Risk Factors and Treatment of Refractory Anaphylaxis - a review of case reports

Wojciech Francuzik

Sabine Dölle

Margitta Worm, MD

21.02.2018

**Introduction:** Patients experiencing anaphylaxis who do not recover after the treatment with intramuscular adrenaline are regarded to suffer from refractory anaphylaxis. The incidence of refractory anaphylaxis is estimated to range between 3–5% of anaphylaxis cases. The risk factors for refractory anaphylaxis are unknown.

**Areas covered:** 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.

**Expert commentary:** According to the international guidelines adrenaline given intramuscular (i.m.) is a rapid and safe treatment but may be insufficient. Therefore defined standardized treatment protocols for such cases of refractory anaphylaxis are needed to optimize the treatment. Point-of-care diagnostics may enable doctors to identify patients experiencing severe, refractory anaphylaxis early in order to initiate intensified critical care treatment.

Department of Dermatology, Venerology, and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Charitéplatz 1, 10117 Berlin,

**Corresponding author:**  Prof. Dr. med. M. Worm [margitta.worm@charite.de](mailto:margitta.worm@charite.de) Phone: +49 30 450 529 005; Fax: +49 30 450 529 902

**Keywords:** anaphylaxis; epinephrine; glucagon; hypotension; methylene blue; shock

# Introduction

Anaphylaxis is a potentially life-threatening, primarily mast cell-dependent reaction to most frequently food, drugs, insect venom. Although anaphylaxis remains to be a clinical diagnosis [1], it is highly likely if any of the following 3 criterita are fulfilled: 1) Acute onset of an illness with generalized skin / mucosal involvemt with flushing, hives or pruritus; 2) acute cutaneous, cardiorespiratory or gastrointestinal symptoms after exposure to a likely allegen; c) acute reduction of blood pressure (BP) after exposure to a known allergen [2]. The definition of anaphylaxis remains controverse [3]. 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 [4].

By contrast, the definition of refractory anaphylaxis has not been established yet. For the purpose of this review, we define refractory anaphylaxis as anaphylaxis (meeting the criteria by NIAID/FAAN [2]) unresponsive to the treatment with at least 2 doses of a minimum 300 µg adrenaline. Unresponsiveness, in this case, is defined as a lack of expected normalization of clinical symptoms (i.e. rapid increase in blood pressure, bronchodilatation, tachycardia). Previously authors suggested using the term in cases of persistent severe shock symptoms after 10 minutes of adequate resustitation [5].

It is important to distinguish refractory anaphylaxis (which is unresponsive to treatment) from recurrent anaphylaxis which can be defined as multiple episodes of anaphylaxis over a period of time that responsed to treatment with adrenaline [6]. 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 [7] 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.

The incidence of anaphylaxis is increasing worldwide [8] 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% [9]. It is widely believed to be an underrecognized and undertreated medical emergency [10]. Anaphylaxis in children is in the majority of cases food dependent and most likely less severe than episodes in adulthood [11]. Cases of refractory anaphylaxis are extremely rare. The incidence of refractory anaphylaxis was not investigated earlier and we estimate it to range between 3–5% of all cases of anaphylaxis (based on our clinical experience).

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 mast cell activation syndromes) [12]. Severe anaphylaxis is more likely to be elicited in elderly patients, patients suffering from mastocytosis, and in temporal proximity to vigorous exercise (e.g. jogging) [13]. Risk factors for *refractory* anaphylaxis were not investigated previously.

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. To date, the acute treatment of anaphylaxis is uniquely recommended in the international guidelines and the mainstay of therapy is the early administration of intramuscular (i.m.) adrenaline [14]. However, an optimal anaphylaxis treatment in a given patient is difficult to study because it is an emergency condition and placebo-controlled studies are limited for ethical reasons. 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.

We performed a database search in the “PubMed” database using the “RISmed”[15] package for R statistical software [16]. 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 151 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 articles not containing a 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. 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. 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. It is important to mention that as a review of case reports this study did not use control groups to compare outcomes and its statistical validity is therefore limited.

We finally included 30 Papers reporting 42 cases of anaphylaxis (Table 1)

## Risk factors for refractory anaphylaxis

A major risk factor for refractory anaphylaxis is perioperative anaphylaxis. In 30 (71.4%) cases the anaphylactic reaction occurred 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). Indirectly concomitant treatment with protimne-containing insulins might predispose to refractory anaphylaxis as these patiens have 40 to 50 times greater risk for developing anaphylaxis perioperatively [17,18]. Surprisingly, no cases of insect venom anaphylaxis were found among these reports (see Table 2). 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. [19]

The patomechanisms which are responsible for refractory anaphylaxis are not well understood. There are however theories why extensive therapeutic efforts fail in certain cases. Figure ?? summarizes the potential factors contributing to refctorinness of anaphylaxis. These can be divided into patient dependent (e.g. concomitant coronary disease, older age or bronchial hyperresponsiveness) or therapy-dependent (e.g. suboptimal management, concomitant beta blocker use, or idopathic triggers).

