## Code Anaphylaxis: Enhancing the Management of Hymenoptera Venom Anaphylaxis

Santana M[1], Armisén M[1], Feás X[2,3], Vidal C[1,4]
[1]*Allergy Service, Complejo Hospitalario Universitario de Santiago, Faculty of Medicine, University of Santiago de Compostela, Spain*
[2]*Academy of Veterinary Sciences of Galicia, Santiago de Compostela, Spain*
[3]*Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS), Hospital Clínico, Santiago de Compostela, Spain*
[4]*Research Methods Group (RESMET), Health Research Institute of Santiago de Compostela (IDIS), Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS-ISCIII/RD21/0016/0022), University Hospital of Santiago de Compostela, Spain*

J Investig Allergol Clin Immunol 2025; Vol. 35(4): 308-311
doi: 10.18176/jiaci.1082

Key words: Anaphylaxis. Code Anaphylaxis. Adrenaline. Tryptase. Adrenaline autoinjector. Emergency department. Primary care.

Palabras clave: Anafilaxia. Código Anafilaxia. Adrenalina. Triptasa. Autoinyector de adrenalina. Urgencias. Atención primaria.

Anaphylaxis is a potentially life-threatening hypersensitivity reaction. Timely diagnosis and appropriate management are essential if we are to improve outcomes [1-5]. Several gaps in the management of affected patients have been identified, including treatment with intramuscular adrenaline during the acute phase, a period of observation after the reaction, measurement of tryptase during and after the event, prescription of adrenaline autoinjectors, and referral to specialized allergy clinics [3,6].

In September 2021, the so-called Code Anaphylaxis was launched in Galicia (northwest Spain) to standardize the identification and management of anaphylaxis (available at: https://www.sergas.es/Asistencia-sanitaria/Documents/1396/2804_Plan_asistencia_C%C3%B3digo_Anafilaxia_cas.pdf).

The aim of this study was to assess the impact of Code Anaphylaxis in a homogeneous group of patients who experienced anaphylaxis following a Vespidae sting. We analyzed data from a period of 31 months before the implementation of the Code up to 26 months after its initiation (February 2019 to November 2023).

A total of 219 patients were included in the study (median [IQR] age, 61 [51-71] years; males, 80.8%). Of these, 134 patients were in the pre-Code period, and 85 were in the post-Code period. A structured case report form was completed for each patient. This integrated data from the electronic records of the emergency department (ED) or primary care (PC) and the allergy department's files. The data included the following: (*a*) identification of the Vespidae species; (*b*) time between the

 

sting and onset of symptoms; (*c*) signs and symptoms reported by the patient; (*d*) clinical findings documented by health care professionals; (*e*) severity of the reaction; (*f*) treatment administered in the ED/PC; (*g*) availability of tryptase measurements (ImmunoCAP 250 tryptase assay) within 2-3 hours after the reaction; (*h*) prescription of an adrenaline autoinjector; and (*i*) time between the allergic reaction and first visit to our allergy department. Most of the patients resided in rural areas, as the health area covers 500 000 inhabitants, of whom only 100 000 live in an urban setting. The study was

**Table.** Clinical Data of Study Patients Stratified by Pre- and Post-Code Periods.[a]

| | Period analyzed | | *P* Value |
|---|---|---|---|
| | *Pre-Code* (n=134) | *Post-Code* (n=85) | |
| Age, y | 61.5 (56-71) | 61 (52-72) | .626 |
| Female sex | 19 (14.2%) | 23 (27.1%) | .018 |
| Vespid responsible for the reaction | | | |
| *Vespula vulgaris* | 40 (29.9%) | 14 (16.5%) | .060 |
| *Vespa velutina nigrithorax* | 81 (60.4%) | 64 (75.3%) | |
| Unknown | 13 (9.7%) | 7 (8.2%) | |
| Habitat (rural) | 128 (95.5%) | 81(95.3%) | .937 |
| Occupational exposure (outdoors) | 97 (72.4%) | 66 (77.6%) | .385 |
| Previous cardiovascular disease | 58 (43.3%) | 40 (47.1%) | .584 |
| Previous respiratory disease | 14 (10.4%) | 13 (15.3%) | .288 |
| Treatment with ACEI/β-blockers | 37 (27.6%) | 22 (25.9%) | .779 |
| Grade of anaphylaxis | | | |
| Grade I | 36 (26.9%) | 20 (23.5%) | .802 |
| Grade II | 39 (29.1%) | 24 (28.2%) | |
| Grade III | 59 (44%) | 41 (48.2%) | |
| Time to reaction | | | |
| Less than 15 min | 106 (79.1%) | 71 (83.5%) | .720 |
| 15-30 min | 24 (17.9%) | 12 (14.1%) | |
| More than 30 min | 4 (3.0%) | 2 (2.4%) | |
| Use of adrenaline | 63 (47.4%)[b] | 44 (51.8%) | .527 |
| ≤60 y (n=104) | 33/62 (53.2%) | 22/42 (52.4%) | .933 |
| >60 y (n=115) | 30/71 (42.3%)[b] | 22/43 (51.2%) | .355 |
| Hospital care | 85 (63.4%) | 61 (72.6%)b | .104 |
| ≤60 y (n=104) | 40/62 (64.5%) | 28/42 (66.7%) | .821 |
| >60 y (n=115) | 45/72 (62.5%) | 33/42 (78.6%)[b] | .075 |
| Tryptase determination (reaction) | 31 (23.1%) | 43 (50.6%) | <.001 |
| ≤60 y (n=104) | 21/62 (33.9%) | 15/42 (35.7%) | .846 |
| >60 y (n=115) | 10/72 (13.9%) | 28/43 (65.1%) | <.001 |
| Prescription of autoinjector | 65 (48.5%) | 46 (54.1%) | .418 |
| ≤60 y (n=104) | 29/62 (46.8%) | 28/42 (66.7%) | .045 |
| >60 y (n=115) | 36/72 (50.0%) | 18/43 (41.9%) | .397 |
| Time from reaction to specialized consultation, d | 20 (7-98) | 11 (7-32) | .030 |
| ≤60 y (n=104) | 21 (7-55) | 15 (7-36) | .741 |
| >60 y (n=115) | 19 (7-139) | 10 (6-19) | .009 |

