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 life-threathening immunologic reaction to an allergen (most frequently food, drugs, insect venom) that is hardly avoidable in clinical practice of various medical specialties.

Anaphylaxis is considered a clinical diagnosis and it is highly likely if there is an acute onset of skin symptoms with either hypotension or repiratory compromise, or when the allergen is known or likely [1]. Its pathogenesis relies on a sudden, systemic, (mostly IgE dependent) degranulation of mast cells or basophils. *Anaphylaxis is classically initiated by allergen cross-linking of IgE on mast cells and basophils, leading to degranulation and release of histamine, tryptase, chymase, platelet-activating factor, prostaglandins, and leukotrienes.5,6 [2]*

*Anaphylaxis remains a clinical diagnosis based on probability and pattern recognition. It has no universally accepted clinical definition [1,5]. [3]*

The definition of *refractory* anaphylaxis is not established. For the purpose of this review we will define it 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 distingush refractory anaphylaxis from recurrent anaphylaxis. In one case report authors used the term refractory anahpylaxis to describe 6 recurrent episodes of anaphylaxis assosciated 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 in our analysis and advise on using the term “recurrent” anphylaxis istead 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]. Anaphylaxis in children is usally food dependent and less severe than episodes in adulthood. Cases of *refractory* anaphylaxis are extremely rare. The incidence of refractory anaphylaxis was not investigated earlier and it is estimated (based on our experience) to be 3-5% of all cases of anaphylaxis.

*The exact prevalence of anaphylaxis in the general population is not known, but it is widely believed to be an underrecognized and undertreated medical emergency.1e9 [7]*

## 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 vigourous exercise (e.g. jogging) **???**. Risk factors for *refractory* anaphylaxis were not invesigated previously.

## Management

The managment 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. The mainstay of therapy is early administration of intramuscular (IM) adrenalin [9]. However, research in anaphylaxis treatment is difficult because it is an emergency condition and placebo controlled studies are impossible. Therefore most of the knowledge is based on expert recommendations which are graded as low-level evidence sources.

We aimed to reevaluate the management and risk factors of refractory anaphylaxis to highlight possible clinical implications for updating current managment algorithms.

## Literature search strategy

We have 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. Published case reports of anaphylaxis treated with repeated doses of epinephrine were included into the study (articles in English, Poltugese, French and Spanish were included into the analysis, one article in japanese was excluded). Additionally, case reports referenced in the included sources were added. We excluded reviews and papers not containg case description as well as cases which documented an appropriate response to injected adrenalin. Also cases describing Mast cell activation syndrome and refractory vasoplegia without the definitive diagnosis of anaphylaxis were not included. 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.

All of the studies were case reports therfore the evidence level was classified as low.

The review protocol was not established prior to the review and the review did not undergo preregistration.

We have performed literature research identifying case reports of refractory anaphylaxis. All case reports of patients who experienced an anaphylactic event and did not respond to at least 600 µg of adrenalin were included into this study. We investigated which interventions were reported as succesfull in the treatment of anaphylactic hypotension that was not reponding to injected (i.v. or i.m) adrenailn. Study outcomes were defined as time to elicit a response and mortality. Most of these reports described refractory anaphylaxis in a perioperative setting, but they also included cases of food and drug anaphylaxis. Suprisingly, no cases of insect venom anphylaxis were found among these reports.

Outcomes: successful and unsuccesful managment of anaphylaxis was one of the most important outcomes we evaluated. This information was availible in all cases. Neurological deficits directly after the episode were also evaluated, but this measure might be biased.

|  |  |  |  |
| --- | --- | --- | --- |
| Elicitor | Age | Male fraction | Operative fraction |
| contrast | 47.0 | 100.0 | 100.0 |
| drug | 57.2 | 50.0 | 85.0 |
| other | 40.0 | 33.3 | 50.0 |
| unknown | 52.0 | 33.3 | 66.7 |

# Risk factors of refractory anaphylaxis

The risk factors for refractory anaphylaxis include perioperative anaphylaxis. We observed XXX cases. Fatality rate of anaphylaxis during anaesthesia is estimated in about 3-10% of cases [12].

Asthma poses higher risk of anaphylaxis [5] but we have not noted any cases of asthma in the reporter refractory anaphylaxis case reports.

The most common causes of refractory anaphylaxis based on the analyzed case reports were iatrogenic procedures including anaesthesia drugs, aprotinin and protamine, radiocontrast media (RCM).

While the incidence of perioperative anaphylaxis has been reported to be between 1 in 10,000—20,000 anesthesia pro- cedures, it is responsible for 3—10% of the perioperative fatalities. [13]

1. In our two cases ETco2 collapse was the first sign preceding cardiac arrest. Several authors have underlined the value of this early clinical sign for the suspicion of anaphylactic shock, even in the absence of any cutaneous manifestations. [14]

# Therapy of refractory anaphylaxis

Most of the treatment strategies were according to the guidelines of anaphylaxis management [source], but were supplemented by additional procedures that saved patients’ lives. We report the most frequent procedures in order to evaluate them in the treatment of refractory anaphylaxis.

