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Management of Refractory Anaphylaxis: An Overview of Current Guidelines

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ABSTRACT

In this review, we compare different refractory anaphylaxis (RA) management guidelines focusing on cardiovascular involvement and best practice recommendations, discuss postulated pathogenic mechanisms underlining RA and highlight knowledge gaps and research priorities. There is a paucity of data supporting existing management guidelines. Therapeutic recommendations include the need for the timely administration of appropriate doses of aggressive fluid resuscitation and intravenous (IV) adrenaline in RA. The preferred second-line vasopressor (noradrenaline, vasopressin, metaraminol and dopamine) is unknown. Most guidelines recommend IV glucagon for patients on beta-blockers, despite a lack of evidence. The use of methylene blue or extracorporeal life support (ECLS) is also suggested as rescue therapy. Despite recent advances in understanding the pathogenesis of anaphylaxis, the factors that lead to a lack of response to the initial adrenaline and thus RA are unclear. Genetic factors,

Abbreviations: AAAAI/ACAAI, American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology; AAGBI, Association of Anaesthetists of Great Britain and Ireland; ANZCA/ANZAAG, Australian and New Zealand College of Anaesthetists/Australian and New Zealand Anaesthetic Allergy group; ASA, American Society of Anesthesiologists; ASCIA, Australian Society of Clinical Immunology and Allergy; BSA/ASBAI, Brazilian Society of Anesthesiology/Brazilian Association of Allergy and Immunology; CI, confidence interval; DGAKI, German Society for Allergology and Clinical Immunology; EAACI, European Academy of Allergy and Clinical Immunology; IAP, Indian Academy of Paediatrics; IM, intramuscular; IO, intraosseous; ISPAR, International Suspected Perioperative Allergic Reaction; IV, intravenous; JSA, Japanese Society of Anesthesiologists; NAP6, National Audit Project 6; NCMSA, National Center for Medical Service Administration; NMBA, Neuromuscular Blocking Agent; PA, perioperative anaphylaxis; PHR, perioperative hypersensitivity reaction; RA, refractory anaphylaxis; RCUK, Resuscitation Council of United Kingdom; SEAIC/SEDAR, Spanish Society of Allergy and Clinical Immunology/Spanish Anaesthesia Society; SFAR/SFA, Société Française d'Anesthésie et Réanimation/Société Française d'Allergologie; SFMU/SFA/GFRUP, Société Française de Médecine d'Urgence/Société Française d'Allergologie/Groupe Francophone de Réanimation et d'Urgences Pédiatriques; SSAI, Scandinavian Society of Anaesthesiology and Intensive care medicine; WAO, World Allergy Organization.

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such as deficiency in platelet activating factor-acetyl hydrolase or hereditary alpha-tryptasaemia, mastocytosis may modulate reaction severity or response to treatment. Further research into the underlying pathophysiology of RA may help define potential new therapeutic approaches and reduce the morbidity and mortality of anaphylaxis.

Key messages

- Titrated diluted intravenous adrenaline infusion and adequate fluid resuscitation are the cornerstones of RA treatment.
- There are no high-quality studies to support the choice of second-line treatments in RA.
- Most guidelines recommend noradrenaline for persistent hypotension despite adequate treatment.

1 | Introduction

Large case series report that less than 20% of anaphylaxis reactions are treated with adrenaline [1, 2]. Patel et al. [3] recently undertook a systematic review and meta-analysis and found that around 90% of anaphylaxis events respond to a single dose of adrenaline. These data suggest that the majority of anaphylaxis reactions resolve spontaneously or with just a single dose of adrenaline. However, life-threatening anaphylaxis does occur, with an estimated mortality of 0.5%–1%, up to 5% in the perioperative setting [4, 5]. Severe anaphylaxis is unpredictable [6–8]. All international guidelines recommend that adrenaline is the first-line anaphylaxis therapy and should be repeated for persistent or worsening signs combined with fluid resuscitation.

Recently, an entity of treatment-refractory anaphylaxis (RA) has been proposed in the literature, although slightly different definitions have been proposed [9] (Table 1). The Resuscitation Council United Kingdom (RCUK) defines RA as an anaphylaxis which fails to adequately respond to 2 doses of IM adrenaline, the aim being that this scenario should immediately prompt escalation in terms of both treatment and the need for staff with appropriate expertise in managing severe reactions [10]. This is similar to that used in an analysis of data from the European Anaphylaxis Registry [11] and also very close to the definition proposed by a 19-member panel of experts in the United States (US) using Delphi methodology, which suggested RA is a reaction 'treated with 3 or more appropriate doses of adrenaline (or initiation of an intravenous [IV] adrenaline infusion) in addition to symptom directed medical management' [12].

The Consortium for Food Allergy Research (CoFAR) recently proposed that RA might be considered by a need for >3 doses of IM adrenaline, that is one more than the previous definitions [13]. However, one factor which led to this proposal was the scenario whereby someone might receive an initial adrenaline dose but then develop further symptoms later which require further adrenaline (S. Chinthrajah, personal communication).

The International Suspected Perioperative Allergic Reaction (ISPAR) group considered that anaphylaxis in the perioperative setting was refractory 'after 10 min where there is a sustained insufficient response despite adequate dosing of adrenaline and fluids' which is akin to the administration of 2–3 doses of adrenaline during the first 10 min of anaphylaxis management [14].

An analysis from the European Anaphylaxis Registry recently reported 11,596 cases of anaphylaxis, of which 268 (2.3%) were treated with at least two doses of adrenaline; 42 (0.36%) were considered refractory to two adrenaline doses [11]. In contrast, a meta-analysis reported an estimated rate of 2.2% (95% CI, 1.1%–4.1%) of 6111 anaphylaxis events which were treated with ≥3 adrenaline doses [3]. This difference may be due to the inclusion of different cohorts in the latter study. In the European Anaphylaxis Registry analysis, the rate of RA was 9.3 times more common in the medical compared to the community setting; the majority of cases occurred in the perioperative setting [11]. Anaphylaxis in the perioperative setting is frequently more severe than that in the community, perhaps because of concurrent cardiovascular compromise induced by the anaesthetic drugs [15]. The case fatality rate for perioperative anaphylaxis is estimated between 1.4% and 4.8%; in contrast, that for food anaphylaxis is much lower than 1% [15].

Although adrenaline is the cornerstone of anaphylaxis treatment (IM for most settings, although in the perioperative setting, guidelines recommend the IV route) [14, 16], the management of RA is less clear. RA can occur in the emergency setting, in perioperative settings, but also during food challenges [5, 17].

Optimal treatment requires both prompt recognition and appropriate management. The need for adrenaline (via an IV infusion) and fluid resuscitation have been flagged by recent publications [9–11, 14–16, 18]. The preferred choice of second-line RA treatments in patients with cardiovascular compromise is unclear owing to the lack of high-quality studies both observational and randomised clinical trials. In patients with a predominant respiratory compromise (severe bronchospasm and severe laryngeal oedema), the use of short-acting bronchodilator treatment (including adrenaline) or of inhaled adrenaline is recommended in most guidelines but not detailed. Despite promising advances in the knowledge of anaphylaxis pathophysiology, mechanisms leading to RA are not well known.

Allergists, emergency physicians, intensivists, paediatricians and anaesthetists need to be aware of RA management, even if this is a rare event.

Whereas a previous article focused on the need for a consensus on RA definition, in this narrative (nonsystematic) review on published guidelines regarding the management of

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TABLE 1 | Current definitions of refractory anaphylaxis.