An early diagnosis of anaphylaxis during operative procedures can be suggested based on end-tidal CO2 collapse [5], which often is preceding cardiac arrest, even in the absence of any cutaneous manifestations [20]. In such case - treatment with adrenalin should be immediately initiated as delayed adrenaline use has been linked to increased mortality [21] and refractoriness to adrenaline [10].

## Therapy of refractory anaphylaxis

Most of the treatment strategies were in accordance with the guidelines of anaphylaxis management [22] but were supplemented by additional procedures that have saved patients’ lives when first-line therapy failed (Table 3). We report on the most frequent procedures in order to evaluate them in the treatment of refractory anaphylaxis.

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

4 fatal cases (16.7%) which did not respond to any therapy are listed in the table 4.

The World Allergy Organisation guidelines on anaphylaxis management suggest that refractory anaphylaxis should be treated with intubation, ventilation, intravenous vasopressors, glucagon and anticholinergic drugs [22]. Patients should be transported to a critical care unit. The AAAAI [23] is suggesting a similar treatment but include dopamine, vasopressin, glucagon atropine, and methylene blue if epinephrine injections and volume expansion fail to alleviate hypotension. Also, the EAACI [24] guidelines suggest using glucagon in case of concomitant beta-blockade.

## Methylene blue for the treatment of refractory hypotension

11 reports (26.2%) 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 [25] 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) [26]. This leads to the opening of the calcium ion channels in smooth muscle tissues and the subsequent loss of vascular muscle contractility [27].

Methylene blue is a well-investigated drug to treat patients with methemoglobinemia [28]. Buzato et al. investigated its properties as an inhibitor of the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway in rabbits and suggested that the primary action of methylene blue is mediated by the sGC inhibition. Therefore it is able to stop the vasoplegia mediated through the increased production of cGMP [29].

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 [30]. The authors suggested that the inhibition of GC may result in a decrease of histamine and platelet-activating factor (PAF) production which are potent mediators of anaphylaxis [31].

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

In case of a refractory anaphylaxis with severe persisting hypotension we propose to apply a 100 mg bolus i.v. followed by 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 [32]). It may be considered a safe option for the treatment of anaphylaxis upon intensive care conditions. No side effects were reported due to methylene blue use in the reported-cases.

Clinicians must be aware that methylene blue may provoke false pulse-oximetry readings as the blue dye mimics cyanosis [33].

## Vasopressors

In case of a hypotension refractory to adrenaline or volume replacement therapy – vasopressors can be considered. Vasopressors were used in 21 (50%) of refractory cases. Vasopressin or its synthetic analogue terlipressin were used in 13 cases. In 8 of these reports (61.5%) the injection of vasopressin reversed the refractory hypotension within minutes. Other vasopressors included metaraminol [34–36], methoxamine [37], dopamine [19,38–40], and noradrenaline [19,35,39,41–47] infusions. Drugs given perioperatively were the eliciting factors in all but two of these cases (90%) and all patients reacted within minutes (range 5 - 20) upon exposition to the suspected drug. One patient reacted to systemic immune therapy (SIT) injection that was inadvertently extremely high-concentrated [48] and in one case the elicitor could not be established [34].

The use of vasopressin in refractory anaphylaxis was only suggested in the management recommendations from the AAAAI [23] and was never vastly investigated. Dopamine, however, is recommended by 2 out of three guidelines. Nevertheless, dopamine might be related to a higher risk of mortality and adverse events than epinephrine or norepinephrine [49]. 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 [50].

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 adrenaline (total 2 mg), antihistamines and hydrocortisone [51]. A rapid response was achieved with the last resort injection of 1 U ornipressin that was repeatedly effective when the biphasic reaction occurred. The authors concluded that vasopressin or ornipressin should be considered for the treatment of adrenaline-resistant anaphylactic shock before resuscitation is discontinued [51]. 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 [48]. Although this can be hardly available in critical care centers we want to point out this minimally invasive method as a possible alternative measure in achieving normotension.

## Glucagon in anaphylaxis with concomitant beta blockers

Adrenaline may fail to inhibit an anaphylactic event in patients taking beta-blockers as both heart and lung express beta-adrenergic receptors. Glucagon, a polypeptide hormone with potent ino- and chronotropic actions was given in two cases of refractory hypotension in analyzed cases[39,52]. Both patients receiving glucagon were undergoing refractory anaphylaxis with the concomittant use of atenolol for arterial hypertension. Both patients reacted to contrast medium and after minutes developed severe anaphylaxis not responding to repeated doses of adrenaline. An infusion of 1 mg glucagon per hour or 1 mg glucagon as a bolus relieved the refractory shock in both cases and it also successfully treated a recurrent biphasic reaction [39].

Adrenergic effects of glucagon are minimally influenced by beta-blockers [52] as glucagon activates adenylyl cyclase directly [1] Therefore, it is especially useful in patients who are on long term beta-blocker treatments. Patients with concomittant beta-blockers often show bradycardia or normocardia during anaphylaxis [19], as the reflexory tachycardia is suppressed by the beta-blockade. Authors who reported a fatal anaphylaxis case potentiated with beta blockers did not treat with glucagon but discuss this therapeutic option positively as well [53].

## 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 anaphylactic symptoms and the patient recovered completely. These authors concluded that external gastric drainage should be considered an integral part of the treatment of severe life-threatening food-induced anaphylaxis [14].

