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Refractory Anaphylaxis: A New Entity for Severe Anaphylaxis

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Abstract

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Anaphylaxis reactions lie on a spectrum of severity, ranging from relatively mild lower respiratory involvement (depending on the definition of anaphylaxis used) to more severe reactions that are refractory to initial treatment with epinephrine and may rarely cause death. A variety of grading scales exist to characterize severe reactions, but there is a lack of consensus about the optimal approach to define severity. More recently, a new entity called refractory anaphylaxis (RA) has emerged in the literature, characterized by the persistence of anaphylaxis despite initial epinephrine treatment. However, slightly different definitions have been proposed to date. In this Rostrum, we review these definitions as well as data relating to epidemiology, elicitors, risk factors, and management of RA. We propose a need to align the different definitions for RA, to improve epidemiological surveillance, advance our understanding of the pathophysiology of RA, and optimize management strategies to reduce morbidity and mortality.

Keywords

Food allergy; Anaphylaxis; Epinephrine; Auto-injector; Emergency management; Intensive care; Refractory

Anaphylaxis is described by the World Allergy Organization as “a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in airway, breathing, and/or the circulation, and may occur without typical skin features or circulatory shock being present.”¹ It is the most severe clinical presentation of acute systemic allergic reactions, but evidence suggests that the majority of less severe anaphylaxis reactions resolve spontaneously without treatment.^{2–4} Significant underuse of epinephrine to treat anaphylaxis in medical settings and the community is well documented.² Large case series, including the European Anaphylaxis Registry (Network for Online Registration of Anaphylaxis [NORA]), report that only less than 20% of anaphylaxis reactions are treated with epinephrine.^{3,4} Despite this, fatal anaphylaxis remains a very rare event with a fatality rate ranging from 0.5 to 1 death/million person-years.^{5,6} Consistent with these data, a recent systematic review and meta-analysis found that around 90% of anaphylaxis events respond to a single dose of epinephrine.⁶

However, 2% to 3% of anaphylaxis reactions do not respond to 2 epinephrine doses,⁶ and these reactions are unpredictable. Our current inability to identify those at greatest risk of more severe reactions remains one of the biggest evidence gaps in allergy.^{7,8} One contributory factor is the wide variation in how best to define severity, with different definitions used in the literature and even inconsistency in applying the same severity grading system by different authors.^{9,10} Work in this area is often focused on fatal anaphylaxis, perhaps because there is no question over severity with respect to these tragic events. However, it is difficult to identify predictors of fatal reactions because fatalities are very rare and details often lacking in terms of the circumstances leading up to the fatal event.^{5,11,12} Near-fatal anaphylaxis should be an easier entity in terms of identifying potential risk factors because it is more common and easier to investigate (owing to the ability to capture accurate data about the reaction onset [triggers, risk factors], treatment, and progression). However, there is a paucity of data on near-fatal anaphylaxis. Among 3,510

anaphylaxis cases documented in the Allergy-Vigilance Network (2002–2022), there were 45 near-fatal events and 25 fatalities.¹³ In the United Kingdom, intensive care unit (ICU) admissions for food anaphylaxis are almost 10 times higher than fatal food anaphylaxis.¹⁴ However, ICU admission is not synonymous with near-fatal anaphylaxis. In the United States, Motosue et al¹⁵ reported an ICU admission rate of 5.3% among 38,695 patients of all ages seen in emergency departments for food anaphylaxis (2005–2014); 2,057 (5.3%) were admitted to the ICU, but only 174 (0.45%) were classified as having a near-fatal episode. Ramsey et al¹⁶ described 1,989 children admitted between 2010 and 2015 to 131 ICUs in North America with anaphylaxis, of whom 1,631 had a primary diagnosis of anaphylaxis; only 5% had hypotension and 19% required intubation, which in the context of a median admission duration of 19 hours, implies that the majority were admitted for observation rather than critical care management. Similarly, the discord between ICU admission and reaction severity was documented in a case series of 166 children admitted to an ICU in France (2003–2013),¹⁷ where a quarter of cases were only categorized as grade 2 reactions (according to Ring and Messmer classification, ie, nonsevere anaphylaxis), and only 52 of 134 (39%, data missing for 32 cases) were treated with 3 or more doses of adrenaline.¹⁸