Source	Location	Definition of refractory anaphylaxis
19-Member expert panel (USA) [12]	Non defined	'Anaphylaxis that must be treated with three or more appropriate doses of adrenaline (or initiation of an intravenous adrenaline 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 [11]	Non defined	'Anaphylaxis which, despite treatment with at least two doses of minimum 300 mcg adrenaline, does not achieve normalization of symptoms*' *That is, persistence of significant hypoxia, hypotension, confusion, collapse and loss of consciousness or incontinence
RCUK [10]	Non defined	'Anaphylaxis requiring ongoing treatment* despite two (appropriate) doses of intramuscular adrenaline' *That is, further adrenaline is indicated, due to suboptimal improvement in respiratory and/or cardiovascular symptoms
CoFAR [13]	Non defined	Lower respiratory symptoms (e.g., throat tightness with stridor, wheezing, chest tightness, dyspnoea or cough) associated with a requirement for supplemental oxygen and refractoriness to short-acting bronchodilator treatment (including IM adrenaline)* OR Respiratory compromise requiring mechanical support OR Reduced blood pressure with associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse) and syncope) *Examples of refractoriness could include continuous albuterol nebuliser or adrenaline IV infusion or >3 IM adrenaline injections
ISPAR [14]	Perioperative setting	Anaphylaxis is refractory 'after 10 min where there is a sustained insufficient response despite adequate dosing of adrenaline and fluids'

Abbreviations: CoFAR, Consortium for Food Allergy Research; IM, intramuscular; ISPAR, International Suspected Perioperative Allergic Reaction; IV, intravenous; RCUK, Resuscitation Council United Kingdom; USA, United States of America.

difficult-to-treat anaphylaxis, we identify slightly different approaches according to community or perioperative settings and knowledge gaps in RA management, we discuss postulated pathogenic mechanisms underlining RA and highlight recent research which might yield potential new therapeutic interventions [9].

2 | Methods

We have focused this review on adrenaline administration, fluid therapy and second-line medication used for cardiovascular compromise (vasopressors, glucagon, methylene blue and extracorporeal life support [ECLS]). We did not include second- or third-line medication used to treat respiratory compromise. We performed a search of PubMed online databank based on English titles and abstracts from studies in humans, from 2002 to October 2023. We combined the terms "anaphylaxis", "immediate hypersensitivity", "adrenaline", "epinephrine", "refractory", "fatal", and "death", "perioperative", 'fluid therapy", "vascular filling", "vasopressin", "vasopressors", "noradrenaline", "methylene blue", "glucagon", "extracorporeal life support", "guidelines", "recommendations", "meta-analysis", "review", "task force". The identification of the articles was performed independently by two authors (GP and CT). We also reviewed the reference lists of included articles to identify additional relevant articles.

3 | Results

3.1 | Treatment of Refractory Anaphylaxis

3.1.1 | Adrenaline Is the Cornerstone of Anaphylaxis Treatment

IM adrenaline is the first-line anaphylaxis treatment in all current guidelines for the treatment of anaphylaxis in the community or hospital setting [10, 14, 16, 19–36] (Tables 2 and 3).

IM adrenaline is generally well-tolerated, in contrast to the IV route, where side effects are more common (sometimes due to dosing errors), including life-threatening arrhythmia when used by personnel not familiar with administering IV adrenaline [37, 38]. For this reason, the IV route is not recommended for the initial treatment of anaphylaxis in community and hospital settings except the perioperative setting. In the perioperative setting, adrenaline is always administered by personnel appropriately trained in the preparation and administration of adrenaline via the IV route, in well-monitored patients and thus the IV route is recommended [14, 16, 30–35] (Tables 2 and 3). In addition, the absorption of IM adrenaline is slower than by IV route, less predictable and dependent on adequate circulation which is more likely to be compromised in perioperative anaphylaxis [16, 23].

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TABLE 2 | Guidelines for the use of adrenaline during anaphylaxis in adults.

Source	First adrenaline injection	Adrenaline treatment in refractory anaphylaxis
Anaphylaxis in the community		
Australia-New Zealand (ASCIA) [29]	IM, 10 μg/kg (max 0.5 mg per dose), repeat every 5 min if needed Use AAI if available or ampoule/syringe	IV infusion if no response after 2–3 adrenaline doses, two protocols (prehospital settings and emergency departments/tertiary hospital settings), starting 0.1 μg/kg/min, titrate rate up or down to response and side effects IV bolus are not recommended
Europe (EAACI) [20]	IM, 0.3 mg using an AAI (0.5 mg may be considered if the adult is overweight or has experienced a previous life-threatening anaphylaxis), repeat after 5–10 min if needed	Not documented
World Allergy Organization (WAO) [21]	IM, 10 μg/kg per dose (maximum of 0.5 mg for adults), repeat if needed every 5–15 min	Refer to protocol for low-dose IV adrenaline infusion developed by Brown et al. and used as part of anaphylaxis guidelines in Spain, Australia and New Zealand
China (NCMSA) [28]	IM, 10 μg/kg (max 0.5 mg), every 5–15 min if no response Grade 2–3: IV may be considered for IV bolus if they have already an IV access and are being monitored (ICU, perioperative setting) Grade 2: 10–50 μg Grade 3: 0.1–0.2 mg Grade 4: 1 mg	Repeat IV bolus every 3–5 min (grade 4), every 1–2 min (grade 2–3) Grade 2–3: if no response after 2–3 bolus IV, start IV infusion Grade 4: start IV infusion when patients begin to stabilise IV infusion: 0.05–0.5 μg/kg/min
France (SFMU/SFA/GFRUP) [25]	IM, 10 μg/kg (maximum 0.5 mg), repeat every 5–10 min if needed	IV infusion, starting 0.05–0.1 μg/kg/min, titrate according clinical response
Germany (DGAKI) [26]	IM, 0.15–0.6 mg, repeat every 5–10 min IO if no IV access	If symptoms fail to stabilise and circulatory or respiratory decompensation is imminent, IV, bolus 1 μg/kg, every 3–5 min (1 mg if cardiac arrest)
Saudi Arabia (Ministry of Health, 2020) [27]	IM, 0.3–0.5 mg, repeat every 5–15 min if needed	For patients with inadequate response to IM adrenaline and IV saline, consider IV infusion, starting 0.1 μg/kg/min, titrate to response and side effects
United Kingdom (RCUK) [10, 23, 24]	IM (IV in the perioperative setting), every 5 min if needed. Adrenaline must be supported by IV crystalloid fluid	IV infusion, starting 5–10 μg/kg/h (0.08–0.17 μg/kg/min), titrate according to clinical response
United States of America (AAAAI/ACAAI) [19, 22]	IM, 10 μg/kg (maximum 0.5 mg), repeat every 5–15 min if needed, for up to three injections	IV infusion, starting 2 μg/min and increase up to 10 μg/min, titrate dose continuously according to blood pressure, cardiac rate and function and oxygenation
Anaphylaxis in the perioperative setting		
Australia-New Zealand (ANZAAG/ANZCA) [32]	Grade 2 (moderate): IV bolus 20 μg Grade 3 (life-threatening): 100–200 μg, every 1–2 min if needed, increase dose if unresponsive Grade 4: IV bolus, 1 mg, every 1–2 min if needed If no IV access IM 0.5 mg every 5 min if needed	IV infusion (after 3 IV bolus), starting 3 μg/min, titrate to maximum 40 μg/min (infusion rate 0.05–0.5 μg/kg/min)

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TABLE 2 | (Continued)

Source	First adrenaline injection	Adrenaline treatment in refractory anaphylaxis
ISPAR [14]	Grade 2: IV bolus 20 μg, then 50 μg if no response after 2 min, repeat every 2 min Grade 3: IV bolus 50–100 μg, then 200 μg if no response at 2 min, repeat every 2 min Grade 4: IV bolus 1 mg Consider IM bolus 300–500 μg if no IV access	Where inadequate response after 10 min: doubling the bolus dose of adrenaline, IV infusion when more than three boli have been administered, starting 0.05–0.1 μg/kg/min
Scandinavia (SSAI) [30]	Mild–moderate: IV bolus 10–50 μg Circulatory collapse: IV bolus 100 μg-1 mg, titrate dose to response If no IV access: 0.5–0.8 mg	If larger doses are needed: IV infusion, starting at 0.05–0.1 μg/kg/min, titrate dose to response
Brazil (BSA/ASBAI) [34]	Grade 2: IV bolus 10–20 μg, repeat every 2 min if needed Grade 3: IV bolus 100–200 μg, repeat every 2 min if needed Grade 4: IV bolus 1 mg	IV infusion after 3 boluses of IV adrenaline if needed, starting 3 μg/min, titrate up to 40 μg/min, infusion rate 0.05–0.5 μg/kg/min
France (SFAR/SFA) [31]	Grade 2: IV bolus 10–20 μg, repeat every 1–2 min as necessary, titrate according to response and side effects Grade 3: IV bolus 100–200 μg, repeat every 1–2 min as necessary, if no response, doses should be increased incrementally without delay If no IV access IM bolus 0.3–0.5 mg, repeat every 5–10 min as necessary Grade 4: IV bolus 1 mg every 1–2 min, and titrate according to response	If repeated or large doses are needed: IV infusion, starting at 0.05–0.1 μg/kg/min, titrate dose to response
Japan (JSA) [35]	Low pressure: IV bolus 0.2 μg/kg Circulatory collapse: IV bolus 50–300 μg If no IV access: IM 300 μg	Not documented
Spain (SEAIC/SEDAR) [33]	Grade2: IV bolus 20–30 μg Grade 3: IV bolus 100–200 μg Grade 4: 1 mg	Not documented
United Kingdom (RCUK) [16]	IV bolus 50 μg, repeat if needed (some patients may respond to smaller doses (10–50 μg) titrated to effect). If no IV access, 10 μg/kg IM (max 500 μg) using 1 mg/mL (1:1000) adrenaline and secure IV/IO access Adrenaline must be supported by IV crystalloid fluid	If signs of anaphylaxis persist despite adrenaline boluses, start an adrenaline infusion. A low-dose adrenaline infusion, given via a peripheral venous line, is an effective alternative if central venous access is unavailable

