Refractory anaphylaxis: Data from the European Anaphylaxis Registry

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# Abstract

Refractory anaphylaxis (unresponsive to treatment with at least 2 doses of minimum 300 mg adrenaline) is a rare and often fatal hypersensitivity reaction. Based on this, its definition, prevalence, and risk factors are only vaguely described.  
Using the data from the European Anaphylaxis Registry (11596 cases in total) we were able to identify cases of refractory anaphylaxis (n = 42) and to analyse these in comparison to a control group of severe anaphylaxis cases (n = 4820). The data show that drugs more frequently elicited refractory anaphylaxis (50% of cases, p < 0.0001) than in other severe anaphylaxis cases (18.4%). Cases elicited by insects (n = 8) were more often due to bees in refractory cases (62.5% vs 19.4%, p = 0.00921). The refractory cases occurred more frequently in a perioperative setting E(45.2% vs. 9.05, p < 0.0001). Intramuscular adrenaline (as a first line therapy) was administered in 17.5% of refractory cases, whereas in 87.5% of cases was given intravenously (significantly more often than in severe anaphylaxis cases: 14.1%, p < 0.0001). Second line treatment options (e.g. vasopression with dopamine, methylene blue, glucagon) were not used at all in the treatment of refractory cases. The mortality rate in refractory anaphylaxis was significantly higher (26.2%) than in severe cases (0.353%, p < 0.0001). Although multiple guidelines on anaphylaxis have been published, the clinical adherence to these standards can be improved. The low use of intramuscular adrenaline as a first line therapy might contribute to refractoriness of an episode. Also, the lack of suggested second line medication use in refractory cases indicate that the availability of these drug is restricted or anaphylaxis management guidelines may need a revision in order to provide clear algorithms for severe refractory anaphylaxis.

# Introduction

Anaphylaxis is a non-homogeneous clinical diagnosis, depending on various triggering, and augmenting factors. This variability introduces a wide range of possible reaction-symptom severity. Therefore multiple sub-types of anaphylaxis have been previously identified (i.e. food dependent exercise induced anaphylaxis, venom anaphylaxis, biphasic anaphylaxis).

The mainstay of anaphylaxis management is the intramuscular dose of adrenaline, but in the most severe cases of anaphylaxis it might be insufficient to restore a stable patient status. Refractory anaphylaxis (although the established definition is lacking) might be defined as anaphylaxis meeting the criteria by NIAID/FAAN [1] which, after the treatment with at least 2 doses of minimum 300 mg adrenaline, does not result in an expected normalization of clinical symptoms. Typical elicitors and symptoms of refractory anaphylaxis, as well as the therapeutic strategy for the most severe cases differ from the usual reactions and call for a specific research and targeted guideline development for refractory anaphylaxis cases.

We aimed to distinguish the prevalence of refractory anaphylaxis among anaphylaxis cases and to describe its symptoms and factors which may increase the risk of a refractory anaphylaxis episode.

# Methods

The European Anaphylaxis Registry (described in detail elsewhere [2]) provided data for this analysis status from May 2018. Based on an electronic questionnaire (available at www.anaphylaxie.net), we selected cases where patients received at least two doses of adrenaline, and failed to recover adequately and assigned them to the “refractory anaphylaxis group”. The flowchart in figure 1 represents the detailed cases selection process.

The final database consisted of 42 cases of refractory anaphylaxis from 7 countries: Germany: 19, Austria: 2, Switzerland: 11, Poland: 2, Spain: 1, France: 6, Ireland: 1. We compared these to a group of severe, non-refractory cases of anaphylaxis. Severe reactions were identified based on the definition of by NIAID/FAAN [1] and presented with significant hypoxia, cyanosis, hypotension (SBP < 90 mm Hg in adults), confusion, collapse, loss of conciusness, or incontinence. We compared the frequency of various elicitors, symptoms, and factors known to incease the risk of severe anphylaxis [3] in both groups. We also compared how the cases were managed.