Whereas any epinephrine is not a good indicator of severity,² there is increasing recognition that a sub-optimal response to epinephrine when given appropriately at onset of anaphylaxis can be a useful indicator of severity.^{19–22} Arguably, this circumvents the issues over what symptoms constitute a severe reaction and how these might be assigned a severity grade (and with which grading system), because nonsevere reactions would not be resistant to epinephrine treatment. These events are often referred to in the literature as refractory anaphylaxis (RA), although there are subtle differences between the proposed definitions (Table I). Definitions used by the Resuscitation Council UK (RCUK), World Allergy Organization Consensus on Definition of Food Allergy Severity (DEFASE), and for an analysis of data held by NORA all propose a suboptimal response to at least 2 doses of intramuscular (IM) epinephrine as indicative of RA.^{20–22} Another definition proposed by a 21-member panel of experts in the United States using Delphi methodology proposed a definition of anaphylaxis “that must be treated with three or more appropriate doses of epinephrine (or initiation of an intravenous [IV] epinephrine infusion) in addition to symptom directed medical management, such as an IV fluid bolus for hypotension or supplemental oxygen for hypoxia or shock,”¹⁹ although subsequent clarification with the lead author (T. Dribin, personal communication) noted that mention of additional therapy was to “ensur [e] that patients receive appropriate resuscitative efforts before reactions are classified as refractory” rather than imply a requisite for assigning a label of RA. The Consortium for Food Allergy Research (CoFAR) recently proposed that RA might be considered by a need for more than 3 doses of IM epinephrine,²³ that is, 1 more than the other definitions proposed.

A key distinction, perhaps, is the purpose of the RA definition. The purpose of the RCUK definition²¹ was to guide awareness of a more severe anaphylaxis event (suboptimal response to 2 epinephrine doses, to which at least 98% of anaphylaxis events would usually respond) and, thus, act as a trigger for treatment escalation and calling for additional specialist help—rather than to be used for retrospective analyses.

EPIDEMIOLOGY OF RA

We undertook a review of studies reporting 3 or more individuals treated with 3 or more doses of epinephrine (Table II).^{18,20,24–32} RA (by this definition) occurs in around 2% of anaphylaxis reactions. In a systematic review of 151 individuals with anaphylaxis who received 3 or more epinephrine doses, at meta-analysis, this was equivalent to a rate of 2.2% (95% CI 51.1%–4.1%) of anaphylaxis events.⁶ This is higher than the 0.37% rate reported by NORA, although this database also includes non-anaphylaxis reactions (depending on the definition used).²⁰ RA may be less frequent in children.²⁰ Medications were the most common elicitor in both adults and children, with most reactions occurring in the hospital and mainly in the perioperative setting. Antibiotics and radiocontrast media were the most common drugs involved in both NORA and a French cohort of 52 children admitted to the ICU.^{18,20} Food allergens (particularly peanut, cows' milk, and tree nuts) were the second most common triggers.^{17,18,20} Notably, among 52 children admitted to a French ICU for RA (14 food-related), 6 occurred during diagnostic oral food challenges.¹⁸

MANAGEMENT OF RA

Data from the U.K. Fatal Anaphylaxis Registry indicate that one-third of deaths from food anaphylaxis (in the community setting) occur despite timely administration of epinephrine.³³ Evidence from case series^{34,35} and animal models^{36,37} of severe anaphylaxis suggest that refractory reactions may be due to a combination of³⁸:

- Delayed or insufficient delivery of epinephrine, including hypovolemia that adversely affects systemic distribution
- Ongoing release of inflammatory mediators
- Rarely, tachyphylaxis to further epinephrine administration.