Abbreviations: AAAAI/ACAAI, American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology; AAI, adrenaline autoinjector; ANZAAG/ANZCA, Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists; ASCIA, Australasian Society of Clinical Immunology and Allergy; BSA/ASBAI, Brazilian Society of Anaesthesiology/Brazilian Association of Allergy and Immunology; DGAKI, German Society for Allergology and Clinical Immunology; EAACI, European Academy of Allergy and Clinical immunology; IM, intramuscular; ISPAR, International Suspected Perioperative Allergic Reaction Group; IV, intravenous; JSA, Japanese Society of Anaesthesiologists; NCMSA, National Center for Medical Service Administration (including Chinese Society of Allergy); RCUK, Resuscitation Council of the United Kingdom; SEAIC/SEDAR, Spanish Society of Allergy and Clinical Immunology/Spanish Anaesthesia Society; SFAR/SFA, Société Française d'Anesthésie et Réanimation/Société Française d'Allergologie; SFMU/SFA/GFRUP, Société Française de médecine d'Urgence/Société Française d'Allergologie/Groupe Francophone Réanimation et d'Urgence Pédiatrique; SSAI, Scandinavian Society of Anaesthesiology and intensive care medicine; WAO, World Allergy Organization.

Most guidelines for the treatment of anaphylaxis in the community or hospital setting flag the need to initiate and titrate IV adrenaline infusions for RA, that is persistence of features of anaphylaxis despite initial treatment with 2–3 doses of IM adrenaline, combined with adequate fluid therapy [10, 14, 16, 19–36] (Tables 2 and 3). This recommendation is based on evidence from the management of other forms of distributive shock, case reports of severe human anaphylaxis and animal models of severe anaphylaxis [39, 40]. Low-dose intravenous adrenaline infusion is more effective than IV bolus dosing and resulted

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TABLE 3 | Guidelines for the use of adrenaline during anaphylaxis in children.

Reference	First adrenaline injections	Adrenaline treatment in refractory anaphylaxis
Anaphylaxis outside perioperative setting		
Australia-New Zealand (ASCIA) [29]	IM, 10 μg/kg (max 0.5 mg per dose), repeat every 5 min if needed Use AAI if available OR ampoule/syringe	IV infusion if no response after 2–3 adrenaline doses, two protocols (prehospital settings and emergency departments/tertiary hospital settings), starting 0.1 μg/kg/min, titrate rate up or down to response and side effects IV bolus are not recommended
Europe (EAACI) [20]	IM, use AAI, 0.15 mg for children 25–30 kg, 0.30 mg for children and adolescents 23–30 kg (0.5 mg may be considered if the adolescent is overweight or has experienced a previous life-threatening anaphylaxis) 10 μg/kg for children <7.5 kg using syringe and needle Repeat after 5–10 min if needed	Not documented
World Allergy Organization (WAO) [21]	IM, 10 μg/kg per dose (maximum of 0.3 mg for children), repeat if needed every 5–15 min	Refer to protocol for low-dose IV adrenaline infusion developed by Brown et al. and used as part of anaphylaxis guidelines in Spain, Australia and New Zealand
China (NCMSA) [28]	IM, 10 μg/kg (max 0.5 mg), every 5–15 min if no response Grade 2–3: IV may be considered for IV bolus if they have already an IV access and are being monitored (ICU, perioperative setting) Grade 2: 10–50 μg (>14 years), (1–2 μg/kg) (<14 years) Grade 3: 0.1–0.2 mg (>14 years), 2–10 μg/kg (<14 years) Grade 4: 1 mg (>14 years), 10–20 μg/kg (<14 years)	Repeat IV bolus every 3–5 min (grade 4), every 1–2 min (grade 2–3) Grade 2–3: if no response after 2–3 bolus IV, start IV infusion Grade 4: start IV infusion when patients begin to stabilise IV infusion: 0.05–0.5 μg/kg/min
France, (SFMU/SFA/GFRUP) [25]	IM, 10 μg/kg (maximum 0.5 mg), repeat every 5–10 min if needed, use AAI if available	IV infusion, starting 0.1 μg/kg/min, titrate according clinical response
Germany (DGKAI) [26]	IM, 10 μg/kg, repeat as needed IO if no IV access	If symptoms fail to stabilise and circulatory or respiratory decompensation is imminent, IV, bolus 1 μg/kg, every 3–5 min (10 μg/kg if cardiac arrest)
India (IAP) [36]	IM, 10 μg/kg, repeat at 5–10 min if needed	After 3 doses, IV infusion, starting 0.05 μg/kg/min with titrate by 0.02 μg/kg/min up to effect
Saudi Arabia (Ministry of Health, 2020) [27]	IM, every 5–15 min if needed <10 kg, 10 μg/kg 10–25 kg: 0.15 mg >25–50 kg: 0.3 mg >50 kg: 0.5 mg per dose	For patients with inadequate response to IM adrenaline and IV saline, consider IV infusion, 0.1–1 μg/kg/min, titrate to response and side effects
United Kingdom (RCUK) [10, 23, 24]	IM (IV in the perioperative setting), every 5 min of needed	IV infusion, starting 5–10 μg/kg/h (0.08–0.17 μg/kg/min), titrate according to the clinical response

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TABLE 3 | (Continued)

Reference	First adrenaline injections	Adrenaline treatment in refractory anaphylaxis
United States of America (AAAAI/ACAAI) [19, 22]	IM, 10 μg/kg (maximum 0.5 mg), repeat every 5–15 min if needed, for up to 3 injections	Not documented
Perioperative anaphylaxis		
Australia-New Zealand (ANZAAG/ANZCA) [32]	Grade 2: IV bolus 2 μg/kg Grade 3: IV bolus 4–10 μg/kg, repeat every 1–2 min as necessary Grade 4: IV bolus 10 μg/kg, repeat every 1–4 min if needed If no IV access, IM < 6 years: 0.15 mg, 6–12 years: 0.3 mg, every 5 min if needed	IV infusion, starting 0.1–2 μg/kg/min, titrate according to response
Scandinavia (SSAI) [30]	Mild–moderate: IV bolus 1–5 μg/kg Circulatory collapse: 10 μg/kg, titrate dose according to response If no IV access: IM 5–10 μg/kg	If larger doses are needed: IV infusion, starting 0.05–0.1 μg/kg/min, titrate to response
Brazil (BSA/ASBAI) [34]	Grade 2: IV bolus 1–2 μg/kg, if the response is inadequate in 2 min, increase the dose (maximum of 5 μg/kg), repeat every 2 min Grade 3: IV bolus 4–10 μg/kg, repeat every 1–2 min if needed Grade 4: IV bolus 10 μg/kg, repeat every 1–4 min if needed	IV infusion, starting 0.1–2 μg/kg/min
France (SFAR/SFA) [31]	Grade 2: IV bolus 1 μg/kg Grade 3: IV bolus 1 μg/kg (up to 5–10 μg/kg), titrate according to response Grade 4: IV bolus 10 μg/kg, repeat every 1–2 min	If repeated boluses are needed: IV infusion, starting 0.1 μg/kg/min, titrate up or down according to response and side effects
Japan (JSA) [35]	Low pressure: IV bolus 0.2 μg/kg Circulatory collapse: not documented If no IV access: IM bolus 10 μg/kg	Not documented
United Kingdom (RCUK) [16]	1 μg/kg bolus, titrated to effect If no IV access, 10 μg/kg IM (max 500 μg) using 1 mg/mL (1:1000) adrenaline and secure IV/IO access Adrenaline must be supported by IV crystalloid fluid	If signs of anaphylaxis persist despite adrenaline boluses, start an adrenaline infusion. A low-dose adrenaline infusion, given via a peripheral venous line, is an effective alternative if central venous access is unavailable

