Risk Factors and Treatment of Refractory Anaphylaxis - a systematic review

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(maximum 200 words).

**Introduction:** background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings. Authors are required to describe the significance of the topic under discussion. Areas covered - Authors are required to describe the research discussed and the literature search undertaken.

**Expert commentary:** - The author’s expert view on the current status of the field under discussion. References must not be included in the abstract.

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# Introduction

Anaphylaxis is a potentially life-threatening mast cell dependent reaction to most frequently food, drugs, insect venom. Anaphylaxis is a clinical diagnosis. It is highly likely if there is an acute onset of skin symptoms in conjuction with cardiovascular symptoms like hypotension and/or respiratory compromise [1]. The pathogenesis of anaphylaxis is related to a sudden, systemic, (mostly IgE dependent) degranulation of mast cells or basophils leading to the release of multiple mediators like histamine, tryptase, chymase, platelet-activating factor, prostaglandins, and leukotrienes [2].

Although anaphylaxis remains to be a clinical diagnosis [3], a standardized set of criteria to diagnose anaphylaxis have been established [1].By contrast the term refractory anaphylaxis has not established. For the purpose of this review, we define refractory anaphylaxis as anaphylaxis (meeting the criteria by NIAID/FAAN [1]) unresponsive to the treatment with at least 2 doses of minimum 300 µg adrenalin. Unresponsiveness, in this case, is defined as a lack of expected normalization of clinical symptoms (i.e. rapid increase in blood pressure, bronchodilatation, tachycardia).

It is important to distinguish refractory anaphylaxis from recurrent anaphylaxis. In one case report authors used the term refractory anaphylaxis to describe 6 recurrent episodes of anaphylaxis associated with the monoclonal mast cell activation syndrome, which responded well to intramuscular doses of epinephrine [4] and were ultimately treated with omalizumab. We did not include such reports into our analysis and suggest to use the term “recurrent” anaphylaxis instead of “refractory” in such cases.

## Epidemiology

The incidence of anaphylaxis is increasing worldwide [5] and was lately estimated to be between 50 and 112 episodes per 100,000 person-years and an estimated prevalence of 0.3% to 5.1% [6]. It is widely believed to be an underrecognized and undertreated medical emergency [7]. Anaphylaxis in children is in the majority of cases food dependent and most likely more frequently less severe than episodes in adulthood (Ref). Cases of refractory anaphylaxis are extremely rare. The incidence of refractory anaphylaxis was not investigated earlier and it is estimated (based on our data) to range between 3-5% of all cases of anaphylaxis.

## Risk factors for anaphylaxis

Risk factors for anaphylaxis include age, food elicitors (cow’s milk and hen’s egg) in children and drug-induced anaphylaxis in adults as well as concomitant mastocytosis (or mastocyte activation syndromes) [8]. Severe anaphylaxis is more likely to be elicited in older patients, patients with mastocytosis, and in temporal proximity to vigorous exercise (e.g. jogging) [8]. Risk factors for *refractory* anaphylaxis were not investigated previously.

## Management

The management algorithms for anaphylaxis are based on consensus expert recommendations and might be incomplete when it comes to reactions that are not responding to the first line therapy. Until to day the acute treatment of anaphylaxis is uniquely recommended in international guidelines and the mainstay of therapy is the early administration of intramuscular (i.m.) adrenaline [9]. However, an optimal anaphylaxis treatment in a given patient is difficult to study because it is an emergency condition and placebo-controlled studies are for ethical reasons limited. Therefore most of the knowledge regarding the treatment of anaphylaxis is based on expert recommendations which are graded as low-level evidence sources.

In the present analysis we aimed to evaluate the management and risk factors of refractory anaphylaxis to highlight possible clinical implications for updating current management algorithms.

## Literature search strategy

We performed a database search in the “PubMed” database using the “RISmed”[10] package for R statistical software [11]. The search terms contained the words “refractory anaphylaxis” in articles published from 1950 till 2017. The search was conducted on 16.11.2017 and returned 150 results. All case reports of patients who experienced an anaphylactic event and did not respond to at least 600 µg of adrenaline were included in this study. Articles in English, Portuguese, French, and Spanish were included in the analysis, one article in Japanese was excluded. Additionally, case reports referenced in the included sources were added. We excluded reviews and papers not containing case description as well as cases which documented an appropriate response to injected adrenaline. Also, cases describing mast cell activation syndrome and refractory vasoplegia without the definitive diagnosis of anaphylaxis were not included. We finally included 29 Papers reporting 39 cases of anaphylaxis. The detailed inclusion flowchart is illustrated in Fig 1.