Abbreviation: ACEI, angiotensin-converting enzyme inhibitor.

[a]Age and time from reaction to specialized consultation data are shown as median (IQR). The remaining values are shown as absolute numbers and percentages (within parenthesis). The Mann-Whitney test was used for the comparison of numerical variables between 2 independent groups. The $\chi^2$ test was used for the comparison of proportions, with the trend test if the independent variable was ordinal.

[b]Information missing for 1 patient.

approved by the Institutional Ethics Committee and adhered to the Declaration of Helsinki. Informed consent was obtained from all participants.

As shown in the Table, there were no significant differences between the 2 periods concerning age, environmental exposure, reaction severity, latency period, pre-existing cardiovascular or pulmonary conditions, prior use of ACE inhibitors or ß-blockers, adrenaline treatment, or adrenaline prescription. However, an unexpected increase in the proportion of female patients experiencing anaphylactic reactions was observed in the post-Code period (14.2% [95%CI, 8.7%-21.2%] vs 27.1% [95%CI, 18.0%-37.8%]; *P*=.018).

Around half of the patients in the pre-Code period (47.4% [95%CI, 38.6%-56.2%]) and in the post-Code period (51.8% [95%CI, 40.7%-62.7%]) received intramuscular adrenaline, a significantly higher percentage than in previous reports from the European Registry of Anaphylaxis (27.1%, including self-administered adrenaline) [2,7]. The probability of receiving adrenaline was significantly higher for patients treated in a hospital setting (62.0% [95%CI, 53.6%-70.0%]) than in those treated in PC who were not referred to the ED (22.2% [95%CI, 13.3%-33.6%]) (*P*<.001). Similarly, patients treated in the ED were more likely to be prescribed an adrenaline autoinjector (60.3% [95%CI, 51.8%-68.3%]) than those who were not referred (31.9% [95%CI, 21.4%-44.0%]) (*P*<.001). However, these results were not influenced by the Code.

Serum tryptase measurements were available for 74 patients, with 31 from the pre-Code period (23.1% [95%CI, 16.3%-31.3%]) and 43 from the post-Code period (50.6% [95%CI, 39.5%-61.6%]) (*P*<.001). The association between implementation of the Code and a tryptase request was maintained after adjusting for age, sex, severity of anaphylaxis, and comorbidities in a logistic regression model (OR, 4.24 [95% CI, 2.15-8.33]; *P*<.001). A comparative analysis of acute-phase and baseline tryptase levels obtained 30-45 days after the reaction revealed a significant elevation during the reaction in 80.8% of affected patients.

Finally, the time lapse between reaction and initial consultation in the allergy department was notably reduced in the post-Code period (Table). Specifically, Code implementation was associated with early (≤2 weeks) specialized allergy consultation after adjusting for age, sex, severity of anaphylaxis, and comorbidities (OR, 1.85 [95%CI, 1.03-3.31]; *P*=.038).

Of particular interest is the observation that patient age appears to influence the doctor's decision-making. Those over 60 years of age benefit most from the implementation of the Code, both in terms of tryptase determination and referral to the allergy department. Individuals under the age of 60 only benefit from more frequent prescription of adrenaline autoinjectors (Table).

