT for ceftriaxone was misspelled instead of CFT when intravenous CT was mentioned (1).
In conclusion, I would like to thank the authors for this nice and high-quality study and its results. This study of 9 cases with KS contributed to a better understanding of a rare life-threatening condition. This is a work that later paved the way for future work as well.

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Contributions

ÖÖ contributed entirely to the work.

Conflict of interests

The author declares that he has no conflict of interests.

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edra REPLY | Eur Ann Allergy Clin Immunol | Vol 57, N.1, 43-44, 2025

Giuliana Zisa

Reply to *"Adrenalin use in Kounis syndrome: a well-unknown entity"*

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Key words

Kounis syndrome; anaphylaxis; coronary vasospasm.

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Doi
N/A

I would like to thank Dr. Öner Özdemir for the attention and the constructive criticism given to our article describing the characteristics of nine patients for whom the diagnosis of Kounis syndrome (KS) was made from January 2008 to March 2020 at a single center (Allergy Unit of Novara Hospital).

To answer point by point Dr. Özdemir's questions:

First – according to some authors, epinephrine, which is the drug of choice in anaphylaxis, in KS can aggravate ischemia and worsen coronary vasospasm (1-3).

Note that in our study (4), in patient number 9, the coronary spasm and the peri-cardiac arrest resolved after intracoronary epinephrine injection – see images from coronarography (figure 2). In another study the authors report a case of type II KS treated successfully and safely with the administration of both intravenous epinephrine and a coronary vasodilator (5). Even though myocardial ischemia could occur on rare occasions even with therapeutic doses of adrenalin, this should not prevent the early use of adrenaline since early use of it is life saving and associated with a better outcome than delayed use (6). Physicians should bear in mind this potential adverse effect which can occur in the acute setting. Old age, preexisting coronary artery disease and being on a beta blocker were some of the risk factors for epinephrine induced myocardial ischemia (6). In the absence of specific guidelines, cardiologic management of KS should follow the evidence-based guidelines for the treatment of acute coronary syndrome in particular for patients with diagnosis of KS of type II and III while in type I variant in addition to anti-allergic treatment, vasodilators could be used in order to abolish hypersensitivity induced vasospasm (3, 7). Management of the acute phase of KS still remains a real challenge for the clinician.

Second – In our case history we thought that in the personal history of patient number 1 a diagnosis of KS type I in the first reaction could have been supposed given the presence of an increased in troponin value with doubtful alteration in repolarization, in absence of underlying cardiac diseases. Although the recurrence of KS has not been reported, some authors have hypothesized the possibility that a repeated uncontrolled allergen exposition may cause similar allergic reaction with cardiac involvement (8). We do not know if one condition predisposes to the other.

Third – Hymenoptera venom allergy is not an indicator of atopic status.

For patient number 7 we didn't perform skin tests in relation to the severity of the reaction thinking that in this type of patient at higher risk skin testing may result in systemic response (9). The high tryptase value (92.4 mcg/L) during the reaction is considered significant for an anaphylactic event, with returning to normal

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basal values (5.7 mcg/L) 48 hours after the end of the event. Only persistently elevated tryptase values after an anaphylactic reaction justify the expansion of the diagnosis for the search for mastocytosis (10). Furthermore, the patient had a negative REMA score (< 2), so clinical suspicion of this disease was ruled out.
Minor points – In table I, for the patient number 1, we inserted data regarding the second reaction that occurred during conventional venom immunotherapy with 100 μg of PoD venom, therefore the maintenance dose was increased to 200 mcg after confirmation of sensitization to PoD.
In table II, CT is a mistake instead of CFT (ceftriaxone).

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LETTER TO THE EDITOR

Eur Ann Allergy Clin Immunol Vol 57, N.1, 45-48, 2025

Carlo Maria Rossi[1,2], Marco Vincenzo Lenti[1,2], Stefania Merli[2], Giovanna Achilli[1,2], Antonio di Sabatino[1,2]

Omega 5-gliadin allergy in patients with recurrent acute urticaria

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Key words

Allergy; atopy; skin; urticaria; wheat.

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Doi
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To the Editor,

omega-5 gliadin (O5G) – Tri a 19 – allergy is usually responsible for wheat-dependent exercised-induced anaphylaxis (WDEIA) (1-4) but not all episodes are characterized by a systemic anaphylactic reaction (5) and factors modulating the reaction severity are elusive (6).

