DR. ANDREW F WHYTE (Orcid ID : 0000-0003-3000-3977)

DR. PAUL TURNER (Orcid ID : 0000-0001-9862-5161)

Article type : News & Views: Algorithms in Allergy and Clinical Immunology

REFRACTORY ANAPHYLAXIS: TREATMENTALGORITHM

Manuscript Acceptance Date: 12-Feb-2021

Authors

Nicholas Sargant,¹Amy Dodd,²Anna Hughes,² Andrew F Whyte,³ Jasmeet Soar,^{4#} Paul J. Turner^{5#}

¹Bristol Royal Hospital for Children, Bristol, UK; ²Severn Deanery, UK; ³University Hospitals Plymouth NHS Trust, Plymouth, UK; ⁴North Bristol NHS Trust, Bristol, UK; ⁵National Heart & Lung Institute, Imperial College London, UK

#Joint last authors

Corresponding author:

Dr Paul Turner
National Heart & Lung Institute,
Imperial College London,
Norfolk Place
London, W2 1PG

Tel: +44 (0)20 3312 7754

Email: p.turner@imperial.ac.uk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/all.14780](#)

This article is protected by copyright. All rights reserved

CONFLICTS OF INTEREST

A.F. Whyte is current Chairperson of the Adult Allergy Group of the British Society for Allergy and Clinical Immunology. J. Soar is joint-chair of the Anaphylaxis Working group of the UK Resuscitation Council, Editor of Resuscitation and receives payment from the publisher Elsevier. P.J. Turner reports grants from UK Medical Research Council, NIHR/Imperial Biomedical Research Centre, UK Food Standards Agency, End Allergies Together, and Jon Moulton Charity Trust; personal fees and nonfinancial support from Aimmune Therapeutics, DBV Technologies, and Allergenics; personal fees and other fees from ILSI Europe and UK Food Standards Agency, outside the submitted work; and is current Chairperson of the WAO Anaphylaxis Committee, Chairperson of the Paediatric Allergy Group of the British Society for Allergy and Clinical Immunology, and joint-chair of the Anaphylaxis Working group of the UK Resuscitation Council. The other authors do not report any conflicts of interest.

There is no established definition for refractory anaphylaxis. The European Anaphylaxis Registry use a definition of “anaphylaxis which, despite treatment with at least two doses of minimum 300µg adrenaline, does not achieve normalization” of symptoms.¹ A USA-based panel recently proposed a reaction which “must be treated with 3+ appropriate doses of epinephrine (or initiation of an intravenous epinephrine infusion)”² – a definition which does not specifically refer to treatment response, although this is implied. The Resuscitation Council UK (RCUK) recently updated its guideline on the emergency treatment of anaphylaxis, defining refractory anaphylaxis as a reaction “requiring ongoing treatment despite two (appropriate) doses of intramuscular adrenaline” and proposes an algorithm to facilitate management (Figure 1).³

Refractory anaphylaxis is rare: the European Registry reported a rate of 0.37% of all anaphylaxis cases reported in the registry, with such reactions being 9 times more likely in the perioperative setting compared to community reactions.¹ A systematic review and meta-analysis reported that an estimated 3.4% (95%CI 1.9%-5.9%) of adrenaline-treated reactions have a suboptimal response to two doses of adrenaline, although most respond to three.⁴ Refractory anaphylaxis probably occurs as a result of the ongoing release of inflammatory mediators, insufficient adrenaline (both due to insufficient dosing and lack of circulating volume to ensure drug delivery), and possibly tachyphylaxis.³

Early recognition is essential, in order to obtain the necessary support to rapidly escalate treatment safely. Effective adrenaline causes vasoconstriction and bronchodilation, increases myocardial contractility and inhibits mast cell degranulation.³ Plasma extravasation equivalent to one third of the circulating blood volume can occur within minutes in severe reactions;⁵ however, venous return is significantly compromised even in those without overt haemodynamic compromise.⁶ Intravenous fluid support is therefore necessary, both to treat shock but also maintain adequate circulatory volume to optimise adrenaline delivery.

Data from human case series^{7,8} and animal models⁹ suggest that low-dose intravenous adrenaline infusions may be more effective than intramuscular or intravenous boluses. We therefore recommend a low-dose intravenous infusion in all patients whose reaction

is refractory to initial adrenaline. In the absence of a local protocol, one proposed by Brown et al (Box 1) has proven efficacy,⁷ and is already included in guidelines from Australia and Spain.

All patients must have continuous monitoring including ECG, pulse oximetry and blood pressure. Local critical care support must be obtained to mitigate against the risk of harmful side effects (including tachyarrhythmia, severe hypertension, myocardial infarction and stroke) and dosing errors associated with intravenous adrenaline. Where the clinical response remains suboptimal, there is little evidence on which to recommend second-line vasopressors. Animal models suggest that vasopressors (e.g. vasopressin, metaraminol and noradrenaline) should be used in conjunction with an adrenaline infusion rather than alone.¹⁰ In patients taking beta-blockers, the evidence for glucagon is limited, but should be considered; if administered, monitor for adverse effects including hyperglycaemia, hypokalaemia, hypocalcaemia and vomiting.