We collected information about the elicitors, clinical setting, concomitant diseases, medication, reaction symptoms, therapy and outcomes of the treatment. We used piloted polls to gather the data and all reports were screened once by the same researcher. We investigated which interventions were reported as successful in the treatment of anaphylactic hypotension that was not responding to injected (i.v. or i.m.) adrenaline. Study outcomes were defined as time to elicit a response and mortality. Successful and unsuccessful management of anaphylaxis was one of the most important outcomes we evaluated. This information was available in all cases. All of the studies were case reports therefore the evidence level was classified as low. The review protocol was not established prior to the review and the review did not undergo preregistration.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Elicitor | No. cases | Age | Male fraction [%] | Surgical intervention [%] |
| contrast | 6 | 55.3 | 66.7 | 33.3 |
| drug | 21 | 56.1 | 47.6 | 85.7 |
| other | 6 | 40.0 | 33.3 | 50.0 |
| unknown | 6 | 52.0 | 33.3 | 66.7 |

# Risk factors for refractory anaphylaxis

A major risk factor for refractory anaphylaxis is perioperative anaphylaxis. In 27 (69.2%) cases the anaphylactic reaction occured during a diagnostic or surgical procedure. The most common causes of refractory anaphylaxis based on the analyzed case reports were iatrogenic procedures including anesthesia drugs, aprotinin, and protamine, radiocontrast media (RCM). Surprisingly, no cases of insect venom anaphylaxis were found among these reports. While the incidence of perioperative anaphylaxis has been reported to be between 1 in 10,000 – 20,000 anesthesia procedures, it has a relatively high fatality rate of 3 – 10% of the perioperative fatalities. [12]

An early diagnosis of anaphylaxis during operative procedures can be suggested based on end-tidal CO2 collapse, which often is preceding cardiac arrest, even in the absence of any cutaneous manifestations. [13] In such case - treatment with adrenalin should be immediately initiated.

# Therapy of refractory anaphylaxis

Most of the treatment strategies were according to the guidelines of anaphylaxis management [14] but were supplemented by additional procedures that have saved patients’ lives when first-line therapy failed. We report the most frequent procedures in order to evaluate them in the treatment of refractory anaphylaxis.

Based on the analyzed reports, ambulatory patients were first treated with adrenaline were patients experiencing anaphylaxis under anesthesia were usually first given intravenous volume replacement and 100% oxygen, followed by steroid and antihistaminic agents. Epinephrine was given in 100% of cases in various doses.

4 fatal cases (10.3%) which did not respond to any therapy are listed in the table below.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Elicitor | Age | Sex | Situation | Steroids | Antihistamines | Epinephrine [mg] | Fluids [L] | Vasopressors |
| succinylocholine | 74 | woman | OP | - | - | 25.0 | 1.5 | + |
| succinylocholine | 49 | man | OP | - | - | 20.2 | 2.5 | + |
| platin | 58 | woman | chemo | + | - | NA | 0.0 | - |
| telebrix 38 | 47 | man | OP | - | - | 0.6 | 2.0 | + |

World Allergy Organisation guidelines on anaphylaxis management suggest that refractory anaphylaxis should be treated with intubation, ventilation, intravenous vasopressors, glucagon and anticholinergic drugs [14]. Patients should be transported to a critical care unit. The AAAAI [15] is suggesting a similar treatment but include dopamine and vasopressin, glucagon atropine, and methylene blue if epinephrine injections and volume expansion fail to alleviate hypotension. Also the EAACI [16] guidelines suggest to use glucagon in case of concomitant beta-blockade.

# Methylene blue for the treatment of refractory hypotension

11 reports (28.2%) reported using methylene blue to treat refractory anaphylaxis and indicated a rapid (within minutes) increase in blood pressure after the injection of methylene blue. It was both given as a bolus and as an infusion with the doses ranging from 0.5-2mg/kg. Patients responded well to the treatment with methylene blue and a second infusion (or bolus) were successfully given in case of a recurrent hypotension within hours of the anaphylactic episode.

The hypotension in anaphylaxis is mediated mainly through histamine [17] which stimulates the endothelial nitric oxide synthase (eNOS) to produce Nitric oxide (NO). NO subsequently activates the soluble guanylate cyclase (sGC) which is responsible for the production of cGMP out of guanosine triphosphate (GTP) [18]. This in effect leads to the opening of the calcium ion channels in smooth muscle tissues and subsequent loss of vascular muscle contractility [19].

Methylene blue is a well-investigated drug used for treating patients with methemoglobinemia [20]. Buzato et al. investigated its properties as an inhibitor of nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway in rabbits and suggested that the primary action of methylene blue was mediated by the sGC inhibition. Therefore it is able to stop the vasoplegia mediated through the increased production of cGMP [21].