We evaluated the prevalence and clinical/laboratory features of O5G in patients presenting with recurrent acute urticaria in a retrospective study in an Italian tertiary referral center. We enrolled all consecutive adult patients referred in 2021-2023 for recurrent acute urticaria (3), *i.e.*, > 1 episode of acute urticaria over 6 months, not induced by physical factors and not present daily and continuously for > 6 weeks (7).

Patients underwent skin prick tests for aero- and food-allergens (Lofarma, Italy) according to clinical history and specific IgE (FEIA, ImmunoCAP®, Thermo fischer, Sweden), to wheat, O5G, gluten/gliadin were systematically performed. Patients underwent screening for *H. pylori*, anti-thyroglobulin/thyroid peroxidase antibodies. Wheat challenge (100 g of boiled pasta) followed by 15-minute running was offered to confirm the diagnosis.

Data from 31 patients, median age 33 years, IQR 23-47, F:M ratio: 1.4:1.1 (**table I**), were retrieved. Patients were classified according to O5G IgE (cut-off 0.1 kU/L) into O5G positive (n = 7, 22.6%) and negative (n = 24, 77.4%).

Among O5G negative patients, the identified cause of urticaria were *H. pylori* infection (n = 5, 16.1%), non-steroidal anti-inflammatory drug allergy (n = 4, 12.9%), food allergy (n = 3, 9.6%), cholinergic urticaria (n = 1, 3.2%). Most cases were defined as idiopathic (n = 11, 35.4%). All patients with *H. pylori* were urticaria-free after eradication.

Six out of seven patients with positive specific IgE for O5G were offered a challenge with wheat and exercise (since one patient displayed anaphylaxis after wheat ingestion); eventually only two accepted (four deemed it unnecessary). Challenged patients presented urticaria. The patients who declined the challenge didn't experience any episodes after avoiding gluten within 4 hours of exercise, or by completely avoiding gluten. Collectively, the diagnosis of O5G-allergy was confirmed in all seven patients sensitized to O5G (7).

Comparing O5G positive patients to negative ones, no statistically significant demographical difference was observed (**table I**), though female sex was highly represented in this sample. Notably,

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Table I *- Demographical, clinical and etiological features and sensitization profile of the urticaria patients at the time of diagnosis.*

Parameter*	Overall population (n = 31)	O5G negative (n = 24)	O5G positive (n = 7)	P-value O5G positive *vs* negative
Demographics and clinical characteristics				
Sex, male, n (%)	13 (41.9)	11 (45.8)	2 (28.5)	0.41
Age, years, median, (IQR)	33 (23-47)	33 (22.7-46.5)	33 (26.5-43.5)	0.89
Ethnicity, white, n (%)	29 (93.5)	24 (100)	5 (71.4)	0.21
Smoking, n (%)	9 (29.0)	7 (29.1)	2 (28.5)	0.65
Heavy work n (%)	4 (12.9)	4 (16.6)	0 (0)	0.87
Onset age of sy, years, median (IQR)	28 (21.5-44.7)	28.5 (21.7-45.5)	28 (24-40)	0.91
Episode range number, n (%)§	0, 5 (16.1) 1, 0 (0) 2, 3 (9.6) 3, 1 (3.2) 4, 0 (0) 5, 0 (0) 6, 3 (9.6) 7, 6 (19.3) 8, 13 (41.9)	0, 4 (16.6) 1, 0 (0) 2, 3 (12.5) 3, 1 (4.16) 4, 0 (0) 5, 0 (0) 6, 2 (8.3) 7, 4 (16.6) 8, 10 (41.6)	0, 1 (14.2) 1, 0 (0) 2, 0 (0) 3, 0 (0) 4, 0 (0) 5, 0 (0) 6, 1 (14.2) 7, 2 (28.5) 8, 3 (42.8)	0.48
Anaphylaxis, n (%)	3 (9.7)	1 (4.2)	2 (28.5)	0.05
Autoimmunity, n (%)	5 (16)	4 (16.6)	1 (14.2)	0.66
IBS, n (%)	1 (3.2)	0 (0)	1 (14.2)	0.06
Etiology of urticaria				
Helicobacter pylori, n (%)	5 (16.1)	5 (20.8)	/	
Idiopathic, n (%)	11 (35.4)	11 (45.8)	/	
NSAID, n (%)	4 (12.9)	4 (16.6)	/	
Food allergy, n (%)	10 (32.2)	3 (8.3)	7 (100)	**0.01**
Cholinergic, n (%)	1 (3.2)	1 (4.1)	/	
Atopy				
Eczema, n (%)	1 (3)	1 (4.1)	0 (0)	0.58
Allergic rhinitis, n (%)	10 (32.3)	4 (16.6)	5 (71.4)	**0.01**
Asthma, n (%)	4 (12.9)	3 (12.5)	1 (14.2)	0.90
Drug allergy, n (%)	2 (6.4)	0	2 (28.5)	0.05