Abbreviations: AAAAI/ACAAI, American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology; AAI, adrenaline autoinjector; ANZAAG/ANZCA, Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists; ASCIA, Australasian Society of Clinical Immunology and Allergy; BSA/ASBAI, Brazilian Society of Anaesthesiology/Brazilian Association of Allergy and Immunology; DGAKI, German Society for Allergology and Clinical Immunology; EAACI, European Academy of Allergy and Clinical Immunology; IM, intramuscular; IAP, Indian Academy of Paediatrics; IV, intravenous; JSA, Japanese Society of Anaesthesiologists; NCMSA, National Center for Medical Service Administration (including Chinese Society of Allergy); RCUK, Resuscitation Council of the United Kingdom; SFAR/SFA, Société Française d'Anesthésie et Réanimation/Société Française d'Allergologie; SFMU/SFA/GFRUP, Société Française de Médecine d'Urgence/Société Française d'Allergologie/Groupe Francophone Réanimation et d'Urgence Pédiatrique; SSAI, Scandinavian Society of Anaesthesiology and Intensive care medicine; WAO, World Allergy Organization.

in a lower total dose requirement and a favourable safety profile [39–41]. However, there is wide variation in the doses recommend for adrenaline bolus and infusion in guidelines with IV infusion dosing (Tables 2 and 3).

Consistent with the observation that adrenaline is underused in managing anaphylaxis in both the community and emergency setting, for perioperative anaphylaxis evidence also suggests that adrenaline is underused (mainly for less severe cases). In the NAP6 audit of perioperative anaphylaxis in the UK, no adrenaline was administered in 11% of cases, and metaraminol boluses were administered in 69% of patients, of whom 74% also received adrenaline [42]. In a single-centre case series of perioperative anaphylaxis in Denmark, 17% of cases did not receive any adrenaline, and there were significant delays (more than 10 min from onset of reported hypotension to adrenaline treatment) in adrenaline administration in approximately one-third of cases [43]. These data highlight the need for timely recognition of anaphylaxis and prompt treatment with adrenaline. However, anaphylaxis fatalities have also been observed even

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when management was judged as 'good' including timely fluid therapy and rapid administration of adrenaline at the right time and in the right doses [18, 42, 44]. Such cases suggest that some forms of anaphylactic shock may be resistant to adrenaline, as a consequence of a combination of potential intrinsic and extrinsic factors [11, 15].

All guidelines emphasise the need for close cardiopulmonary monitoring in patients treated with IV adrenaline and to titrate adrenaline according to the clinical response and side effects (tachyarrhythmia, myocardial infarction, stroke, severe hypertension, cerebral haemorrhage and pulmonary oedema) [38]. Tachycardia, tremor and pallor with a normal or raised blood pressure may indicate excessive adrenaline treatment [24]. Most guidelines recommend starting the administration of adrenaline and other IV medications by trained staff and using a peripheral IV access (eventually intraosseous if no IV access or need for additional access points) but to establish central venous access and, if possible, arterial canula for accurate haemodynamic monitoring [16].

3.1.2 | Fluid Therapy Plays a Major Role in the Management of Refractory Anaphylaxis

Timely fluid resuscitation is a crucial part of the treatment for RA (Table 4). Plasma extravasation equivalent to one-third of the circulating blood volume can occur within minutes in severe anaphylaxis [45] and venous return can be impaired even in those without clinically evident haemodynamic compromise [46]. There is absolute hypovolaemia due to massive capillary leakage during anaphylaxis but also a relative hypovolaemia due to splanchnic vasoconstriction, portal hypertension, transient pulmonary hypertension and increased intrathoracic pressure due to bronchospasm. Therefore, adequate fluid therapy is vital to provide sufficient circulating volume to maintain cardiac output and delivery of adrenaline at the tissue level. In the NAP6 survey of perioperative anaphylaxis in UK, as well as in patients admitted to French ICUs for severe anaphylaxis, the volume and rate of fluid resuscitation were insufficient [18, 42, 44]. In the French survey, more than half of patients with a Grade 3–4 anaphylaxis did not receive the recommended dose of IV fluids of 30 mL/kg within the first 4 h after ICU admission [18]. However, there is a wide variation in the volumes of fluid therapy recommended, from childhood to adulthood [10, 14, 16, 19–32, 34–36, 39, 47] (Table 4).

For the treatment of haemorrhagic shock or sepsis, all guidelines recommend fluid resuscitation using crystalloids as first-line treatment, to avoid renal failure and haemostasis disorders due to the use of colloids. Balanced crystalloids are generally preferred to 0.9% saline to avoid the consequences of a high chloride ion load, responsible for metabolic acidosis and renal vasoconstriction [48, 49]. Guidelines recommend initial fluid therapy of 20–30 mL/kg, administered as soon as possible and preferably through a dedicated, large bore venous cannula.

For anaphylaxis, clinical data are lacking to justify the choice of one solute over another, as anaphylaxis has always been excluded from clinical studies of vascular filling. Crystalloid resuscitation may not be effective in restoring cardiac preload, because of the massive and persistent vascular leak observed in severe anaphylaxis. In a rat model of lethal anaphylaxis, colloid-based resuscitation (using hydroxyethyl starch [HES]) significantly decreased the time to restoration of normal blood pressure and reduced cerebral hypoxia compared with crystalloids [50]. Given these considerations, the safety issues associated with HES and the fact that colloids (particularly if gelatin-based) can themselves induce allergic reactions, it is difficult to make clear recommendations [51]. Gelatin-based colloids are contraindicated in patients with α-Gal syndrome and anti-α-Gal IgE [52]. In this context, colloids should only be considered as a second-line treatment when hypovolaemia persists despite the administration of an adequate volume of crystalloids.

Most guidelines recommend that patients with persisting RA should be monitored to assess preload dependency, stroke volume or cardiac output and adjust fluid therapy. Echocardiography should be performed to ensure there is no cardiac dysfunction as this may impact therapeutic decisions including the need for inotropic medications. Guidelines also emphasise the need for appropriate positioning to increase venous return, perfusion and myocardial filling [16, 24]. Individuals with cardiovascular collapse should remain flat, with legs raised (or head-down in the Trendelenburg position, something achievable with most surgical tables). Changes in posture from supine to standing in the community setting are associated with worsening of cardiovascular collapse and even death [4, 53]. In case of predominant respiratory signs, patients may prefer to sit up with elevated legs [20].

3.1.3 | Second-Line Treatment for the Most Severe Reactions

The evidence for second-line treatment of RA with cardiovascular compromise is limited, and mostly consists of case reports (Table 5, Figure 1). This constitutes a publication bias, as only positive clinical outcomes related to the use of these medications are generally reported. The relationship and causality between the administration of such treatment and clinical improvement reported is not proven.

3.1.3.1 | Vasopressors. Beyond the use of continuous adrenaline as the first-line vasopressor, the administration of second-line vasopressors (i.e., noradrenaline, vasopressin and metaraminol) is proposed in most guidelines, but there is limited evidence to support the use of one vasopressor of another (Table 5) [54]. There are no strict guidelines on when to introduce a second vasopressor. In current practice, noradrenaline appears to be the most common second-line vasopressor used in anaphylactic shock. It was used in 77 (23%) out of 339 patients (of whom 28 [55%] out of 51 with grade IV) admitted to ICUs for severe anaphylaxis in France and in 18 (42%) out of 43 patients admitted for perioperative anaphylaxis in Japan [18, 55]. However, no evidence exists to justify noradrenaline in preference to another vasopressor in RA. Animal models suggest that vasopressors should be used in RA with persistent cardiovascular collapse, *in addition to* adrenaline infusion rather than as an alternative [56]. Metaraminol is frequently used in many countries for perioperative anaphylaxis,

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TABLE 4 | Guidelines for the use of fluid therapy during refractory anaphylaxis in adults and children.