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 [54].

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 [47].

## Extracorporeal life support

In the most severe cases, where all pharmacologic attempts fail to alleviate symptoms of anaphylaxis clinicians turned to last resort of extracorporeal life support (ECLS) options. There were 4 reports where patients reacted extremely severe and all were operated on because of a heart condition in general anesthesia [36,41,42,55]. Two patients reacted to chlorhexidine, one to rocuronium and in one case the elicitor could not be established. Only one of these patients was taking a beta blocker [41]. All these patients received multiple doses of adrenaline (total dose ranged 1 – 15 mg), vasopressors, high volume replacement therapy, corticosteroids, and antihistaminics. Upon prolonged resuscitation procedures two of these patients were placed on cardiopulmonary bypass (CPB) and two on an extracorporeal membrane oxygenation (ECMO) device. After stabilizing of their condition, patients were weaned off from these supportive measures without neurological sequelae.

Life-threatening anaphylactic reactions occur in approximately 1 in 6000 anesthetic procedures and are associated with 5% mortality [36]. ECMO is widely used for the treatment of cardiogenic shock [56] and may also be used in cases of anaphylaxis. It is especially helpful where there is refractory anaphylaxis with cardiac or respiratory arrest. Its use may gain time to eliminate the responsible elicitor (metabolize the drug or find the occluded elicitor). One of the reported cases identified the chlorhexidine coated catheter to be responsible for the refractory shock, and after its removal patient responded immediately to therapy. The use of ECMO facilitated the elicitor discovery [55].

## Conclusion

We analyzed case reports from the literature and critically evaluated the undertaken therapeutic approaches. These cases of refractory anaphylaxis were most frequently elicited by drugs and happened during a medical procedure. All patients were treated with adrenaline as a first line therapy, nearly all of them were given oxygen, steroids i.v. and fluid replacement therapy.

We highlight therapeutic options that should be evaluated in case of anaphylaxis non-responsive to first-line therapy with adrenaline: methylene blue, vasopressors, glucagon and extracorporeal life support. We suggest a management algorithm for refractory anaphylaxis (see Fig. 2) that is supplementary to the established protocols.

# Expert Commentary

Severe anaphylaxis is a critical medical condition requiring an immediate intervention. According to the international guidelines adrenaline given intramuscular (i.m.) 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, concomitantly to repeating its doses, other therapeutical measures will need to be applied. Such cases are regarded as refractory anaphylaxis and are particularly 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 plasma kallikrein and to enhancement of vascular permeability [57].

In clinical practice, it is necessary to identify patients at risk. Such risk factors should particularly be assessed in patients undergoing medical diagnostic and therapeutic measures. The diagnosis of anaphylaxis is based on non-specific clinical presentation, most frequently with hypotension, bronchospasm and skin flushing. In cases where anaphylaxis is possible but the symptoms are not clearly apparent introduction of a point-of-case test could confirm the suspition in order to introduce immediate therapy with adrenaline. The measurement of tryptase enables to identify patients who are at risk for severe anaphylaxis (specificity of 0.93) but its sensitivity of 0.36 is insufficient [58].

# Five year View

For the future, measurements [59] at a bedside 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 save the life in a given patient.

# Key issues

* Drug elicited reactions in perioperative setting and concomitant beta-blocker use are the most important risk factors for refractory anaphylaxis.
* Epinephrine in appropriate doses is still the mainstay of anaphylaxis therapy without any absolute contraindications and should be given as soon as anaphylaxis is suspected.
* Glucagon infusion should be considered when patients receive beta-blockers.
* Methylene blue and vasopressors i.v. should be considered together with volume replacement therapy in cases of refractory hypotension.
* In cases of severe refractory anaphylaxis with prolonged resuscitation an extracorporeal life support should be evaluated.

# Annotated bibliography

[1] Kemp AM, Kemp SF. Pharmacotherapy in refractory anaphylaxis. Current Opinion in Allergy and Clinical Immunology [Internet]. 2014;14:371–378. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage{\&}an=00130832-201408000-00018>.

[2] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Annals of Emergency Medicine. 2006;47:373–380.

[3] Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxisa practice parameter update 2015. Annals of Allergy, Asthma & Immunology [Internet]. 2015;115:341–384. Available from: <https://doi.org/10.1016/j.anai.2015.07.019>.

[4] Houser SM, Weng C, Liu Y-C. A Patient With an Allergy Emergency. JAMA Otolaryngology–Head & Neck Surgery [Internet]. 2015;141:382. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25675291 http://archotol.jamanetwork.com/article.aspx?doi=10.1001/jamaoto.2015.8>.

[5] Gouel-Chéron A, Harpan A, Mertes P-M, et al. Management of anaphylactic shock in the operating room. La Presse Médicale [Internet]. 2016;45:774–783. Available from: <https://doi.org/10.1016/j.lpm.2016.04.002>.

[6] Mullins RJ. Anaphylaxis: Risk factors for recurrence. Clinical html\_ent glyph=“@amp$\mathsemicolon$” ascii=“&amp$\mathsemicolon$”/ Experimental Allergy [Internet]. 2003;33:1033–1040. Available from: <https://doi.org/10.1046/j.1365-2222.2003.01671.x>.