The statistical analysis was performed in the R Statistical Package [4]. Simple comparison of nominal variables was performed using Fischer’s exact test, continous variables were analysed using Mann-Whithney U test. We defined statistical significance as α = 0.05. Data along with the analysis script can be accessed here…

# Results

## Refractory anaphylaxis accounts for less than 0.5% of severe anaphylaxis cases in the register

The European Anaphylaxis Registry captured 42 cases of refractory anaphylaxis and 4820 severe, non-refractory anaphylaxis. The frequency of refractory anaphylaxis was 0.37% of all anaphylaxis cases reported in the registry from European countries in years 2007 - 2017. Each year approximately 1% (0.853% 0.765%) of severe anaphylactic episodes are refractory to treatment with adrenaline. When considering patients undergoing a medical procedure (who experience anaphylaxis in a perioperative setting), nearly 3.72% (4.36 times more) patients present with reactions that do not respond to adrenaline.

## Increased Frequency of previous reactions in patients with refractory anaphylaxis

The mean age at the reaction was 41.4 ± 20.8 years, which did not differ from severe, non-refractory cases, p = 0.897). The percentage of males within the refractory anaphylaxis group was 47.6%. Significantly more patients suffered from a concomitant malignant disease in the refractory anaphylaxis group. Most strikingly, patients with refractory reactions more often had a previous anaphylactic reaction in their medical history (p = 0.0336). The demographic summary of refractory cases is shown in table 1.

## Drugs are the most frequent elicitors of refractory anaphylaxis

Refractory anaphylaxis was most commonly elicited by drugs (significantly more often than in severe, non-refractory cases), followed by food and insects (table 2). The most common drugs eliciting anaphylaxis refractory to adrenaline were antibiotics and X-ray contrast medium. Patients with refractory anaphylaxis more frequently experienced the reaction while undergoing a medical procedure (54.8% vs. 12.3 in severe, non-refractory cases, p < 0.0001)

33.3% of food elicited cases had a previously confirmed diagnosis of food allergy. Severe cases of anaphylaxis were most frequently elicited by insects and food triggers. Insect-venom-elicited, refractory cases were significantly more often elicited by bee-stings than severe, non-refractory cases, whereas the yellow-jacket-stings were most common in non-refractory anaphylaxis cases (table 3).

## Refractory anaphylaxis is life-threathening

Milder anaphylaxis symptoms (i.e. pruritus, gastrointestinal symptoms, vertigo, chest and throat tightness) showed significantly more often in severe anaphylaxis cases, whereas respiratory and cardiac arrest, as well as inspiratory and expiratory distress, and death were associated more often with the refractory anaphylaxis cases. Table 4 summarizes the most prominent differences in anaphylaxis symptoms among both groups. Fatal reactions frequently occurred 30 minutes to 120 minutes after exposure - when the CPR was unsuccessful. In cases where patients responded to life support procedures, but failed to be reanimated due to post-resuscitative complication (e.g. hypoxic brain injury), death occured in the next 3-8 days.

## Adrenaline i.v. as first-line treatment was given frequently in refractory anaphylaxis

When evaluating the therapeutic procedures, adrenaline iv. as a first-line treatment of anaphylaxis was significantly more often given in refractory cases (87.5% vs. 17.5%, p < 0.0001) it has been also given more often as a second line therapy in refractory cases. Median time to the second dose of adrenaline was also shorter in refractory cases (2 minutes). In 77.5% of refractory cases, the second dose of adrenaline was given by a professional (significantly more than in non-refractory cases 9.08%, p < 0.0001).

Corticosteroids iv. were the second most frequently administered group of drugs in refractory cases (as a first and second line treatment), outpacing antihistaminic drugs and volume replacement therapy, and were significantly more often given in refractory cases. Volume replacement therapy was given initially in 65% of refractory cases but was sustained only in 27.6% as the therapy progressed in the hospital environment.