On this basis, the RCUK Anaphylaxis working group developed an approach to identify reactions that need more intensive management and seek appropriate help early—hence, the rationale to define RA as a suboptimal response to 2 rather than 3 doses of epinephrine. The RCUK algorithm for RA (Figure 1) specifically includes strategies to ensure effective airway management and tissue oxygenation and optimize systemic delivery of epinephrine.³⁹ The cornerstone of this is to initiate a low-dose, IV epinephrine infusion while simultaneously giving sufficient fluid resuscitation (which can amount to 3–5 L in adults) to counteract the massive fluid shifts that occur in anaphylaxis and support delivery of epinephrine at a tissue level.²¹ This recommendation is based on evidence from case reports of severe human anaphylaxis^{34,35} and animal models⁴⁰ that suggest that low-dose IV epinephrine infusions may be more efficient in the treatment of anaphylaxis than the use of other routes of administration and/or IV bolus therapy. In terms of second-line vasopressors, there is insufficient evidence to recommend any particular vasopressor (ie, norepinephrine, vasopressin, or meta-raminol) at this time.⁴¹ A reasonable approach is to start additional vasopressors, preferably via a central line, in patients who continue to be hypotensive despite maximal epinephrine and fluid resuscitation. Metaraminol is commonly used in many countries in perioperative settings, but it is unlikely to be effective in reactions refractory to IV epinephrine, given their shared pharmacological effects. Glucagon is

recommended as adjunct therapy in patients with RA on concomitant betablockers.³⁹ These gaps in evidence might be better addressed if a consensus on defining RA and systematic data collection of such cases could be implemented.

RISK PREDICTION

It is challenging for clinicians to identify allergic patients at risk of more severe reactions, and in many cases, the proposed risk factors (such as any asthma) are so common that they lack any real clinical utility.⁷ This results in food-allergic individuals often managed as being at equal risk of severe and even fatal reactions—causing unnecessary anxiety, excessive dietary restriction, and reduced health-related quality of life.⁷

Because RA is more common than near-fatal and fatal anaphylaxis, using this outcome may better define specific risk factors for severity—although for this to happen constructively, there needs to be consensus on how to define RA. Existing data confirm that the most common cause of RA is medication (Table II). An analysis of data from the EAR reported a variety of potential risk factors (including asthma and malignant disease) at univariate analysis, but unfortunately, the low number of cases identified (n = 42) precluded a suitably powered multivariate analysis to be undertaken to control for confounding factors (eg, the triggering allergen).²⁰ No risk factors were identified in a cohort of 52 children with RA in France, although hypotonia at presentation (related to the reaction) was noted to be associated with a higher risk of RA.¹⁸

CONCLUSIONS

Anaphylaxis is a highly dynamic, potentially life-threatening emergency condition that requires early recognition. Most reactions respond to first-line treatment with IM epinephrine; reactions that do not require urgent treatment escalation. A global consensus on how best to define RA may reduce morbidity and mortality by improving the recognition of RA, particularly by those with less experience in managing anaphylaxis. In addition, an aligned definition of RA applied across multiple cohorts may help identify predictors of more severe reactions as well as inform optimal second-line management of more severe anaphylaxis events.

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Abbreviations used

EAR	European Anaphylaxis Registry
ICU	Intensive care unit
IM	Intramuscular
IV	Intravenous
RA	Refractory anaphylaxis
RCUK	Resuscitation Council United Kingdom