*Data are shown as a proportion or median and IQR; §a score of 0 is assigned if the number of episodes is 2, 1 if 3 episodes, 2 if 4 episodes, 3 if 5 episodes, 4 if the number of episodes is 6-10 episodes, 5 if the number of episodes is 11-15 episodes, 7 if 16-20 or more 8 if more than 20 episodes are present. Heavy work included job as carpenter, electrician, mason, *etc*. O5G: omega-5 gliadin; IBS: irritable bowel syndrome; IQR: interquartile range; NSAID: non-steroidal; anti-inflammatory drug; PR-10: pathogenesis related-10; LTP: lipid transfer protein; sy: symptoms.

patients with O5G-allergy displayed more frequently allergic rhinitis among atopic comorbidities (p = 0.01).

Among patients with O5G, four displayed more than 20 urticaria episodes. The mean age of those with more frequent episodes, as opposed to those with fewer ones, was lower (24.7 ± 4 years and 49.3 ± 12.2 years respectively, p < 0.05), while no difference was found with regard to total IgE (p = 0.6), specific IgE for wheat (p = 0.8), gliadin mix (p = 0.2), gluten (p = 0.7), O5G (p = 0.4), Bet v1 (p = 0.5), Phl p12 (p = 0.9), and Pru p 3 (p = 0.7).

No difference was found between having at least one episode with systemic manifestations and level of total IgE, and specific IgE for wheat (p = 0.7), gliadin mix (p = 0.8), gluten (p = 0.8), O5G (p = 0.9). Two patients displayed extracutaneous features during follow-up (median 17 months, IQR 12.5-19.5) (**table II**).

Table II *- Clinical and serological features of the seven patients with omega-5 gliadin allergy.*

#	Age	Sex	Symptoms at diagnosis	Type of cofactor	Total IgE	Wheat IgE (kU/L)	Gluten IgE (kU/L)	Gliadin IgE (kU/L)	Tri a 19 IgE (kU/L)	Bet v 1 IgE (kU/L)	Phl 12 IgE (kU/L)	Therapy	Adherence*	Follow-up (months)	Clinical manifestations at last follow-up
1	57	M	A (U+C)	E	144	0.90	3.99	2.74	18.40	13.50	< 0.10	D	T	22	No sy
2	28	M	U	NSAID	389	< 0.10	< 0.10	< 0.10	2.74	< 0.10	0.32	D	T	6	No Sy
3	18	F	A (U, D, Dy)	E E+ AL E+ M NSAID	1147	3.59	1.69	< 0.10	7.04	9.51	< 0.10	D	P	19	1 episode of anaphylaxis (U+V/N)
4	44	F	U	-	1170	0.13	< 0.10	< 0.10	0.53	< 0.10	< 0.10	C	T	14	No sy
5	45	F	U	-	133	< 0.10	< 0.10	< 0.10	0.15	< 0.10	< 0.10	C	P	17	No sy
6	20	F	U	E	115	< 0.10	4.89	< 0.10	0.23	< 0.10	< 0.10	D	P	11	1 episode of anaphylaxis (U+Co)
7	28	F	U	-	534	< 0.10	< 0.10	< 0.10	0.93	< 0.10	< 0.10	C	P	20	No sy

A: anaphylaxis; AL: alcohol; C: cofactor avoidance; Co: conjunctivitis; D: gluten-free diet; Dy: dyspnea E: exercise; M: menses; N: nausea NSAID: non-steroidal antinflammatory drug; R: rhinitis; Sy: symptoms: U: urticaria: V: vomiting. *Adherence was rated as total (T) or partial (P), if in more than 20% of meals gluten was theoretically present of if cofactor was not avoided within 5 hours of gluten-containing food ingestion.