Although the mechanism of action is thought to counteract the vasoplegia related hypotension, one case report successfully used methylene blue in the treatment of anaphylaxis without hypotension [22]. Authors suggested that the inhibition of GC may result in the decrease of histamine and platelet-activating factor (PAF) *[7-9]* production which is a potent mediator of anaphylaxis [].

The use of methylene blue in current management of anaphylaxis is scarce. We received no reports of methylene blue use in our International Registry of Anaphylaxis which contains over 10,000 cases to date.

We propose to initiate the therapy in case of a refractory anaphylaxis with hypotension using 100 mg bolus i.v. and follow it with an infusion of 50 µg/kg/min. As a vector, a 100 mL of 5% dextrose can be used.

As methylene blue does not block nitric oxide production its side effects are minimal (nausea, vomiting, abdominal pain, fever, hemolysis, hypotension, methemoglobinemia, arrhythmias, bluish skin, urine discol- oration, and hyperbilirubinemia [23]). It may be considered a safe option for the treatment of anaphylaxis. No side effects were reported due to methylene blue use in the above cases.

It is important to be aware that methylene blue may provoke false pulse oximetry readings as the blue dye mimics cyanosis [24].

# Vasopressors Vasopressin as a supplementary vasopressor

In case of a hypotension refractory to adrenaline or volume replacement therapy – vasopressors can be evaluated.

Vasopressors were used in 21 (53.8%) of refractory cases. Vasopressin or its synthetic analogue terlipressin were used in 13 cases. In 8 of these reports (61.5%) injection of vasopressin reversed the refractory hypotension within minutes. Other vasopressors included metaraminol [25]–[27],[27], methoxamine [28], dopamine [12],[29]–[31], and noradrenaline infusions.

The European anaphylaxis register lists 18 cases where dopamine was used. None of these reactions were fatal.

Use of vasopressin in refractory anaphylaxis was only suggested in management recommendations from the AAAAI [15] and was never vastly investigated. Dopamine, however, is recommended by 2 out of three guidelines. Nevertheless, dopamine might be related to higher risk of mortality and adverse events than epinephrine or norepinephrine [32]. Both norepinephrine and vasopressin may be appropriate second-line agents for the management of refractory hypotension. Vasopressin acts on the V1 receptors, while Norepinephrine acts primarily on the alfa-adrenergic receptors, their synergistic effects may result in effective vasoconstriction [33].

Seedat et al. described a case of anaphylaxis while undergoing a bilateral knee arthroscopy under general anesthesia. The refractory shock was not responding to repeated adrenalin (total 2mg), antihistaminics and hydrocortisone. Rapid response was achieved with the last resort injection of 1 U ornipressin that was repeatedly effective when biphasic reaction occurred. Authors concluded that vasopressin or ornipressin should be considered for the treatment of adrenaline-resistant anaphylactic shock before resuscitation is discontinued. [34] We support the use of vasopressin in refractory hypotension, combined with norepinephrine infusions.

One case report described the use of military anti-shock trousers to perform external vasopressin on a patient who received inadvertently high doses of systemic immune therapy allergen [35]. Although this can be hardly available in critical care centers we would like to point out this minimally invasive method as a possible alternative measure in achieving normotension.

# Glucagon in anaphylaxis with concomitant beta blockers

Glucagon, a polypeptide hormone with potent inotropic and chronotropic actions was given in two cases of refractory hypotension in analyzed cases[30],[36]. Patients

Adrenergic effects of glucagon are minimally influenced by beta-blockers [36], Glucagon activates adenylyl cyclase directly [3], therefore it is especially useful in patients who are chronically treated with beta-blockers.

Patients with concomitant beta-blockers often show bradycardia or normocardia during anaphylaxis. [12]\*

# Stopping the elicitor exposure

In cases where the elicitor of anaphylaxis is known, and first-line therapy fails it is advisable to stop the exposition to the likely allergen. Three case reports described the rapid improvement of a refractory anaphylaxis after preventing further contact with the allergen.

A 15-year-old boy who was exposed to cow’s milk underwent near-fatal anaphylaxis with refractory hypotension. After 150 minutes of resuscitative measures, a gastric drainage performed as a last resort treatment surprisingly led to a quick alleviation of anaphylaxis symptoms and patient recovered fully. Authors concluded that external gastric drainage should be considered an integral part of the treatment of severe life-threatening food-induced anaphylaxis [9].

Another report used sugammadex which is a compound strongly binding to rocuronium, to decrease its bioavailability in a patient under anesthesia and therefore allow for a cessation of a refractory anaphylaxis episode [37].