Second line medication like dopamine, glucagon and methylene blue were neglected in all refractory anaphylaxis cases as well as in severe non-refractory ones, however patients with refractory anaphylaxis were more frequently admitted to the hospital and treated at the ICUs. Table 5 illustrated the therapy of refractory anaphylaxis cases.

## Cofactors of refractory anaphylaxis

Patients with refractory anaphylaxis more often had concomitant asthma and malignant diseases in the past. Also other unspecified concomitant conditions were significantly more often reported in refractory cases (although they were not explicitly stated in the questionnaire). It is worth noticing that concomitant cardiologic conditions, diabetes and mastocytosis were similarly frequent in both groups.

Patients with refractory anaphylaxis more often used proton pump inhibitors and acetylsalicilic acid than patients with severe non-refractory anaphylaxis. Other (non-disclosed) medications were also more frequent in refractory cases.

The intensity of of physical exercise exceeding the reaction was indifferent between groups, however the psychological burden was reported 3 times more frequently in refractory cases (see table 6).

# Discussion

## Frequency and patients at risk

Our findings suggest that around 1 in 100 severe anaphylaxis patients will not respond to the standard therapy with adrenaline, commonly outlined in anaphylaxis management guidelines. Such cases have the highest risk of a fatal outcome, and therefore need to be treated adequately.

Overall, the severity of anaphylaxis and its probable transition into a refractory episode might be described as in the figure 2. Patients who undergo anaphylaxis have four main aspects that influence the severity of a particular episode: 1) compensation - how well is the body able to compensate symptoms i.e. hypotension; 2) elicitors - what was the eliciting agent and duration of the exposition; 3) cofactors - is the presence of other factors which may increase the severity of a given reaction i.e. concomitant use of betablocker etc.; 4) therapy - how fast and accurate the therapeutic procedures were introduced.

## Compensation

Patients who underwent refractory anahpylaxis more often had perioperative reactions and therefore a decreased ablity to compensate the reaction symptoms. Age is also a factor that may correlate with the inabillity to retain homeostasis as many comorbidities are more likely to occure along with older age.

## Elicitors

Drugs were the most commonly occurring elicitor, what is in concordance with our previous findings [**???**]. Multiple medications given in a perioperative setting increase the chance of a hypersensitivity reaction and drug interactions. Perioperative cases of refractoriness have been previously published to be the most common in case series analysis [**???**]. Therefore patients who undergo medical procedures and have a history of anaphylaxis should remain under special caution.

Antibiotics, although commonly triggering type IV hypersensitivity reactions, are rarely reported in the literature as the cause of a refractory anaphylaxis. We saw multiple refractory reactions to antibiotics but in clinical practice, these might be overestimated, as patients in a perioperative setting receive multiple drugs along with antibiotics.

Radio-contrast media (RCM) are however common in eliciting hypersensitivity episodes refractory to adrenaline and are responsible for 1-5 deaths per 100,000 administrations [Greenberger1991]. RCM was the most frequent elicitor of refractory anaphylaxis. One of the plausible explanation to this is that RCM promote CARPA and pseudoallergic reactions which might depend on a different mechanism than anaphylaxis [5], and therfore the treatment with adrenaline may be less effective in these reactions.

Literature describes many cases of hypersenitivity due to cancer drugs. We saw more cases of refractory anaphylaxis in patient who reported having a malignant disease in the past. Is it possible that the cancer drugs made them more susceptible to refractory anaphylaxis?

It also might be that patients with reported malignancies were simply older (mean age of 34.5755385 vs 58.2538655 p < ) and therefore less able to compensate the anaphylactic shock.

There were also relatively less refractory cases elicited by yellow jacket stings (but not bee-stings). The question we could ask here is if chemical properties of bee and yellow jacket venom have various affinities to mast cells? Plausible explanations for this observation, might include either longer exposition to the allergen (longer stings predispose to deeper deposition of the venom and slower metabolizing) or more efficient vasodilation due to biochemical differences between wasp and bee venom. [insekt sting anaphylaxis, Golden, 2007]. In such case - patients might benefit from vasopressive medication [source].