[7] Jagdis A, Vadas P. Omalizumab effectively prevents recurrent refractory anaphylaxis in a patient with monoclonal mast cell activation syndrome. Annals of Allergy, Asthma & Immunology [Internet]. 2014;113:115–116. Available from: <http://dx.doi.org/10.1016/j.anai.2014.05.001 http://linkinghub.elsevier.com/retrieve/pii/S1081120614002993>.

[8] Koplin JJ, Martin PE, Allen KJ. An update on epidemiology of anaphylaxis in children and adults. Current Opinion in Allergy and Clinical Immunology [Internet]. 2011;11:492–496. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage{\&}an=00130832-201110000-00017>.

[9] Tejedor Alonso MA, Moro Moro M, Múgica García MV. Epidemiology of anaphylaxis. Clinical & Experimental Allergy [Internet]. 2015;45:1027–1039. Available from: <http://doi.wiley.com/10.1111/cea.12418>.

[10] Fineman SM, Bowman SH, Campbell RL, et al. Addressing barriers to emergency anaphylaxis care: from emergency medical services to emergency department to outpatient follow-up. Annals of Allergy, Asthma & Immunology [Internet]. 2015;115:301–305. Available from: <http://dx.doi.org/10.1016/j.anai.2015.07.008 http://linkinghub.elsevier.com/retrieve/pii/S1081120615004548>.

[11] Braganza SC, Acworth JP, Mckinnon DRL, et al. Paediatric emergency department anaphylaxis: different patterns from adults. Archives of disease in childhood [Internet]. 2006;91:159–163. Available from: <http://adc.bmj.com/content/91/2/159.short http://adc.bmj.com/cgi/doi/10.1136/adc.2004.069914 http://www.ncbi.nlm.nih.gov/pubmed/16308410 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2082667>.

[12] Worm M, Francuzik W, Renaudin J-M, et al. Factors increasing the risk for a severe reaction in anaphylaxis: An analysis of data from the european anaphylaxis registry. Allergy [Internet]. 2018; Available from: <https://doi.org/10.1111/all.13380>.

[13] Worm M, Babina M, Hompes S. Causes and risk factors for anaphylaxis. JDDG: Journal der Deutschen Dermatologischen Gesellschaft [Internet]. 2013;11:44–50. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23181736 http://doi.wiley.com/10.1111/j.1610-0387.2012.08045.x>.

[14] Lazar I, Cavari Y, Levitas A, et al. Gastric Drainage in the Treatment of Near-Fatal Food-Induced Anaphylaxis. Pediatric Emergency Care [Internet]. 2017;00:1. Available from: <http://insights.ovid.com/crossref?an=00006565-900000000-98600>.

[15] Kovalchik S. RISmed: Download content from ncbi databases [Internet]. 2017. Available from: <https://CRAN.R-project.org/package=RISmed>.

[16] R Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2017. Available from: <https://www.R-project.org/>.

[17] Stewart WJ, McSweeney SM, Kellett MA, et al. Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. Circulation [Internet]. 1984;70:788–792. Available from: <https://doi.org/10.1161/01.cir.70.5.788>.

[18] Drug allergy: An updated practice parameter. Annals of Allergy, Asthma & Immunology [Internet]. 2010;105:259–273.e78. Available from: <https://doi.org/10.1016/j.anai.2010.08.002>.

[19] Nag DS, Samaddar DP, Kant S, et al. Perianesthetic refractory anaphylactic shock with cefuroxime in a patient with history of penicillin allergy on multiple antihypertensive medications. Brazilian Journal of Anesthesiology (English Edition) [Internet]. 2017;67:217–220. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0104001414001821>.

[20] Baumann A, Studnicska D, Audibert G, et al. Refractory anaphylactic cardiac arrest after succinylcholine administration. Anesthesia and Analgesia. 2009;109:137–140.

[21] Simons KJ, Simons FER. Epinephrine and its use in anaphylaxis: current issues. Current Opinion in Allergy and Clinical Immunology [Internet]. 2010;10:354–361. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20543673 http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage{\&}an=00130832-201008000-00016>.

[22] Simons FER, Ardusso LRF, Bilò MB, et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. World Allergy Organization Journal [Internet]. 2011;4:13–36. Available from: <http://www.waojournal.org/content/4/2/13>.

[23] Lieberman P, Kemp SF, Oppenheimer J, et al. The diagnosis and management of anaphylaxis: An updated practice parameter. Available from: <https://pdfs.semanticscholar.org/ff0c/b81c88a48ecc2087ad9c3d431a50258e6fe7.pdf>.

[24] Muraro A, Roberts G, Worm M, et al. Anaphylaxis: Guidelines from the european academy of allergy and clinical immunology. Allergy [Internet]. 2014;69:1026–1045. Available from: <http://dx.doi.org/10.1111/all.12437>.

[25] Enjeti S, Bleecker ER, Smith PL, et al. Hemodynamic mechanisms in anaphylaxis. Circulatory shock [Internet]. 1983;11:297–309. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6661813>.