Ambulatory patients and not in hospital-setting were first treated with adrenaline wether patients experiencing anaphylaxis under anesthesia were usually first given intraveous volume replacement and 100% oxygen, followed by eithe epinephrine or alfa-adrenergic vasopressors or both.

Epinephrine was given in 100% of cases in various doses.

In Table X we provided therapeutic approaches used in the treatment of anaphylaxis.

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

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Elicitor | age | sex | Situation. | t\_steroids | t\_antihistamines | Epinephrine..mg. | Fluids..L. | vasopressors |
| 16 | succinylocholine | 74 | woman | anesthesia / emegency appendectomy | FALSE | FALSE | 25.0 | 1.5 | TRUE |
| 17 | succinylocholine | 49 | man | anesthesia / emegency appendectomy | FALSE | FALSE | 20.2 | 2.5 | TRUE |
| 23 | platin | 58 | woman | Chemotherapy | TRUE | FALSE | NA | 0.0 | FALSE |
| 24 | telebrix 38 | 47 | man | surgery in total anesthesia | FALSE | FALSE | 0.6 | 2.0 | TRUE |

*The AAAAI/ACAAI Guidelines show info about refractory anaphylaxis [15] The three guidelines on the management of refractory anaphylaxis: [15] Management of refractory anaphylaxis WAO: intubation; ventilation; IV vasopressors; glucagon; anticholinergic; transfer to hospital (preferably to an emergency medicine, critical care medicine, or anesthesiology) team for ventilatory and inotropic support; checklist of needed items; Table 6 AAAAI: vasopressors; dopamine; give vasopressin if epinephrine injections and volume expansion fail to alleviate hypotension; transfer to hospital; glucagon; atropine; methylene blue; includes checklist of supplies and equipment; Figures E2, E3 EAACI: glucagon*

*Management of anaphylaxis refractory to initial treatment The guidelines differ in emphasis on refractory anaphylaxis treatment. The WAO Guidelines stress the importance of prompt initial treatment to prevent escalation of symptoms [2]. They suggest that if possible, patients with anaphylaxis refractory to epinephrine, supplemental oxygen, IV fluids, and second-line medications should be transferred to the care of a specialist team for ventilatory and inotropic support and continuous electronic monitoring [2]. The AAAAI/ACAAI Guidelines provide details about interven- tions for cardiopulmonary arrest, airway management, and IV administration of vasopressors including epinephrine, dopamine, and vasopressin [3]. The EAACI Guidelines in- clude brief specific instructions about when to call for In- tensiveCareUnit support* [*4*](Table4)*. Studies relevant to refractory anaphylaxis treatment are of interest. A Cochrane review of randomized con- trolled trials (RCT) in more than 20,000 critically ill pa- tients with distributive shock supports administration of crystalloids such as 0.9% saline, because administration of colloids such as albumin or hetastarch did not correlate with increased survival [82]. Methylene blue administration for vasoplegia in anaphylaxis refractory to epinephrine and IV fluid resuscitation is based on case reports and extrapolation from use in other forms of shock [83]. [15]*

*Management of anaphylaxis refractory to initial treatment Even in high-resource countries, optimal treatment of re- fractory anaphylaxis is not available universally; for ex- ample, in remote, inaccessible, or impoverished areas or in specific situations such as anaphylaxis on airplanes. In limited-resource situations, lack of availability of basic es- sentials such as epinephrine, supplemental oxygen and IV fluid resuscitation is more critical than lack of second-line medications such as antihistamines and glucocorticoids. Lack of availability of advanced life-support management can be a major barrier to survival [72-76,128] (Table 8). In any limited-resource situation, resuscitation efforts pro- longed over hours using a hand-held bag valve mask (manual resuscitator) are often successful in anaphylaxis [2] (Table 8). In mid- and low-resource countries, striving to ensure more consistent availability of medications, supplies, and equipment for anaphylaxis treatment is an important goal [2,5-7]. The World Health Organization has devel- oped a tool kit containing evidence-based guidelines and a framework for quality improvement in the hospital care of critically ill children in such environments [126], where despite many obstacles, improvements can be documented [130]. [15]*

*No high-quality studies at present permit recommendations concerning the use of intravenous epinephrine in anaphylaxis [18] Parameters and international guidelines support its use in refractory anaphylaxis [20–23] (Table 1). BUt it can cause arrythmias that are lethal. [3]*

# Methylene blue for the treatment of refractory hypotension

The hypotension in anaphylaxis is mediated mainly through histamine **???** which stimulates the endothelial nitric oxide synthase (eNOS) to produce Nitric oxide (NO). NO subsequently activates the soluble guanyl cyclase (sGC) which is responsible for the producion of cGMP out of guanosine triphosphate (GTP) **???**. This in effect leads to the opening of the calcium ion channels in smooth muscle tissues and subsequent loss of vasal muscle contractility **???**.