Only 146 out of 218 patients (66.9%) were admitted to the ED for observation, with no significant differences between the 2 periods. An analysis of the referral patterns revealed that the species responsible for the reaction did play a role: referrals were more frequent for *Vespa velutina* stings (103/145, 71% [95%CI, 62.9%-78.3%]) than for stings by *Vespula* species (30/54, 55.6% [95%CI, 41.4%-69.1%]) (*P*=.039). Moreover, more male patients were referred for observation (71.6% [95%CI, 64.3%-78.1%] vs 47.6% [95%CI, 32.0%-63.5%]; *P*=.003). Finally, as reaction severity increased from mild to moderate to severe, the referral rate rose from 37.5% to 67.7% to 83.0%, respectively (*P*<.001), independent of the time period analyzed.

Emergency protocols such as Code Stroke, Code Sepsis, and Code Heart Attack have been shown to enhance patient safety, speed of care, and accuracy of treatment in health systems [8,9]. The Code Anaphylaxis initiative was spearheaded by regional allergy departments, ED and PC providers, and the Servizo Galego de Saúde (SERGAS). The scope of the protocol extends beyond the specific context of anaphylaxis caused by Hymenoptera stings, encompassing all forms of anaphylaxis, irrespective of the underlying cause. It also includes an application for identifying registered patients who have previously experienced anaphylaxis, allowing for faster response times and more efficient resource deployment (eg, ambulances or helicopters) when the system is activated.

To the best of our knowledge, this is the first published initiative of its kind. We demonstrate substantially enhanced outcomes, particularly in terms of the expediency of referral to specialized allergy clinics and the measurement of tryptase during the acute phase, which has proven beneficial in most patients who had an available result for comparison with baseline tryptase level [10-12]. While progress has been made, there is still room for improvement, particularly in the administration of adrenaline as the first-line treatment and in helping health professionals overcome their fear of prescribing it. Based on our experience, a Code Anaphylaxis protocol could be useful in public health systems similar to that of Spain, where there is a PC network linked to hospitals. The Code is expected to be particularly useful in more densely populated areas, since the population in our region is widely dispersed.

*Acknowledgments*

The authors would like to thank Professor González-Quintela for his invaluable support in the statistical analysis.

*Funding*

The authors declare that no funding was received for the present study.

*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

## References

1. Simons FE, Ardusso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J. 2014;7:9.
2. Grabenhenrich LB, Dölle S, Ruëff F, Renaudin JM, Scherer K, Pföhler C, et al. Epinephrine in severe allergic reactions: The European Anaphylaxis Register. J Allergy Clin Immunol Pract. 2018;6:1898-906.

 

3. Prieto-Moreno A, Puente-Crespo Y, Cardona V, de la Hoz B, Dieguez MC, González-de-Olano D, et al. Anaphylaxis Management in the GALAXIA 2022 Update. J Investig Allergol Clin Immunol. 2023;33:486-7.
4. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. European Academy of Allergy and Clinical Immunology, Food Allergy, Anaphylaxis Guidelines Group. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022;77:357-77.
5. de Silva D, Singh C, Muraro A, Worm M, Alviani C, Cardona V, et al. Diagnosing, managing and preventing anaphylaxis: Systematic review. Allergy. 2021;76:1493-506.
6. Dribin TE, Schnadower D, Wang J, Camargo CA Jr, Michelson KA, Shaker M, et al. Anaphylaxis knowledge gaps and future research priorities: A consensus report. J Allergy Clin Immunol. 2022;149:999-1009.
7. Francuzik W, Ruëff F, Bauer A, Bilò MB, Cardona V, Christoff G, et al. Phenotype and risk factors of venom-induced anaphylaxis: A case-control study of the European Anaphylaxis Registry. J Allergy Clin Immunol. 2021;147:653-62.e9.
8. Yakhkind A, Yu W, Li Q, Goldstein JN, Mayer SA. Code-ICH: A New Paradigm for Emergency Intervention. Curr Neurol Neurosci Rep. 2024;24:365-71.
9. Giglio A, Aranda M, Ferre A, Borges M. Adult Code Sepsis: A narrative review of its implementation and impact. J Intensive Care Med. 2024;3:8850666241293034.
10. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int Arch Allergy Immunol. 2013;160:192-9.
11. Francis A, Fatovich DM, Arendts G, Macdonald SP, Bosio E, Nagree Y, et al. Serum mast cell tryptase measurements: sensitivity and specificity for a diagnosis of anaphylaxis in emergency department patients with shock or hypoxaemia. Emerg Med Australas. 2018;30:366-74.
12. Vitte J, Amadei L, Gouitaa M, Mezouar S, Zieleskiewicz L, Albanese J, et al. Paired acute-baseline serum tryptase levels in perioperative anaphylaxis: an observational study. Allergy. 2019;74:1157-65.

*Manuscript received February 11, 2025; accepted for publication March 6, 2025.*

**Carmen Vidal**
Allergy Department
Complejo Hospitalario Universitario de Santiago
Faculty of Medicine, University of Santiago
Rúa Ramón Baltar, s/n
15706 Santiago de Compostela, Spain
E-mail: mdelcarmen.vidal@usc.es
carmen.vidal.pan@sergas.es