[26] Lucas KA, Pitari GM, Kazerounian S, et al. Guanylyl cyclases and signaling by cyclic GMP. Pharmacological reviews [Internet]. 2000;52:375–414. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10977868>.

[27] Omar S, Zedan A, Nugent K. Cardiac Vasoplegia Syndrome: Pathophysiology, Risk Factors and Treatment. The American Journal of the Medical Sciences [Internet]. 2015;349:80–88. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25247756 http://linkinghub.elsevier.com/retrieve/pii/S0002962915301506>.

[28] Schirmer RH, Coulibaly B, Stich A, et al. Methylene blue as an antimalarial agent. Redox Report [Internet]. 2003;8:272–275. Available from: <http://www.tandfonline.com/doi/full/10.1179/135100003225002899>.

[29] Buzato MAS, Viaro F, Piccinato CE, et al. The use of methylene blue in the treatment of anaphylactic shock induced by compound 48/80: experimental studies in rabbits. Shock (Augusta, Ga.) [Internet]. 2005;23:582–587. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15897814>.

[30] Bauer C, Vadas P, Kelly K. Methylene blue for the treatment of refractory anaphylaxis without hypotension. The American Journal of Emergency Medicine [Internet]. 2013;31:753. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0735675713000715>.

[31] Moritoki H, Hisayama T, Takeuchi S, et al. Involvement of nitric oxide pathway in the PAF-induced relaxation of rat thoracic aorta. British Journal of Pharmacology [Internet]. 1992;107:196–201. Available from: <http://doi.wiley.com/10.1111/j.1476-5381.1992.tb14486.x>.

[32] Evora PR, Simon MR. Role of nitric oxide production in anaphylaxis and its relevance for the treatment of anaphylactic hypotension with methylene blue. Annals of Allergy, Asthma & Immunology [Internet]. 2007;99:306–313. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17941276 http://linkinghub.elsevier.com/retrieve/pii/S1081120610605455>.

[33] Kessler MR, Eide T, Humayun B, et al. Spurious pulse oximeter desaturation with methylene blue injection. Anesthesiology [Internet]. 1986;65:435–436. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3767045>.

[34] Heytman M, Rainbird A. Use of alpha-agonists for management of anaphylaxis occurring under anaesthesia: Case studies and review. Anaesthesia. 2004;59:1210–1215.

[35] Da Silva PS, Furtado P. Methylene Blue to Treat Refractory Latex-Induced Anaphylactic Shock. A & A Case Reports [Internet]. 2017;XXX:1. Available from: <http://insights.ovid.com/crossref?an=01720097-900000000-99628>.

[36] Weiss GM, Fandrick AD, Sidebotham D. Successful Rescue of an Adult With Refractory Anaphylactic Shock and Abdominal Compartment Syndrome With Venoarterial Extracorporeal Membrane Oxygenation and Bedside Laparotomy. Seminars in Cardiothoracic and Vascular Anesthesia [Internet]. 2015;19:66–70. Available from: <http://journals.sagepub.com/doi/10.1177/1089253214564192>.

[37] Higgins DJ, Gayatri P. Methoxamine in the management of severe anaphylaxis. Anaesthesia [Internet]. 1999;54:1126. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10540117>.

[38] Oliveira Neto AM, Duarte NM, Vicente WV a, et al. Methylene blue: an effective treatment for contrast medium-induced anaphylaxis. Medical science monitor : international medical journal of experimental and clinical research [Internet]. 2003;9:CS102–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14586280>.

[39] Javeed N, Javeed H, Javeed S, et al. Refractory anaphylactoid shock potentiated by beta-blockers. 1996. pp. 383–384.

[40] Gibbs MW, Kuczkowski KM, Benumof JL. Complete recovery from prolonged cardio-pulmonary resuscitation following anaphylactic reaction to readministered intravenous cefazolin. Acta anaesthesiologica Scandinavica [Internet]. 2003;47:230–232. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12631055>.

[41] Yee KFH, Wasowicz M. Anaphylaxis and cardiac surgery for hypertrophic obstructive cardiomyopathy: a case report and review of anaesthetic management. Anestezjologia Intensywna Terapia [Internet]. 2016;48:252–256. Available from: <https://journals.viamedica.pl/anaesthesiology{\_}intensivetherapy/article/view/47580>.

[42] Allen SJ, Gallagher A, Paxton LD. Anaphylaxis to rocuronium. Anaesthesia [Internet]. 2000;55:1223–1224. Available from: <http://doi.wiley.com/10.1046/j.1365-2044.2000.01798-15.x>.

[43] Schummer C, Wirsing M, Schummer W. The pivotal role of vasopressin in refractory anaphylactic shock. Anesthesia and Analgesia. 2008;107:620–624.

[44] Schummer W, Schummer C, Wippermann J, et al. Anaphylactic shock: is vasopressin the drug of choice? Anesthesiology [Internet]. 2004;101:1025–1027. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15448540>.

[45] Alicia Weissgerber LJ. Methylene Blue for Refractory Hypotension: A Case Report. AANA Journal August [Internet]. 2007;76. Available from: <www.aana.com/aanajournal.aspx>.