Mastoparans are a potent family of mast cell activators through G-protein coupled receptors (GPCRs). It is likely that their affinity to GPCRs might vary and the composition of mastoparans might depend on the species [source].

## Cofactors

Although we have previously identified older age and male sex to be associated with more severe anaphylaxis, these factors seem to be less important when refractory anaphylaxis is considered. Asthma and malignant diseases in the medical history were more frequent in the refractory anaphylaxis group and the reason for this is unclear. It is however interesting that past malignant diseases were mostly recognized in male refractory anaphylaxis patients.

After performing a thorough analysis of co-factors associated with an increased risk of severe anaphylaxis [3] we saw that concomitant asthma rather had a protective effect. This association is probably non-linear as the present analysis indicated concomitant asthma as a risk factor for a refractory episode. Either patients receive already antihistaminic and mast cell blocking agents and their reaction to adrenaline is therefore restricted, or the episode elicits a bronchospasm that is refractory to adrenaline and therefore results in a prolonged anaphylactic episode. This would also clarify why we saw more respiratory distress symptoms in the refractory anaphylaxis cases.

We have previously proven the role of acetysalicylic acid in increasing the risk of severe anaphylaxis. The role of proton pump inhibitors (PPI) however has not been identified as a co-factor, and there are only reports on PPI as elicitors of anaphylaxis.

## Therapy

After revising the therapeutic procedures we saw significantly more adrenaline use in the refractory cases, but it could have been used even more extensively in these life-threatening reactions. This observation might indicate that in fact the emergency teams are using these life-saving measures too cautiously.

Methylene blue and vasopressors have been described to successfully restore refractory hypotension, but their actual use in anaphylaxis patients is scarce, although they are mentioned in recognized guidelines on the management of anaphylaxis. Adrenaline i.v. as first-line therapy use was higher in the refractory cases, probably due to most of them happening in a medical setting, however, other second-line therapeutic options were rarely used.

## Limitations and strength

Low number of refractory cases prevented us from analyzing the data with more advanced statistical models, however, our analysis it is the first published report on over 30 refractory anaphylaxis cases.

Definition of refractory anaphylaxis is not universal, and confirming the refractory anaphylaxis based on the answers to our online questionnaire poses additional difficulties. If fatal reaction occurs before the second dose of adrenaline could be administered to the patient - it cannot be diagnosed as refractory (as we now require at least two doses of minimum 300 µg adrenaline). although it as well could be refractory.

Comparison of refractory anaphylaxis to patients with severe anaphylaxis gave us the possibility to describe which patients have a higher risk of developing a refractory episode, however we can not answer the question which patients have the higher risk of developing anaphylaxis per se.

## Conclusion

Refractory anaphylaxis is a rare form of life-threatening hypersensitivity reaction with high mortality. We propose to increase the use of second line medication such as methylene blue, vasopressin and glucagon in cases where 2 doses of adrenaline did not result in rapid normalization of anaphylaxis symptoms.

# Acknowledgements

We thank the members of The European Anaphylaxis Registry.

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# Figures

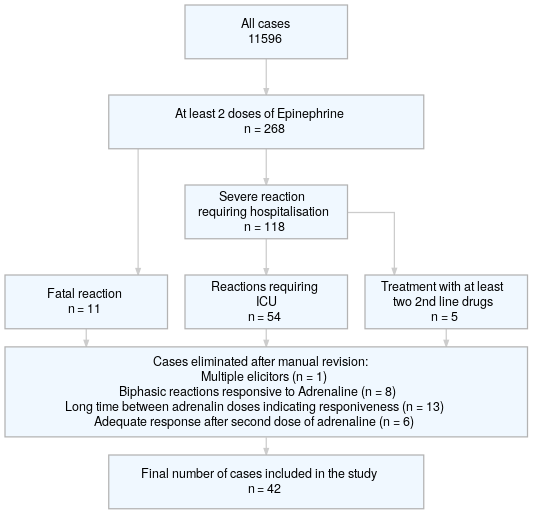


Figure 1 Flowchart illustrating the cases selection process for the final database.