Source	Type	Volume in adults	Volume in children
Anaphylaxis outside the perioperative setting			
Australia-New Zealand (ASCIA) [29]	Normal saline	20 mL/kg, rapidly (max 50 mL/kg in first 30 min), repeat bolus if hypotension persists	20 mL/kg, rapidly (max 50 mL/kg in first 30 min), repeat bolus if hypotension persists
Europe (EAACI) [20]	Crystalloids	Adults–children >25–30 kg: 500 mL, repeat as needed	Children <25–30 kg: 10 mL/kg (maximum 500 per bolus, repeat as needed
World Allergy Organization (WAO) [21]	Crystalloids (NaCl 0.9%)	1–2 L, 5–10 mL/kg in the first 5–10 min	10 mL/kg in the first 5–10 min
China (NCMSA) [28]	Crystalloids	20 mL/kg, repeat if needed	20 mL/kg, repeat if needed
France (SFMU/SFA/GFRUP) [25]	Isotonic saline solution or ringer	20 mL/kg (5–10 mL/kg within the first 5 min)	20 mL/kg (5–10 mL/kg within the first 5 min)
Germany (DGAKI) [26]	Crystalloids (gelatin and dextran solutions should be not be used)	500–1000 mL, over 5 min, repeat if needed (high volume may be necessary 1–3 L)	20 mL/kg, over 5 min, repeat as needed
India (IAP) [36]	Normal saline	Not documented	20 mL/kg, rapid flush technique, repeat as necessary at 5–10 min
Saudi Arabia (Ministry of Health, 2020) [27]	Normal saline	1–2 L, repeat as needed	20 mL/kg, repeat as needed
United Kingdom (RCUK) [10, 23, 24]	Crystalloid (NaCl 0.9%, Hartmann's for intial bolus, use a nonglucose-containing crystalloid (e.g. Hartmann's or Plasma-Lyte) rather than 0.9% sodium chloride subsequently)	0.5–1 L, repeat if needed and titrate according to response, large volume may be required (e.g., 3–5 L)	10 mL/kg, repeat if needed and titrate according to response
United States of America (AAAAI/ACAAI) [19, 22]	NaCl 0.9%	1–2 L, 5–10 mL/kg within the first 5 min	5–10 mL/kg within the first 5 min, up to 30 mL/kg in the first hour
Perioperative anaphylaxis			
Australia-New Zealand (ANZAAG/ANZCA) [32]	Crystalloids	2 L, repeat as necessary	20 mL/kg, repeat as necessary
ISPAR [14]	Crystalloids (balanced salt solutions or NaCl 0.9%)	Grade 2 = rapid bolus of 500 mL, repeat if needed Grade 3 = rapid bolus of 1 L, repeat if needed If needed, escalate fluid administration up to 20–30 mL/kg	20 mL/kg
Scandinavia (SSAI) [30]	NaCl 0.9%, Ringer's acetate or colloids	20 mL/kg, repeat if needed	20 mL/kg, repeat if needed
Brazil (BSA/ASBAI) [34]	Crystalloids	Fast bolus 20 mL/kg, repeat if needed	Fast bolus 20 mg/kg, repeat if needed

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TABLE 4 | (Continued)

Source	Type	Volume in adults	Volume in children
France (SFAR/SFA) [31]	Crystalloids until 30 mL/kg, then colloids		Crystalloids 20 mL/kg then colloids 10 mL/kg A cumulative dose of 60 mL/kg may be necessary
Japan (JSA) [35]	Crystalloids	5–10 mL/kg during the first 5 min, until recovery of blood pressure	30 mL/kg during the first hour
United Kingdom (AAGBI) [47]	Saline 0.9% or Ringer's solution	'Large volume may be required'	
United Kingdom (RCUK) [16]	Crystalloids	0.5–1 L Multiple fluid boluses may be needed (e.g., up to 3–5 L in adults)	20 mL/kg Multiple fluid boluses may be needed (60–100 mL/kg)

Abbreviations: AAAAI/ACAAI, American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology; AAGBI, Association of Anaesthetists of Great Britain and Ireland; ANZAAG/ANZCA, Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists; ASCIA, Australasian Society of Clinical Immunology and Allergy; BSA/ASBAI, Brazilian Society of Anaesthesiology/Brazilian Association of Allergy and Immunology; DGAKI, German Society for Allergology and Clinical Immunology; EAACI, European Academy of Allergy and Clinical Immunology; IAP, Indian Academy of Paediatrics; ISPAR, International Suspected Perioperative Allergic Reaction Group; JSA, Japanese Society of Anaesthesiologists; NCMSA, National Center for Medical Service Administration (including Chinese Society of Allergy); RCUK, Resuscitation Council of the United Kingdom; SFAR/SFA, Société Française d'Anesthésie et Réanimation/Société Française d'Allergologie; SFMU/SFA/GFRUP, Société Française de Médecine d'Urgence/Société Française d'Allergologie/Groupe Francophone Réanimation et d'Urgence Pédiatrique; SSAI, Scandinavian Society of Anaesthesiology and Intensive care medicine; WAO, World Allergy Organization.

and is cited in 4 out of 18 anaphylaxis guidelines; however, given equivalent mechanisms of action, metaraminol is unlikely to be more effective than IV adrenaline infusion. Noradrenaline and vasopressin may be preferable as vasopressors compared to dopamine due to insufficient efficacy to stabilise blood pressure, and side effects including tachycardia [26].

A reasonable approach is to commence additional vasopressors (noradrenaline or vasopressin), under the supervision of a trained staff, most of time in ICUs, preferably using a central venous access, in patients who continue to be hypotensive despite maximal adrenaline and fluid therapy. In these patients, a close cardiovascular monitoring is required to exclude myocardial dysfunction that would require other treatments.

3.1.3.2 | Glucagon. International guidelines recommend glucagon administration in patients taking beta-blockers regularly, with an adrenaline-resistant anaphylactic shock (Table 5). However, there is very limited data (case studies) to support this medication [57–61]. Glucagon exerts positive inotropic and chronotropic effects by directly activating adenylyl cyclase and bypassing β-adrenergic receptor blockade. When using glucagon, patients must be closely monitored for adverse effects including hyperglycaemia, vomiting, hypocalcaemia and hypokalaemia.

3.1.3.3 | Methylene Blue. The use of methylene blue has been reported in case reports, but current guidelines do not include it in the treatment of RA, with one exception (a Spanish guideline) (Table 5). However, it should be considered case-by-case when other second-line therapies are not effective, including the titration of vasopressors [62, 63]. Methylene blue has been found to increase systemic vascular resistance and reduce the need for vasopressors in patients undergoing cardiac surgery with post cardiopulmonary bypass vasoplegic shock, by inhibiting nitric oxide synthase while inhibiting activation of soluble guanylyl cyclase and preventing vasodilation [64]. In a lethal anaphylaxis model in rats, methylene blue proved particularly effective as an adjunct to adrenaline therapy in restoring blood pressure and cardiac output and reducing cerebral ischaemia [65]. Further clinical studies would be interesting to assess the value of additive methylene blue treatment in the most severe cases of anaphylaxis.

3.1.3.4 | Extracorporeal Life Support. ECLS (extra corporeal membrane oxygenation or cardiopulmonary bypass) where available is an emerging rescue therapy with multiple case reports of successful resuscitation [66–74]. If ECLS is envisaged, this procedure should be initiated as soon as possible given time delays due to technical issues and need for involvement of a collaborative trained team. The Resuscitation Council UK recommends that ECLS should be considered for prolonged anaphylaxis where resuscitation has been instituted in a timely manner and not been delayed [10].

3.2 | Perspectives

3.2.1 | Healthcare Professionals Should Be Trained to Recognise and Treat Severe Anaphylaxis

Given that RA is not a rare occurrence in either the community or hospital setting and the underuse of adrenaline in anaphylaxis, healthcare professionals and prehospital providers must be familiar with the correct recognition of anaphylaxis, understand the steps which are essential to the adequate management of

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TABLE 5 | Guidelines for the use of second-line treatment for cardiovascular compromise in refractory anaphylaxis.