[46] Hussain AM, Yousuf B, Khan MA, et al. Vasopressin for the management of catecholamine-resistant anaphylactic shock. Singapore Medical Journal. 2008;49:225–228.

[47] Lango R, Kowalik MM, Klajbor K, et al. High-Volume Hemofiltration as Rescue Therapy for Refractory Shock After Inadvertent Rapid Aprotinin Administration. Journal of Cardiothoracic and Vascular Anesthesia. 2009;23:526–528.

[48] Bickell WH, Dice WH. Military antishock trousers in a patient with adrenergic-resistant anaphylaxis. Annals of Emergency Medicine. 1984;13:189–190.

[49] Avni T, Lador A, Lev S, et al. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis. PloS one [Internet]. 2015;10:e0129305. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26237037 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4523170>.

[50] Di Chiara L, Stazi GV, Ricci Z, et al. Role of vasopressin in the treatment of anaphylactic shock in a child undergoing surgery for congenital heart disease: a case report. Journal of Medical Case Reports [Internet]. 2008;2:36. Available from: <http://jmedicalcasereports.biomedcentral.com/articles/10.1186/1752-1947-2-36>.

[51] Seedat RY, Westhuizen J van der. ORNIPRESSIN FOR THE TREATMENT OF ADRENALINE-RESISTANT ANAPHYLAXIS. Current Allergy and Immunology [Internet]. 2014;27:130–133. Available from: <http://www.panafrican-med-journal.com/content/article/25/136/full/>.

[52] Zaloga GP, Delacey W, Holmboe E, et al. Glucagon reversal of hypotension in a case of anaphylactoid shock. Annals of Internal Medicine. 1986;105:65–66.

[53] Laxenaire MC, Torrens J, Moneret-Vautrin DA. [Fatal anaphylactic shock in a patient treated with beta-blockers]. Annales francaises d’anesthesie et de reanimation [Internet]. 1984;3:453–455. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6151372>.

[54] Raft J, Leclercq M, Longrois D, et al. Récupération hémodynamique et ventilatoire rapide après injection de sugammadex lors d’un choc anaphylactique au rocuronium, réfractaire au traitement conventionnel. Annales Françaises d’Anesthésie et de Réanimation [Internet]. 2012;31:158–161. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0750765811004436>.

[55] Wang ML, Chang CT, Huang HH, et al. Chlorhexidine-related refractory anaphylactic shock: a case successfully resuscitated with extracorporeal membrane oxygenation. Journal of Clinical Anesthesia [Internet]. 2016;34:654–657. Available from: <http://dx.doi.org/10.1016/j.jclinane.2016.07.002>.

[56] Sidebotham D, McGeorge A, McGuinness S, et al. Extracorporeal Membrane Oxygenation for Treating Severe Cardiac and Respiratory Failure in Adults: Part 2—Technical Considerations. Journal of Cardiothoracic and Vascular Anesthesia [Internet]. 2010;24:164–172. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19875307 http://linkinghub.elsevier.com/retrieve/pii/S1053077009003012>.

[57] Imamura T, Dubin A, Moore W, et al. Induction of vascular permeability enhancement by human tryptase: dependence on activation of prekallikrein and direct release of bradykinin from kininogens. Laboratory investigation; a journal of technical methods and pathology [Internet]. 1996;74:861–870. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8642782>.

[58] Brown SG a, Blackman KE, Heddle RJ. Can serum mast cell tryptase help diagnose anaphylaxis? Emergency medicine Australasia : EMA [Internet]. 2004;16:120–124. Available from: <http://doi.wiley.com/10.1111/j.1742-6723.2004.00562.x>.

[59] Wittenberg M, Nassiri M, Francuzik W, et al. Serum levels of 9,11-PGF <sub>2</sub> and apolipoprotein A1 achieve high predictive power as biomarkers of anaphylaxis. Allergy [Internet]. 2017;72:1801–1805. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28378321 http://doi.wiley.com/10.1111/all.13176>.

[60] Tsai C, Slampak-Cindric A. Use of methylene blue in chemotherapy-induced refractory anaphylactic shock. Critical Care Medicine [Internet]. 2016;44:543. Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS{\&}PAGE=reference{\&}D=emed18{\&}NEWS=N{\&}AN=613521808>.

[61] Del Duca D, Sheth SS, Clarke AE, et al. Use of Methylene Blue for Catecholamine-Refractory Vasoplegia from Protamine and Aprotinin. Annals of Thoracic Surgery [Internet]. 2009;87:640–642. Available from: <http://dx.doi.org/10.1016/j.athoracsur.2008.07.017>.

[62] Rodrigues JM, Pazin Filho A, Rodrigues AJ, et al. Methylene blue for clinical anaphylaxis treatment: A case report. Sao Paulo Medical Journal. 2007;125:60–62.

[63] Zweizig S, Roman LD, Muderspach LI. Death from Anaphylaxis to Cisplatin: A Case Report. Gynecologic Oncology [Internet]. 1994;53:121–122. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0090825884710985>.

[64] Stocche RM, Garcia LV, Reis MPD, et al. Uso do azul de metileno no tratamento de choque anafilático durante anestesia: relato de caso. Revista Brasileira de Anestesiologia. 2004;54:809–814.