In this study we observed the prevalence of O5G-allergy, reaching 22.5% in patients with acute intermittent urticaria. These patients seemed to present peculiar features, *i.e.*, female sex and comorbid atopic diseases, compared to those presenting with exercise-induced anaphylaxis, who are usually male with a low atopic background (9). A study based on the presence of O5G-specific IgE describes recurrent acute urticaria in five of 67 patients with O5G-allergy (6). Another study describes four cases of O5G-allergy presenting with urticaria (6.8%), among 104 patients with WDEIA. Notably, 70.4% of patients presented urticaria episodes before their first anaphylaxis (5). Consistently, in our series two patients displayed an anaphylaxis during the follow-up, highlighting the importance of prescribing adrenaline autoinjectors, given the general low adherence to gluten-free diets and cofactor avoiding recommendations, as reported in literature (10).
To conclude, in patients presenting with recurrent acute urticaria, a screening for O5G-allergy is warranted.

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None.

Contributions

CMR, MVL: conceptualization. CMR, SM, GA: project administration. CMR, MVL: data curation, formal analysis, writing – original draft. ADS: supervision. All authors: methodology, resources, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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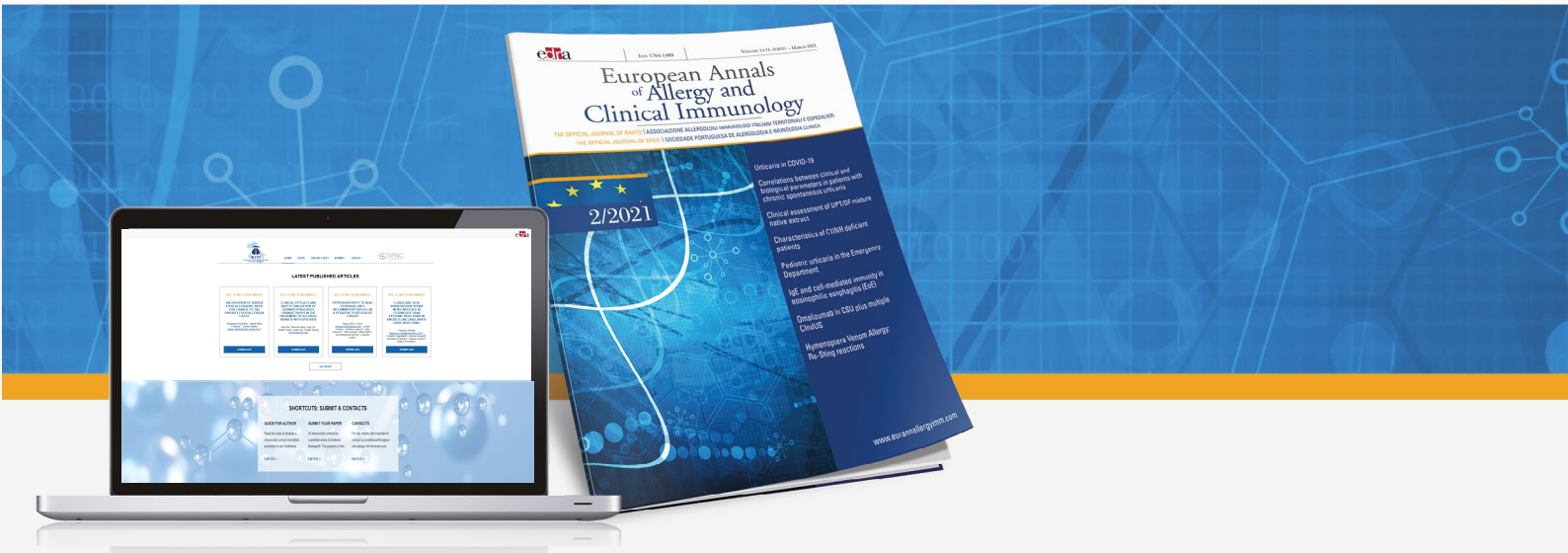
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