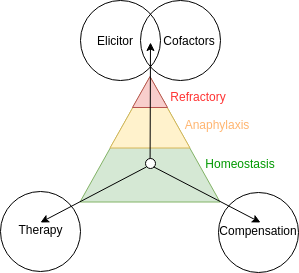


Figure 2 Visual representation of the three forces determining the severity of anaphylaxis. The natural ability of the body to compensate the anaphylaxis symptoms and therapeutic measures act to restore homeostasis to a patient by whom elicitors and cofactors influence synergistically the severity of a given episode.

# Tables

Table 1 Summary of the refractory anaphylaxis cases. Age is represented by a mean value, other as fractions [%]

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Group | n | Age | Cardiologic | DM | Food allergy | Mastocytosis | Malignancy | Atopic dermatitis |
| female | refractory | 22 | 40 | 31.8 | 9.09 | 13.6 | 9.09 | 0 | 18.2 |
| male | refractory | 20 | 43 | 30 | 15 | 5 | 5 | 15 | 5 |
| female | severe | 2421 | 43.4 | 20.6 | 2.27 | 5.37 | 2.56 | 2.19 | 6.73 |
| male | severe | 2399 | 40.2 | 22.9 | 3.58 | 5.84 | 2.54 | 2.08 | 6.25 |
|  | p value | 0.781 | 0.897 | 0.191 | 0.0701 | 1 | 0.0993 | 0.0663 | 0.2 |

Table 2 Summary of elicitors in the refractory anaphylaxis cases and severe, non-refractory anaphylaxis cases as a control. ANA - anaphylaxis, p-value derived from the Fisher exact test.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | n | refractory ANA [%] | severe ANA [%] | p value | Age | Male sex [%] | Perioperative [%] | Food allergy [%] |
| food | 9 | 21.4 | 33.5 | 0.856 | 17.4 | 55.6 | 0 | 33.3 |
| drugs | 21 | 50 | 18.4 | 1.2e-05 | 48.8 | 42.9 | 90.5 | 0 |
| insects | 8 | 19 | 38.7 | 0.00014 | 46.5 | 62.5 | 0 | 0 |
| other | 2 | 4.76 | 3.38 | 0.361 | 38 | 0 | 0 | 50 |
| unkown | 2 | 4.76 | 6.02 | 1.2e-05 | 55.5 | 50 | 0 | 0 |

Table 3 Summary of the elicitors broken down to specific elicitors from each group in the refractory anaphylaxis cases and severe anaphylaxis cases as a control. ANA - anaphylaxis, p-value derived from the Fisher exact test.

|  |  |  |  |
| --- | --- | --- | --- |
| Elicitor | severe ANA [%] | refractory ANA [%] | p value |
| antibiotics | 30.8 | 38.1 | 0.479 |
| xray\_cm | 4.78 | 14.3 | 0.0823 |
| legumes | 16.6 | 33.3 | 0.178 |
| bee | 19.4 | 62.5 | 0.00921 |
| yellow jacket | 69.3 | 25 | 0.013 |

p-value derived from the Fisher exact test.

Table 4 Summary of the symptoms in the refractory anaphylaxis cases and severe, non-refractory anaphylaxis cases as a control. ANA - anaphylaxis, p-value derived from the Fisher exact test.