[65] Liu PY, Lee CH, Lin LJ, et al. Refractory anaphylactic shock associated with ketoconazole treatment. Annals of Pharmacotherapy. 2005;39:547–550.

[66] Gouel-Chéron A, Chaisemartin L de, Jönsson F, et al. Low end-tidal CO 2 as a real-time severity marker of intra-anaesthetic acute hypersensitivity reactions. British Journal of Anaesthesia [Internet]. 2017;119:908–917. Available from: <https://doi.org/10.1093/bja/aex260>.

# Figures and Tables

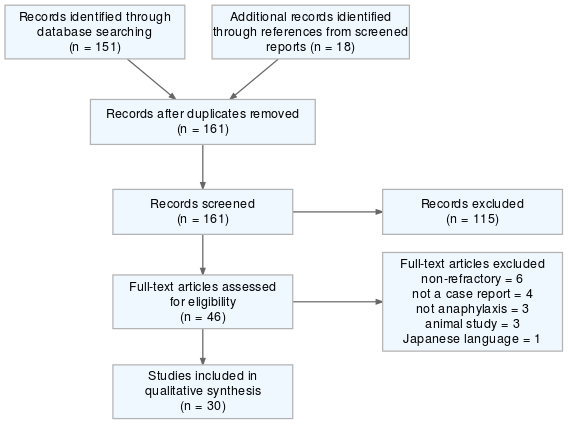


Figure 1 The PRISMA flowchart for included sources. The additional 18 papers were included as a result of screening the referenced sources in the initial 151 screened papres. We screened the pubmed database using the search terms ‘refractory anaphylaxis’ with the help of the RISmed package for R. Only Case reports were included.

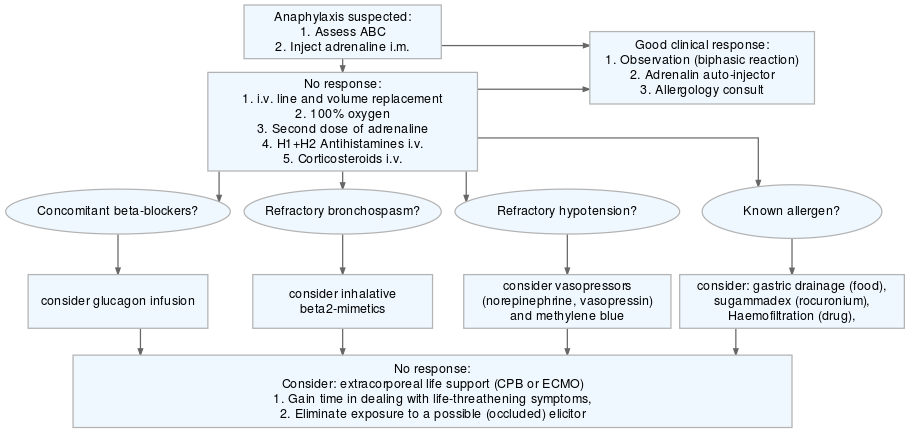


Figure 2 The algorithm for refractory anaphylaxis management

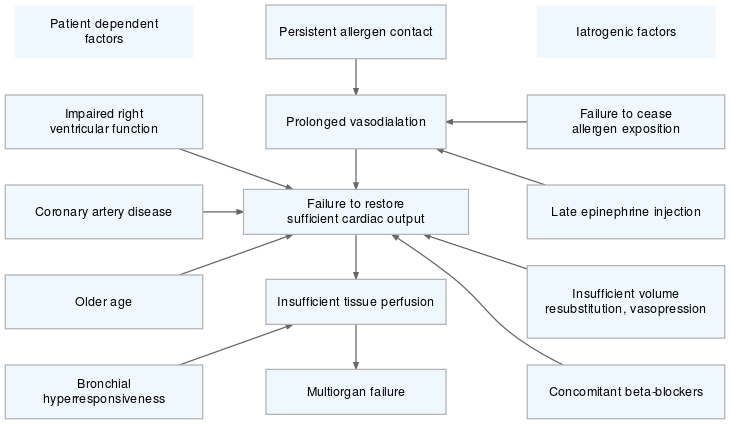


Figure 3 The patophyisiology of refractory anaphylaxis. The proposed mechanisms of anaphylaxis reaction non responding to therapy are divided into patient dependent and iatrogenic factors.

Table 1 Summary of the refractory anaphylxis cases included into the analysis according to concomitant diseases (arterial hypertension and diabetes (either type I or II) expressed as a fraction of included cases). TTR - median time to reaction after exposure to the suspected allergen expressed in minutes. Age is a mean value across evaluated cases in each group.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Sex | n | Age | TTR [min] | Hypertension [%] | Diabetes [%] |
| male | 21 | 57.7 | 5 | 47.6 | 19 |
| female | 21 | 51.6 | 5 | 28.6 | 4.8 |

Table 2 Refractory anaphylaxis cases broken down according to the elicitor of the reaction. Male - percentage of male cases to all cases ina griven group. Perioperative - fraction of anaphylaxis episode that happened either during surgery or in temporal proximity to a surgical procedure. The eliciting drugs were: cefuroxime, chlorhexidine, protamine, aprotinin, succinylocholine, gelofusine, recuronium, chemotherapy, amoxicillin, ketokonazole, metamizole