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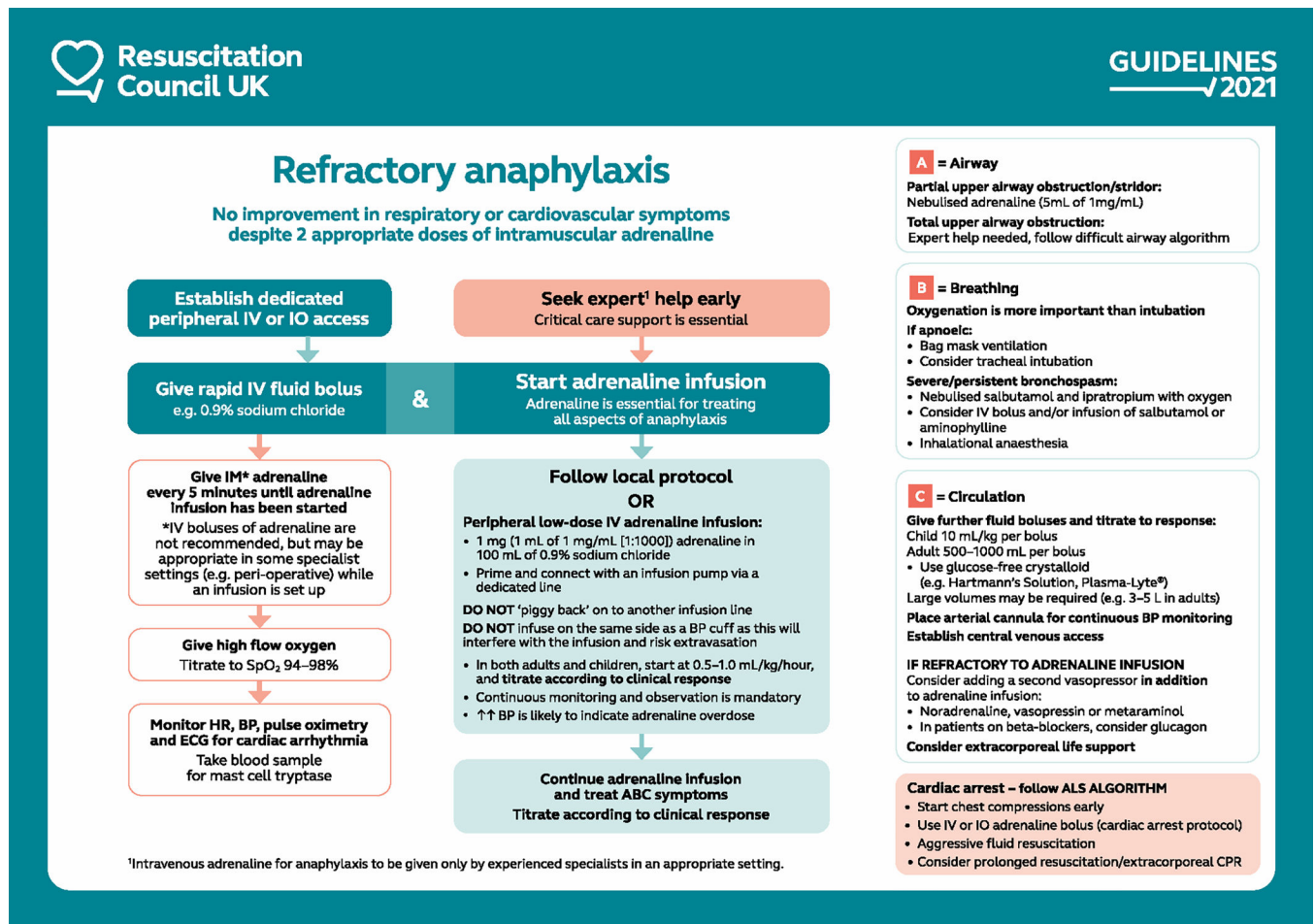


FIGURE 1.

RCUK algorithm for RA. IO, intraosseus. Reprinted with permission.³⁹

TABLE I.