There also was a report where the patient was inadvertently given i.v. high dose of aprotinin in a fast infusion. After 10 hours of refractory hypotension, authors decided to use the last resort treatment with high-volume continuous venovenous hemofiltration (HV-CVVH) which resulted in a rapid improvement of hemodynamic function [38].

# ECLS

3, 6, 19, 38 *The incidence of life-threatening anaphylactic reactions related to anesthesia is approximately 1 in 6000 anesthetics administered and is associated with mortality as high as 5%.1 The use of extracorporeal membrane oxygenation (ECMO) in the setting of refractory shock following anaphylaxis has been documented.2-5 [26]*

*The use of VA ECMO for treating cardiogenic shock is well established, as are the many pitfalls and complica- tions associated with its use.10 VA ECMO may also be used for treating anaphylactic shock,2-5 although its role is less well established than for treating cardiogenic shock of other etiology [26]*

*Patient with refractory anaphylaxis to Chlorhexidine coated CVC. 10 minutes after introducing CVC he became hypotensive - then >30min resuscitation and 3 minutes after CVC removal - the return of spontaneous circulation. [39] This case shows how important it is to get rid of the allergen in refractory anaphylaxis. Treatment with ECMO.*

# Conclusion

# Expert Commentary: 500-1000 words (included in overall word count).

Severe anaphylaxis is a critical medical condition requiring an immediate intervention. According to the international guidelines adrenaline intramuscular given is a rapid and relatively safe treatment stabilizing the symptoms quickly in a given patient. However, in a few patients this intervention might not be sufficient and besides repeating the doses other therapeutical measures will need to be applied. Such cases are regarded as refractory anaphylaxis, which are particulary seen, when the elicitor of the reaction is reaching the organism intravenously. This route is associated with a high systemic load of a given allergen or other mast cell activating molecule inducing a rapid onset of mediator release like histamine, but also tryptase and chymase, which are proteases and which may in addition to histamine promote severely anaphylaxis via activation of the ….clotting …system?? check. In clinical practice it is necessary to identify patients of risk. Such risk factors should particulary be assessed in patients undergoing medical diagnostic and therapeutic measures. The measurement of tryptase enables to identify patients how are at risk for severe anaphylaxis.

For the future, biomarker measurements in a bed side setting may enable doctors to identify patients experiencing severe, refractory anaphylaxis early in order to initiate intensified critical care treatment. Moreover, defined standardized treatment protocols for such cases of refractory anaphylaxis may provide an optimization of the treatment which can safe life in a given patient.

# Key issues

*? Epinephrine in appropriate doses is safe, and there are no abso- lute contraindications for its use in treating anaphylaxis. ? Delay in administration of epinephrine may lead to more severe and treatment resistant anaphylaxis.*[7] \* Glucagon \* Vasopressors \* ECLS \*

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## Annotated bibliography

# Figures and Tables

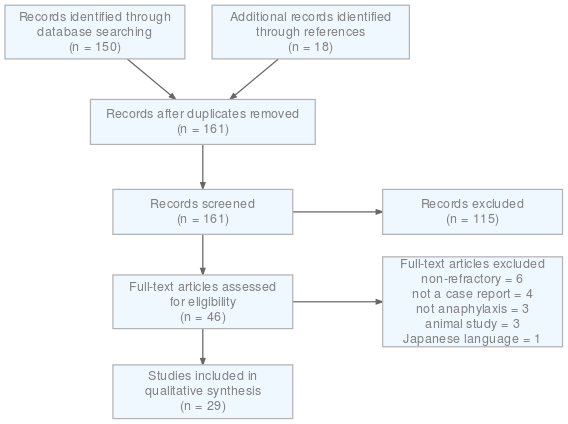


Figure 1 The PRISMA flowchart for included sources

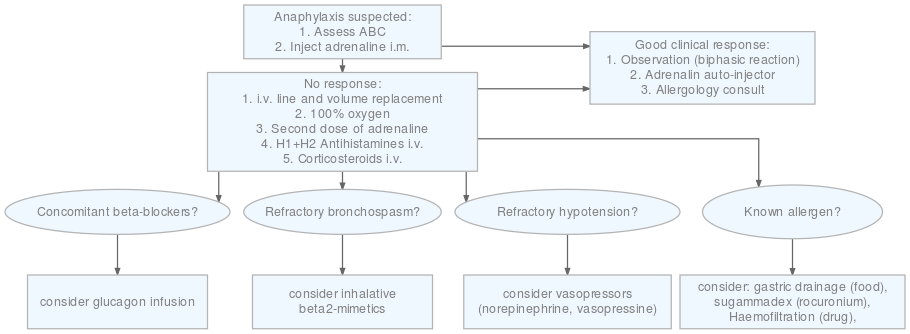


Figure 2 The algorithm for refractory anaphylaxis management