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Elicitor | No. cases | Age | Male [%] | Perioperative [%] |
| contrast | 6 | 55.3 [44.5 - 66.1] | 66.7 | 33.3 |
| drug | 22 | 54.5 [47.7 - 61.3] | 45.5 | 81.8 |
| other | 6 | 40 [25.8 - 54.2] | 33.3 | 50.0 |
| unknown | 8 | 65.5 [49.2 - 81.8] | 37.5 | 87.5 |

Table 3 List of papers and anaphylaxis cases included in the study, summarizing their elicitors, and effective therapy interventions. Cases where the reaction was fatal and all therapeutic options fialed were indicated with the asterix (\*). Other cases resulted with full recovery of the patient.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Elicitor | Age | Sex | Setting | What.helped | Conc..diseases | Vasopressors |
| Silva [35] | latex | 49 | woman | OP | methylene blue |  | yes |
| Nag [19] | cefuroxime | 46 | woman | OP | vasopressors | HT | yes |
| Yee [41] | chlorhexidine | 40 | woman | OP | ECLS |  | yes |
| Lazar [14] | milk | 15 | man | not hospital | drainage |  | no |
| Tsai [60] | bendamustine | 67 | male | chemo | methylene blue |  | yes |
| Weiss [36] | unknown | 61 | male | OP | ECLS |  | yes |
| Oliviera [38] | contrast | 57 | woman | unknown | methylene blue |  | no |
| Oliviera [38] | contrast | 48 | woman | unknown | methylene blue |  | no |
| Oliviera [38] | contrast | 53 | man | unknown | methylene blue |  | no |
| Duca [61] | protamine | 72 | man | OP | methylene blue | HT, DM | yes |
| Duca [61] | aprotinin | 72 | woman | OP | methylene blue | HT | yes |
| Rodrigues [62] | unknown | 23 | woman | OP | methylene blue |  | no |
| Bauer [30] | menses | 43 | woman | not hospital | methylene blue |  | no |
| Baumann [20] | succinylocholine | 74 | woman | OP | \* | HT | yes |
| Baumann [20] | succinylocholine | 49 | man | OP | \* | HT | yes |
| Heytman [34] | gelofusine | 55 | man | OP | vasopressors |  | yes |
| Heytman [34] | unknown | 66 | man | OP | vasopressors |  | yes |
| Higgins [37] | unknown | 61 | woman | unknown | vasopressors |  | no |
| Allen [42] | rocuronium | 21 | woman | unknown | ECLS | HT | no |
| Zaloga [52] | contrast | 75 | man | CT | glucagon | HT | no |
| Zweizig [63] | platin | 58 | woman | chemo | \* |  | no |
| Lexenaire [53] | contrast | 47 | man | OP | \* | HT | yes |
| Bickell [48] | SIT | 39 | woman | ambulatory | vasopressors |  | no |
| Javeed [39] | contrast | 52 | man | OP | glucagon | HT | no |
| Stocche [64] | dipirone | 53 | man | OP | methylene blue |  | no |
| Liu [65] | ketakonazole | 72 | woman | ambulatory | epi infusion |  | no |
| Schummer [43] | aprotinin | 63 | woman | OP | vasopressors |  | yes |
| Schummer [43] | aprotionin | 53 | man | OP | vasopressors |  | yes |
| Schummer [43] | metamizol | 48 | man | OP | vasopressors | HT, DM | yes |
| Schummer [43] | metamizol | 47 | man | OP | vasopressors |  | yes |
| Schummer [43] | metamizol | 73 | man | OP | vasopressors |  | yes |
| Schummer [43] | gelatin | 43 | woman | OP | vasopressors |  | yes |
| Schummer [44] | gelatin | 59 | woman | OP | vasopressors | HT | yes |
| Weissgerber [45] | unknown | 79 | man | OP | methylene blue | HT, DM | no |
| Hussain [46] | unknown | 24 | woman | OP | vasopressors |  | yes |
| Lango [47] | aprotinin | 66 | man | OP | hemofiltration | HT | yes |
| Raft [54] | recuronium | 51 | man | OP | sugammadex | HT, DM | no |
| Wang [55] | chlorhexidine | 54 | man | OP | ECLS | HT | no |
| Gibbs [40] | cefazolin | 34 | woman | OP | ALS | HT, DM | no |
| Gouel-Cheron [66] | unknown | 90 | woman | OP | \* |  | no |
| Gouel-Cheron [66] | unknown | 76 | man | OP | \* |  | no |
| Gouel-Cheron [66] | unknown | 67 | woman | OP | \* |  | no |

Table 4 Fatal anaphylaxis cases, not responsive to any form of therapy.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | - |
| contrast | 47 | man | OP | - | - | 0.6 | 2.0 | + |
| unknown | 90 | woman | OP | - | - | 8.0 | 0.0 | - |
| unknown | 76 | man | OP | - | - | 20.0 | 0.0 | + |
| unknown | 67 | woman | OP | - | - | 1.3 | 0.5 | + |