Source	Adults	Children
Anaphylaxis in the community		
Australia-New Zealand (ASCIA) [29]	Glucagon in patients on beta-blockers, IV bolus 1–2 mg, repeat if needed or followed by an IV infusion 1–2 mg (hour) Metaraminol (2–10 mg) or vasopressin (10–40 UI) 'after advice from an emergency medicine/critical care specialist' Noradrenaline in ICU only	Glucagon in patients on beta-blockers, IV bolus 20–30 μg/kg (up to 1 mg) Metaraminol 10 μg/kg Noradrenaline in ICU only
Europe (EAACI) [20]	Not documented	Not documented
World Allergy Organization (WAO) [21]	IV glucagon 'may be used in patients taking beta-blockers'	Not documented
China (NCMSA) [28]	Vasopressors (not detailed) Glucagon (not detailed)	Vasopressors (not detailed) Glucagon (not detailed)
France (SFMU/SFA/GFRUP) [25]	IV noradrenaline infusion, starting 0.1 μg/kg/min IV glucagon in patients with beta-blockers 1–2 mg every 5 min followed by an IV infusion of 5–15 μg/min Methylene blue not recommended in clinical practice	Not documented
Germany (DGKAI) [26]	Noradrenaline, IV infusion, 0.02–0.15 μg/kg/min Vasopressin (when treatment with volume and other catecholamines has failed) 0.01–0.03 UI/min Glucagon for patients on beta-blockers Dopamine: no longer used in Germany	Not documented
India (IAP) [36]	Not documented	Noradrenaline IV infusion (persistent hypotension), starting 0.05 μg/kg/min with titrate by 0.02 μg/kg/min up to effect (max: 2 μg/kg/min) Glucagon IV bolus for patients on beta-blockers at 20–30 μg/kg/dose (max: 1 mg) over 5 min followed by 5–15 μg/min, titrated till achievement of clinical effects
Saudi Arabia (Ministry of Health, 2020) [27]	Noradrenaline or dopamine, titrate to response and side effects Glucagon IV bolus for patients on beta-blockers 1–5 mg, over 5 min, followed by IV infusion of 5–15 μg/min	Noradrenaline OR dopamine, titrate to response and side effects
United Kingdom (RCUK) [10, 23, 24]	If refractory to adrenaline infusion: Consider adding a second vasopressor in addition to adrenaline infusion (noradrenaline, vasopressin or metaraminol) Consider glucagon in patients on beta-blockers Consider ECLS	Not documented
United States of America (AAAAI/ACAAI) [19, 22]	Consider administration of dopamine or other vasopressors (in addition to adrenaline infusion) IV glucagon 1–5 mg over 5 min in patients in beta-blockers, followed by IV infusion at 5–15 mg/min titrated	IV glucagon 20–30 mg/kg (maximum 1 mg) over 5 min in patients in beta-blockers

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TABLE 5 | (Continued)

Source	Adults	Children
Anaphylaxis in the perioperative setting		
Australia-New Zealand (ANZAAG/ANZCA) [32]	Noradrenaline IV infusion 0.05–0.5 μg/kg/min AND/OR Vasopressin IV bolus 1–2 UI then 2 UI/h Metaraminol OR phenylephrine infusion Glucagon IV bolus 1–2 mg, every 5 min until response in patients on beta-blockers ECLS where available	Noradrenaline IV infusion 0.1–2 μg/kg/min AND/OR Vasopressin IV infusion 0.02–0.05 UI/kg/h Glucagon IV bolus 40 μg/kg (maximum 1 mg) in children on beta-blockers ECLS where available
ISPAR [14]	Where persistent hypotension after 10 min, add IV infusion of noradrenaline (0.05–0.5 μg/kg/min), phenylephrine or metaraminol Add vasopressin IV bolus 1–2 U with or without infusion (2 U/h) Add IV glucagon (1–2 mg) if patient using beta-blockers Consider ECLS where available Sugammadex not indicated	Not documented
Scandinavia (SSAI) [30]	Lack of response to adrenaline: Noradrenaline IV infusion starting 0.05–0.1 μg/kg/min Vasopressin increments of 2–10 UI IV until response Glucagon (in patients on beta-blockers) increments of 1–2 mg IV until response	Not documented
Brazil (BSA/ASBAI) [34]	If persistent hypotension after 10 min: IV noradrenaline (0.05–0.1 μg/kg/min) IV glucagon for patients using beta-blockers IV bolus 40 μg/kg (up to 1–2 mg) or 5–15 μg/min, repeat after 5 min Vasopressin IV bolus 2–10 UI, repeat if necessary (or infusion 0.2–0.4 UI/min or 2 UI/h) Suggest ECLS when available	Noradrenaline Vasopressin Glucagon (not detailed)
France (SFAR/SFA) [31]	Glucagon for patients on beta-blockers with refractory anaphylaxis, IV bolus 1–2 mg, repeat every 5 min, followed by IV infusion if needed 5–15 μg/kg/min or 0.3–1 mg/h Vasoconstrictors or agonists if refractory to high dose of adrenaline (noradrenaline, IV infusion starting 0.1 μg/kg/min; terlipressin IV bolus 2 mg)	Glucagon for children on beta-blockers with refractory anaphylaxis, IV bolus 20–30 μg/kg, IV infusion 5–15 μg/min according to clinical response (maximum 1 mg within 5 min) No data suggesting the use of vasopressin in children
Japan (JSA) [35]	Vasopressin should be considered for catecholamine-resistant anaphylactic shock	Not documented
Spain (SEAIC/SEDAR) [33]	If no response to adrenaline: IV noradrenaline 0.05–0.1 μg/kg/min IV glucagon 1–2 mg IV each 5 min or infusion 5–15 μg/min Vasopressin bolus 2–10 UI, repeat or infusion 0.2–0.4 UI/min Other vasoactive drugs can be given IV bolus or infusion: dopamine, ephedrine, methoxamine, phenylephrine Methylene blue 'can be useful' Sugammadex: not indicated	Not documented

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TABLE 5 | (Continued)

Source	Adults	Children
United Kingdom (AAGBI) [42]	Consider the administration of an alternative vasopressor according to training and experience of anaesthetist (metaraminol) if blood pressure does not recover	Not documented
United Kingdom (RCUK) [16]	No clear evidence to recommend one vasopressor over another IV glucagon (1 mg) can be considered in adults taking beta-blockers Consider ECLS Sugammadex: not indicated	Not documented

Abbreviations: AAAAI/ACAAI, American Academy of Allergy, Asthma and Immunology and American College of Allergy, Asthma and Immunology; AAGBI, Association of Anaesthetists of Great Britain and Ireland; ANZAAG/ANZCA, Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists; ASCIA, Australasian Society of Clinical immunology and Allergy; BSA/ASBAI, Brazilian Society of Anaesthesiology/Brazilian Association of Allergy and Immunology; DGAKI, German Society for Allergology and Clinical Immunology; EAACI, European Academy of Allergy and Clinical Immunology; ICU, intensive care unit; IAP, Indian Academy of Paediatrics; ISPAR: International Suspected Perioperative Allergic Reaction Group; IV, intravenous; JSA: Japanese Society of Anaesthesiologists; NCMSA, National Center for Medical Service Administration (including Chinese Society of Allergy); RCUK, Resuscitation Council of the United Kingdom; SEAIC/SEDAR, Spanish Society of Allergy and Clinical Immunology/Spanish Anaesthesia Society; SFAR/SFA, Société Française d'Anesthésie et Réanimation/Société Française d'Allergologie; SFMU/SFA/GFRUP, Société Française de Médecine d'Urgence/Société Française d'Allergologie/Groupe Francophone de Réanimation et d'Urgence Pédiatrique; SSAI, Scandinavian Society of Anaesthesiology and Intensive care medicine; WAO, World Allergy Organization; ECLS, extracorporeal life support.