Severe bronchospasm is common in food-induced reactions; adrenaline infusion remains the treatment of choice in refractory reactions, but can be supplemented with nebulised and intravenous bronchodilators. Magnesium sulphate is not recommended as it causes significant vasodilation. Nebulised adrenaline can be helpful to treat upper airway obstruction but should not be prioritised over parenteral adrenaline or delay tracheal intubation in cases of critical upper airway obstruction.

Cardiac arrest following anaphylaxis is a situation when prolonged CPR should be considered (including extracorporeal CPR in settings where it is available). This is because the patients have usually arrested rapidly from a previously well state and have a potentially reversible cause. Recommendations for peri-operative anaphylaxis management are to start chest compressions if systolic blood pressure remains below 50mmHg (in adults), especially in the context of bradycardia.¹¹ Intravenous (or interosseous) adrenaline should be administered as per established cardiac arrest protocols.

Refractory anaphylaxis is rare, but occurs at a similar rate to fatal anaphylaxis in the hospital setting. Early recognition and rapid treatment escalation should hopefully improve outcomes for what should be a treatable disease.

REFERENCES

1. Francuzik W, Dölle-Bierke S, Knop M, et al. Refractory Anaphylaxis: Data From the European Anaphylaxis Registry. *Front Immunol*. 2019 Oct 18;10:2482.
2. Dribin TE, Sampson HA, Camargo CA Jr, et al. Persistent, refractory, and biphasic anaphylaxis: A multidisciplinary Delphi study. *J Allergy Clin Immunol*. 2020 Nov;146(5):1089-1096.
3. Dodd A, Hughes A, Sargant N, et al. Evidence update for the treatment of anaphylaxis. *Resuscitation* 2021 (under review).
4. Patel N, Chong KW, Yip AYG, et al. Use of multiple adrenaline doses in anaphylaxis: A systematic review and meta-analysis. *J. Allergy Clin. Immunol*. 2021 (under review).
5. Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986;14(1):17–21.
6. Ruiz-Garcia M, Bartra J, Alvarez O, et al. Cardiovascular changes during peanut-induced allergic reactions in human subjects. *J Allergy Clin Immunol*. 2021;147(2):633-642.
7. Brown SGA, Blackman KE, Stenlake V, et al. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emerg Med J* 2004;21(2):149–54.
8. Alviani C, Burrell S, Macleod A, et al. Anaphylaxis Refractory to intramuscular adrenaline during in-hospital food challenges: A case series and proposed management. *Clin Exp Allergy*. 2020;50(12):1400-1405.
9. Mink SN, Simons FE, Simons KJ, Becker AB, Duke K. Constant infusion of epinephrine, but not bolus treatment, improves haemodynamic recovery in anaphylactic shock in dogs. *Clin Exp Allergy*. 2004;34(11):1776-83.
10. Dewachter P, Raeth-Fries I, Jouan-Hureaux V, et al. A comparison of epinephrine only, arginine vasopressin only, and epinephrine followed by arginine vasopressin on the survival rate in a rat model of anaphylactic shock. *Anesthesiology* 2007;106(5):977-83.
11. Harper NJN, Nolan JP, Soar J, Cook TM. Why chest compressions should start when systolic arterial blood pressure is below 50mmHg in the anaesthetised patient. *Br J Anaesth*. 2020;124(3):234-238.

Figure 1: Algorithm for refractory anaphylaxis
(with permission from Resuscitation Council (UK))

Box 1: Peripheral IV adrenaline infusion regimen for refractory anaphylaxis (adapted from [7])

PERIPHERAL IV ADRENALINE INFUSION REGIMEN
FOR INITIAL TREATMENT OF REFRACTORY ANAPHYLAXIS

PREPARATION

- **Continuous monitoring and observation mandatory:**
 - > ECG, pulse oximetry, non-invasive BP at least every 5 minutes
- Mix 1 mg (1 mL of 1mg/mL [1:1000]) adrenaline in **100 mL** of 0.9% sodium chloride and connect using an infusion pump via a dedicated line.
 - > **Do not “piggy-back” on to another line** unless using an anti-reflux valve.
- DO NOT infuse on the same side as a BP cuff, as frequent measurements will interfere with the infusion and risks extravasation injury.

INITIATION AND ADJUSTMENT

- **In children and adults, start at 0.5-1.0 mL/kg/hour** depending on severity:
 - > Moderate severity: 0.5mL/kg/hour (~0.1 microgram/kg/min)
 - > Severe (hypotensive or hypoxic): 1mL/kg/hour
- **Titrate** up or down according to response, aiming for the lowest effective rate.
 - > Steady state is reached 5-10 minutes after a change in rate.
 - > Monitor infusion site regularly to ensure patency of cannula

- **Tachycardia, tremor, pallor with a normal or raised BP** may indicate excessive adrenaline treatment: reduce the infusion rate (or stop infusion if severe).
- If refractory to adrenaline infusion, seek urgent further expert help. Patients will require central venous access for prolonged infusions; follow local protocols.

WEANING

- **As symptoms improve, reduce the infusion**, aiming for 50% of the starting rate.
- One hour after resolution of all symptoms and signs, wean the infusion over 30 minutes and then stop; monitor closely for recurrence, and restart if necessary.