|  |  |  |  |
| --- | --- | --- | --- |
| Symptom | severe ANA [%] | refractory ANA [%] | p value |
| Pruritus | 45.4 | 23.8 | 0.00487 |
| Skin symptoms | 44.8 | 26.2 | 0.0186 |
| Respiratory symptoms | 62.1 | 81 | 0.0154 |
| Respiratory arrest | 3.03 | 28.6 | 4.36e-09 |
| Chest tightness | 12 | 2.38 | 0.0543 |
| Throat tightness | 19.2 | 7.14 | 0.0479 |
| Expiratory distress | 6.86 | 26.2 | 0.000108 |
| Inspiratory stridor | 5.31 | 19 | 0.0016 |
| Loss of consciusness | 37.4 | 40.5 | 0.749 |
| Cardiac arrythmia | 4.45 | 11.9 | 0.0397 |
| Cardiac arrest | 3.07 | 42.9 | 2.76e-16 |
| Vertigo | 38.7 | 14.3 | 0.000733 |
| Death | 0.353 | 26.2 | 9.36e-17 |

Table 5 Summary of therapeutic measures in the refractory anaphylaxis cases and severe, non-refractory anaphylaxis cases as a control. 2nd line therapy was performed after the initial rescue individual called for a professional medical emergeny team. ANA - anaphylaxis, p-value derived from the Fisher exact test.

|  |  |  |  |
| --- | --- | --- | --- |
| Therapy | severe ANA [%] | refractory ANA [%] | p value |
| adrenaline im. | 9.59 | 17.5 | 0.102 |
| adrenaline iv. | 14.1 | 87.5 | 1.25e-24 |
| adrenaline iv., 2nd line | 3.23 | 58.6 | 5.21e-17 |
| volume | 23.5 | 65 | 3.43e-08 |
| volume, 2nd line | 14.9 | 27.6 | 0.0678 |
| antihistaminics iv. | 46.8 | 67.5 | 0.0105 |
| antihistaminics iv. 2nd line | 17.1 | 31 | 0.077 |
| corticosteoids, all routes | 33 | 37.5 | 0.724 |
| corticosteroids iv. | 55.8 | 77.5 | 0.00607 |
| corticosteroids iv. 2nd line | 23.9 | 41.4 | 0.0456 |
| beta-2-mimetics iv. | 0.76 | 2.5 | 0.269 |
| beta-2-mimetics inh. 2nd line | 3.32 | 10.3 | 0.0776 |
| theophyline iv. | 0.475 | 0 | 1 |
| 100% oxygen | 10.8 | 50 | 9.82e-10 |
| dopamine iv. | 0.185 | 0 | 1 |
| glucagon iv. | 0.0923 | 0 | 1 |
| methylene blue | 0 | 0 | 1 |
| hospital admission | 52.2 | 92.3 | 1.14e-07 |
| intensive care | 14.1 | 84.6 | 3.72e-22 |

Table 6 Factors potentially increasing the risk of a severe anaphylaxis investigated in refractory cases. ANA - anaphylaxis, p-value derived from the Fisher exact test.

|  |  |  |  |
| --- | --- | --- | --- |
| Factor | severe ANA [%] | refractory ANA [%] | p value |
| Concomitant asthma | 11.5 | 28.6 | 0.00233 |
| Concomitant AD | 6.5 | 11.9 | 0.194 |
| Concomitant diabetes | 5.45 | 13.2 | 0.0565 |
| Concomitant cardiologic condition | 21.7 | 31 | 0.186 |
| Concomitant infection | 3.2 | 4.76 | 0.393 |
| History of malignant disease | 2.8 | 9.52 | 0.0314 |
| Concomitant mastocytosis | 2.55 | 7.14 | 0.0941 |
| Concomitant other disease - unspecified | 14.9 | 35.7 | 0.000752 |
| Exercise prior to reaction | 25.2 | 21.4 | 0.721 |
| Psychological burden | 6.79 | 26.2 | 9.43e-05 |
| Concomitant medication | 35.9 | 54.8 | 0.0148 |
| ASA | 5.87 | 16.7 | 0.0111 |
| Beta-blockers | 9.96 | 14.3 | 0.306 |
| PPI | 5.45 | 18.4 | 0.00454 |
| Other drugs | 17.4 | 40.5 | 0.00068 |
| Alcohol use prior to the reaction | 4.67 | 2.38 | 0.722 |