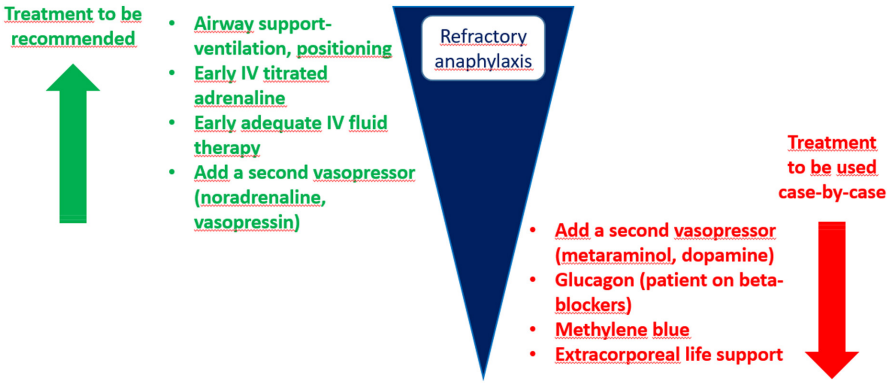

FIGURE 1 | First- and second-line treatment of refractory anaphylaxis according to the current guidelines. IV, intravenous.

RA [2]. For example, staff working in Emergency Departments and Allergy Challenge settings should undergo simulation training which includes the management of RA—something which has been done for staff in the perioperative setting for many years but also in a paediatric emergency department and an allergy clinic [75–77]. High-fidelity simulation training has been shown to improve performance during resuscitation [78], and it is likely that this applies to specific simulation training on RA, although data are limited as to whether this translates into improved outcomes. In the particular context of perioperative anaphylaxis, anaphylaxis may be difficult to recognise as most anaesthetic inductions are associated with a slight, transient drop in blood pressure. However, most of these situations resolve spontaneously or after administration of a small dose of vasopressor. In anaphylaxis, hypotension is generally more severe, resistant to low-dose vasopressors, associated with tachycardia and often bronchospasm (32% of cases in the French GERAP cohort) and cutaneous signs (43% of cases in the French GERAP cohort) [79]. Interestingly, anaphylaxis is also associated with a sharp drop in end-tidal CO2, which is particularly specific to this situation and considered as a potential marker of severity [80].

3.2.2 | Identifying Risk Factors of Refractory Anaphylaxis

RA is unpredictable, and likely to be multifactorial [9]. A rapid review and meta-analysis evaluating risk factors for severe food-induced allergic reactions concluded that significant uncertainties remain with respect to the prediction of severe and RA [8]. Evidence for an impact of cofactors on severity were lacking, except for food-dependent exercise-induced anaphylaxis. Medications such as beta-blockers or angiotensin-converting enzyme inhibitors may increase severity, but there is likely to be confounding because these drugs are often prescribed to those with ischaemic heart disease who are more likely have poor outcomes from anaphylaxis. Prior anaphylaxis, a diagnosis of asthma, IgE sensitisation or basophil activation tests were not good predictors [8].

Patients with clonal mast cell disorders mastocytosis may be at higher risk of perioperative hypersensitivity reactions, although this is more based on expert consensus than data, which are limited to a handful of retrospective studies [81, 82]. In a cohort of 226 patients with a suspected anaphylaxis diagnosed

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in an emergency setting, the anaphylaxis diagnosis was finally confirmed in 124 (54.9%); 7.7% of adults had a mastocytosis which was associated with a more severe anaphylaxis [83]. In the European Anaphylaxis Registry, data on 305 fatal and near-fatal anaphylaxis found that male sex, higher age, mastocytosis and cardiovascular disease was associated with a poor outcome [84]. We could not find any data to inform specific management of RA in patients with mastocytosis. There is no evidence for avoiding specific medications in patients with mastocytosis but no previous history of reactions to the drug, although it would seem prudent to exercise caution as specific drugs which have a marked histamine-releasing effect (such as vancomycin, opioids and curare alkaloids) [14]. Raised mast cell tryptase (MCT) due to hereditary alpha-tryptasaemia (HAT) affects around 5% of the population and is associated with severity in hymenoptera allergy [85]. However, this has not been demonstrated for food allergy [8], and data are lacking with respect to perioperative anaphylaxis.

In the perioperative setting, male gender, cardiovascular diseases, obesity and ongoing treatment with beta-blockers are associated with fatal outcomes [15, 42, 44]. Other risk factors have been reported in various studies: treatment with angiotensin-converting enzyme inhibitors, patient undergoing a cardiac procedure, comorbid conditions of weight loss, nonmetastatic solid tumours, metastatic cancer, paralysis, coagulopathy, renal failure, congestive heart failure, fluid and electrolyte disorder and neurological disorders [15]. However, there is a lack of evidence as to how individual and external risk factors may interact and/or interrelate, emphasising the need of further research.

Strikingly, refractory and fatal anaphylaxis cases appear to be more frequent in adulthood. The impact of age on anaphylaxis severity is not clear because of confounding factors, such as triggers, comorbidities (in particular cardiovascular diseases) and concomitant medications. Older age may correlate with the decreased ability to compensate and retain homeostasis during anaphylaxis [11]. However, for food anaphylaxis, the greatest risk appears to be in adolescence and young adulthood with no clear explanation, except possible risk-taking behaviours [8].

TABLE 6 | Knowledge gaps and areas of improvement in the management of refractory anaphylaxis.

Knowledge gaps	Areas of improvement
Lack of epidemiological data describing severe refractory anaphylaxis cases (e.g., timing, route and doses of adrenaline administration and timing, volume and type of fluid therapy, use of second-line treatment, outcomes) and data in specific population (children, pregnancy)	Provide a consensus on the definition of refractory anaphylaxis (in both community and perioperative settings)
Research on pathophysiological mechanisms, mediators and effectors, involved in severe refractory anaphylaxis including non-IgE-regulated reactions (role of genetic modulators such as HAT, PAF-AH...)	Optimise correct recognition of anaphylaxis and specificities in the perioperative setting
Need for novel biomarkers of anaphylaxis that could be useful in real time	Provide international consensual guidelines regarding the management of severe anaphylaxis (optimal route and doses of IV adrenaline, optimal volume and rate of fluid therapy) and the use of second-line treatment (vasopressors, methylene blue, glucagon, ECLS)
Lack of data and high-quality level studies regarding optimal adrenaline and fluid therapy administration as well as the use of second-line treatment (vasopressors, methylene blue, glucagon, ECLS)	Consider haemodynamic monitoring (echocardiography) when available in patients with refractory anaphylaxis
Research on novel therapeutic approaches (PAF receptor antagonists, DARPins...)	Promote simulation of anaphylaxis scenarios for training of individuals and teams working in emergency care and perioperative setting
	Optimise the determination of tryptase levels (paired acute and basal levels) to improve diagnosis
	Promote a systematic allergy follow-up for each patient suspected of anaphylaxis with shared medical records to help for the correct diagnosis
	Improve the collaboration between emergency physicians, anaesthetics and allergists regarding severe anaphylaxis to create cross-specialty national/international reporting systems for suspected anaphylaxis reactions including life-threatening and fatal reactions

Abbreviations: DARPins, designed ankyrin repeat proteins; ECLS, extracorporeal life support; HAT, hereditary alpha-tryptasaemia; IV, intravenous; PAF, platelet activating factor; PAF-AH, platelet activating factor-acetyl hydrolase.

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3.2.3 | From Pathophysiological Mechanism to Treatment for the Future

In recent years, major advances in understanding pathophysiological mechanisms underlying severe anaphylaxis have been made [86]. However, knowledge gaps remain (Table 6). Evidence from case series and animal models of severe anaphylaxis suggest that RA may be due to a combination of delayed or insufficient delivery of adrenaline and fluids, including hypovolaemia, ongoing release of inflammatory mediators, rarely, tachyphylaxis to further adrenaline administration [9, 11, 18]. The severity of anaphylaxis and its progression into a RA may depend on additional co-influencing mechanisms including elicitors (type, dose and route of exposure), extrinsic and intrinsic cofactors and physiological compensation [11].