Methylene blue is a well investigated drug used for treating patients with methemoglobinemia **???**. 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 **???**.

11 reports (28.2%) repoted 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.

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 withouth hypotension **???**. 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 managment of anaphylaxis is scarce. We recieved 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 **???**). 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 remember that methylene blue may provoke false pulseoximetry readings as the blue dye mimics cyanosis **???**.

# Vasopressors Vasopressin as a supplementary vasopressor

In case of a hypotension refractory to adrenaline or volume replacement therapy use of 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, methoxamine, dopamine and noradrenaline infusions.

Interantional guidelines support the use of dopamine in refractory hypotension **???**.

Our register lists r 18 cases where dopamine was used. None were fatal.

*The authors state that “current recommendations are to start with an infusion of epinephrine for unresponsive anaphylaxis; and if there is re- fractory hypotension, then add dopamine as a second vaso- pressor.”1 The literature supports the use of epinephrine infusion in refractory anaphylactic shock because it reverses most of the cardiovascular effects of anaphylaxis.3 At low doses, dopamine exerts its effects on the b-adrenergic receptors, causing an in- crease in myocardial function, heart rate, and some vasodilata- tion. However, there is no clear evidence for the use of dopamine as a second-line vasopressor in anaphylactic shock. This is particularly important given that dopamine has been associated with a higher risk of mortality and major adverse events compared with epinephrine and norepinephrine.4,5 The literature suggests that norepinephrine or vasopressin may be appropriate second-line agents. Norepinephrine acts primarily on the a-adrenergic receptors, whereas vasopressin acts on the V1 re- ceptors, both leading to vasoconstriction.2,6 Methylene blue has also been used with good success in catecholamine-refractory vasoplegic anaphylactic shock.7* ***???***

Seedat et al described a case of anaphylaxis while undergoing a bilateral knee arthroscopy under general anaesthesia. Reafractory shock was not responding to repeated adrenalin (total 2mg), antihistaminics and hydrocortisone. Rapid response was achieved as a last resort injection of 1 U ornipressin that was repeatedly effective when biphasic reaction occured. Authors concluded that vasopressin or ornipressin should be considered for the treatment of adrenaline-resistant anaphylactic shock before resuscitation is discontinued. [16]

# Glucagon in anaphylaxis with concomitant beta blockers

*There is evidence that glucagon is also helpful in refractory anaphylaxis especially for patients on beta-blockers. Glucagon activates adenylyl cyclase directly and can bypass the beta blockade.11,12 [2]*

*Histamine release also increases cardiac rate, cardiac contractility, and bronchoconstriction.2,5 Therefore, it is suggested that beta-blockers mask cardiac signs of anaphylaxis and lead to unopposed alpha-adrenergic activity, causing severe bronchoconstriction. [2]*

*Finally, we would like to suggest a correction in the published glucagon dose. In children, the loading dose is 20 to 30 µg/kg (maximum, 1 mg), and the infusion dose is 5 to 15 µg/min rather than the dose recommended in the 2015 update* ***???***

*Bradycardia is an uncommon presentation during anaphylaxis. In our patient, premedication with beta blocker and severe hypoxia could be the probable reason for this uncommon presentation.[13]*

# ECLS

*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 [17]*

*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 [17]*

*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 - return of spontaneaous circulation. [18] This case shows how important it is to get rid of the alergen in refractory anaphylaxis. Traetment with ECMO.*

# 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 rapid improvement of a refractory anaphylaxis after preventing further contact with the alergen.

A 15-year-old boy who whas 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 suprisingle 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 compund strongly binding to rocuronium, to decrease its bioavailiblity in a patient under anaesthesia and therefore allow for cesation of a refractory anaphylaxis episode **???**.

There also was a report where 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 [19].

# Conclusion

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

## What are the key weaknesses in clinical management so far?

## What potential does further research hold? What is the ultimate goal in this field?

## What research or knowledge is needed to achieve this goal and what is the biggest challenge in this goal being achieved?

## Is there any particular area of the research you are finding of interest at present?

# Five-year view

# 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

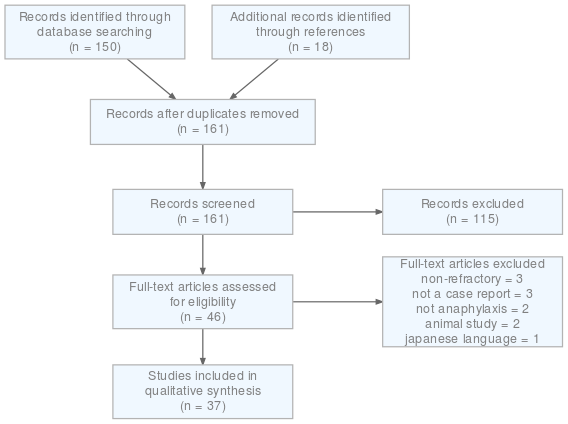


Figure 1 The PRISMA flowchart for included sources