Current definitions of RA

Source	Definition of RA
21-member Expert Panel (US) ¹⁹	“Anaphylaxis that must be treated with three or more appropriate doses of epinephrine (or initiation of an intravenous epinephrine infusion) in addition to symptom directed medical management, such as an intravenous fluid bolus for hypotension or supplemental oxygen for hypoxia or shock.”
European Anaphylaxis Registry (NORA) ²⁰	“Anaphylaxis which, despite treatment with at least two doses of minimum 300mcg adrenaline [epinephrine], does not achieve normalization of symptoms.”* *ie, persistence of significant hypoxia, hypotension, confusion, collapse and loss of consciousness, or incontinence.
Resuscitation Council UK ²¹	“Anaphylaxis requiring ongoing treatment* despite two (appropriate) doses of intramuscular adrenaline [epinephrine].” *ie, further epinephrine is indicated, due to suboptimal improvement in respiratory and/or cardiovascular symptoms.
Consortium for Food Allergy Research (CoFAR) ²³	Lower respiratory symptoms (eg, throat tightness with stridor, wheezing, chest tightness, dyspnea, or cough) associated with a requirement for supplemental oxygen and refractoriness to short-acting bronchodilator treatment (including 1M epinephrine)* OR Respiratory compromise requiring mechanical support OR Reduced blood pressure with associated symptoms of end-organ dysfunction (eg, hypotonia (collapse) and syncope) *Examples of refractoriness could include continuous albuterol nebulizer or epinephrine IV infusion or > 3 IM epinephrine injections.

TABLE II.

Main findings of studies reporting RA (treated with 3+ epinephrine doses)*

Study	Location	n	Elicitors	Age	% Male	Main findings
Schummer et al, 2008 ²⁴	Germany	6	Perioperative drugs 6 of 6	6 adults	66	Vasopressin (with fluid support) successful in managing RA.
Järvinen et al, 2008 ²⁵	United States	6	Foods 6 of 6	6 children Mean age: 6 y	-	PMHx of asthma in 6/6. Peanut is a common cause of RA
Brown et al, 2013 ²⁶	Australia, EDs	45	Oral drugs 16 of 45 Foods 12 of 45 Insect sting 10 of 45	1 child, 44 adults Mean age: 44 y	51	Oral medicines are a common cause of RA. Medication (both oral and injected) is associated with severe reactions (OR ~4). Asthma or COPD associated with hypoxemia (OR 3). Heart disease, diabetes, hypertension, and associated medication are not risk factors after correcting for confounding by age.
Campbell et al, 2015 ²⁷	United States, EDs	9	-	-	-	The overall rate of ≥ 3 epinephrine doses was 1.5%.
Tsuang et al, 2018 ²⁸	United States	5	Foods 5 of 5	5 children	-	-
Anvari et al, 2019 ²⁹	United States	5	-	5 children	-	The overall rate of ≥ 3 epinephrine doses was 1.8%.
Gabrielli et al, 2019 ³⁰	Canada, EDs	48	-	-	-	The overall rate of ≥ 3 epinephrine doses was 1.4%.
Francuzik et al, 2019 ²⁰	Europe, registry	42	Drugs 21 of 42 Foods 9 of 42 Insect sting 8 of 42	Mean age: 41 y	21/42	Drugs are the main triggers for RA, with most events occurring in perioperative settings. Age was not a risk factor for RA.
Liu et al, 2020 ³¹	United States, EDs	16	-	-	-	The overall rate of ≥ 3 epinephrine doses was 3.7%.
Alviani et al, 2020 ³²	United Kingdom	4	Diagnostic OFC for food allergy 4 of 4	4 children	50	Low-dose IV epinephrine is well-tolerated and effective.
Pouessel et al, 2023 ¹⁸	France, PICU admission	52	Drugs 28 of 52 Foods 14 of 52	52 children Mean age: 8.9 y	50	Most reactions occur in hospital (71%), mainly perioperatively (40%). Rescue treatment with IV epinephrine infusion and fluid therapy is suboptimal.

COPD, Chronic obstructive pulmonary disease; EDs, emergency departments; OR, odds ratio; PICU, Pediatric Intensive Care Units; PMHx, past medical history.

* Only studies reporting ≥ 3 cases are included.