Evidence for platelet activating factor (PAF) as a mediator of anaphylaxis was first published by Vadas et al. [87]; the authors also noted that levels PAF-acetyl hydrolase (PAF-AH), the enzyme which degrades PAF, were lower in individuals with more severe reactions. An association between lower PAF-AH and severity has also reported in a prospective multicentre study in emergency departments in Australia [88], and more recently, in a prospective study in 46 children [89], but not in other reports [90]. PAF receptor antagonists have been tested in experimental anaphylaxis with promising results [91, 92]. In a rat model of lethal anaphylaxis induced by ovalbumin, the use of ABT-491 enabled rats to survive for the duration of the experiment. The effect of ABT-491 was also additive to adrenaline, reducing the need for adrenaline to restore blood pressure and cardiac function [92]. In addition, PAF receptor antagonists have been tested in human, in other medical conditions (allergic rhinitis, myocardial infarction and asthma) but not in anaphylaxis [93–96].

Another therapeutic approach has been developed to envisage potent and fast-acting IgE inhibitors with the potential to rapidly terminate anaphylaxis. With this aim, optimised disruptive IgE inhibitors based on designed ankyrin repeat proteins (DARPin) have been generated [97]. These IgE inhibitors rapidly dissociate preformed IgE:FcεRI complexes, terminated IgE-mediated signalling in preactivated human blood basophils in vitro, and shut down preinitiated allergic reactions and anaphylaxis in mice in vivo. Alakhas et al. [98] recently reported that a covalent heterobivalent inhibitor (cHBI) that binds in an allergen-specific manner can not only prevent allergic reactions in a murine model of peanut anaphylaxis but also attenuated severity when administered shortly after the onset of symptoms. Thus, research into the mechanisms which underpin anaphylaxis may define new therapeutic approaches.

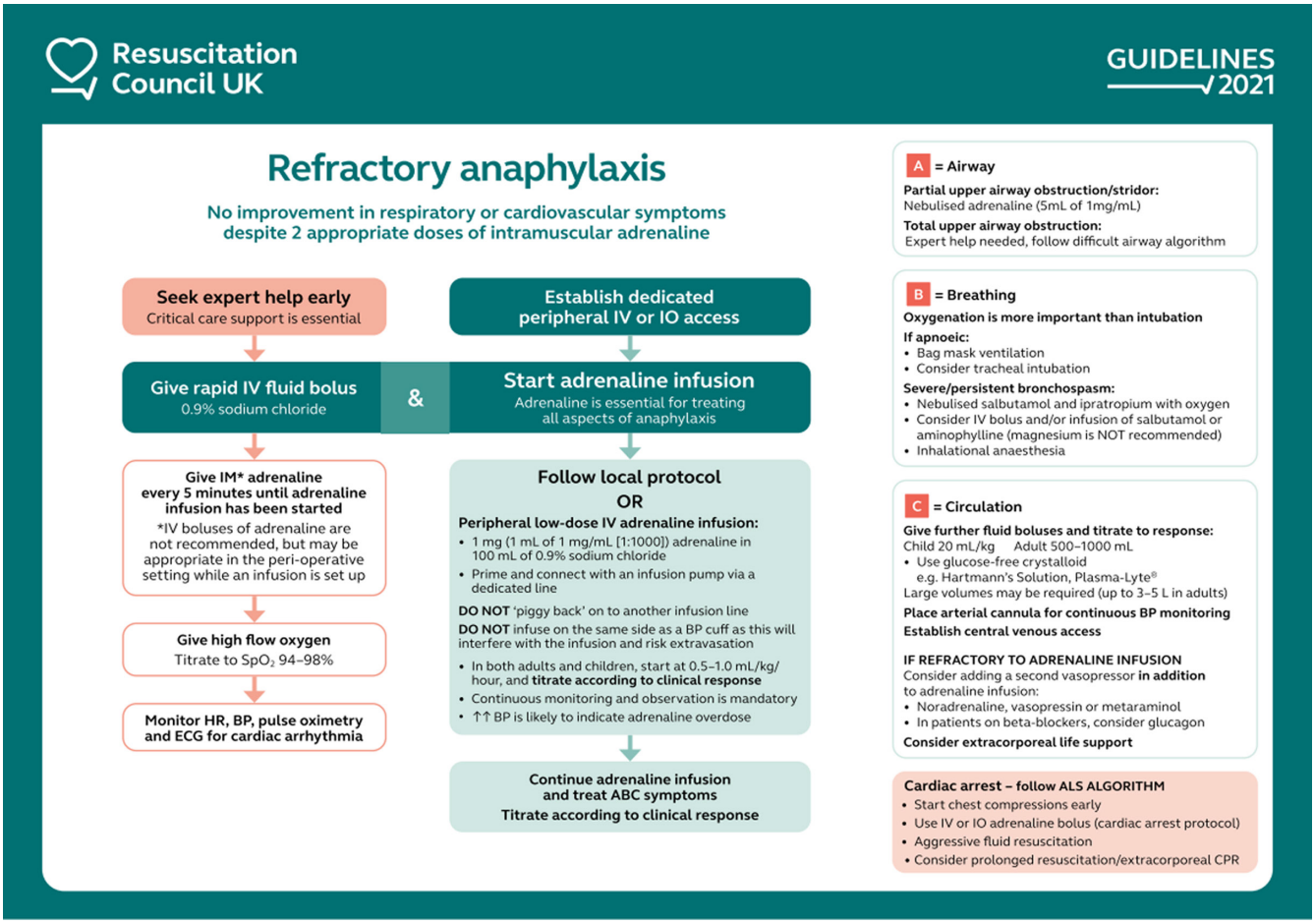

FIGURE 2 | Algorithm for the treatment of refractory anaphylaxis [10]. ALS, advanced life support; BP, blood pressure; CPR, cardiopulmonary resuscitation; ECG, electrocardiography; HR, heart rate; IM, intramuscular; IO, intraosseous; IV, intravenous.

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4 | Conclusions

The management of RA is likely to be improved by improving recognition of severe reactions early, and treating such reactions with appropriate therapy (Figure 2). Defining RA as when anaphylaxis does not respond to two doses of adrenaline and appropriate initial fluid therapy would be a pragmatic choice in flagging the potential for severe reactions, in particular in the perioperative setting, and thus the need to escalate and seek expert help and commence treatment with intravenous adrenaline infusion and additional resuscitative measures. There are limited clinical data to inform the optimal dose of adrenaline IV infusion, fluid therapy (type, timing and volume) and second-line treatment; however, sufficient data exist to inform guidelines in the absence of high-quality studies. Further clinical data are needed to help align current guidelines towards a consensus on how to manage RA.

Author Contributions

G.P.: Design of the study. G.P. and P.J.T.: Initial drafting the manuscript; study conception; data collection. All authors: Analysis and interpretation; revising the manuscript.

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The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

G.P. declares that he has received fees for scientific work or consulting requested by Bausch & Lomb, Meda/Mylan/Viatris, Stallergenes Greer, Novartis, ALK-Abello, DVB Therapeutics, AImmune Therapeutics/ Nestlé, Theravia/CTRS/Admedica. A.M. declares speaker's fees from Aimmune, DVB Technologies, Nestlè Health Science, ALK, Member of Advisoty Board: Novartis, Sanofi, DVB Technologies, ICDM: Regeneron king from Viatris, ALK Nordic, Thermo Fisher Scientific. L.H.G. declares that she has received fees for consulting work for Merck, Bracco, Biomarin and speaker's fees from Viatris, ALK Nordic, Thermo Fisher Scientific. P.J.T. reports grants from UK Medical Research Council, NIHR/Imperial BRC and JM Charitable Foundation; personal fees from UK Food Standards Agency, Aimmune Therapeutics, Allergenis, Aquestive Therapeutics and Novartis, outside of the submitted work; is co-lead of the Resuscitation Council UK Working Group on Anaphylaxis, and current Chairperson of the World Allergy Committee Anaphylaxis Committee. M.W. has received fees for scientific work and/ or consulting requested by Meda/Mylan/Viatris, Novartis, ALK-Abello, DVB Therapeutics, Aimmune, Sanofi, Eli Lilly, Amgen, LEO, Astra Zeneca. A.D. reports personal fees from Novartis, ALK, GSK, Sanofi, Regeneron, Aimmune Therapeutics, DBV Technologies, Nestlé, Stallergenes Greer, DBV Technologies, Nutricia. Grant from Fondation du Souffle, Conseil Régional Hauts-de-France Research Program 2014–2018, outside the submitted work. T.E.D., L.K.T., V.C. and C.T. report no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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