Anaphylaxis Refractory to intramuscular adrenaline during in-hospital food challenges: A case series and proposed management

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Abstract

Background: Anaphylaxis is a severe, systemic hypersensitivity reaction that can be potentially life-threatening. Anaphylaxis during oral food challenge is not uncommon and can usually be effectively managed with intramuscular adrenaline as first line treatment. Although very rare, fatal anaphylaxis during in-hospital food challenge has been reported.

Objective: We describe our experience of cases of refractory anaphylaxis at in-hospital challenge and propose a framework for escalation of treatment in such cases using intravenous infusion of adrenaline which has been adopted for widespread use elsewhere.

Methods: We present four patients who all experienced severe life-threatening anaphylaxis, refractory to intramuscular adrenaline treatment, during supervised oral food challenges.Patient data were collected from contemporaneous notes, and patient consent was obtained.

Results: In all four cases, the anaphylaxis reactions were amenable to treatment with low-dose intravenous adrenaline, with no reported adverse effects.

Conclusion and clinical relevance: These cases demonstrate the need for clinicians undertaking higher risk allergen challenges to be able to manage cases of severe anaphylaxis refractory to intramuscular adrenaline, and to consider a framework for managing these reactions. While peripheral intravenous adrenaline infusions should always be initiated only in conjunction with expert input, the protocol suggested is simple enough to be undertaken within the hospital environment while more experienced support is obtained.

Keywords
adrenaline, allergy, anaphylaxis, food allergy, oral food challenge
### INTRODUCTION

Anaphylaxis is 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 breathing and/or the circulation and may occur without typical skin features or circulatory shock being present." Based on 10 European studies, the incidence of anaphylaxis is around 1.5-7.9 per 10,000 person years, with a prevalence of 0.3%. Hospitalizations due to anaphylaxis have increased over the past two decades, but fatal anaphylaxis is very uncommon and the rate of fatal food anaphylaxis has not increased over the same time period.

Oral food challenges (OFC) are a key tool to confirm the diagnosis or resolution of food allergy. Anaphylaxis during OFC is not uncommon, and rates vary by patient age, food tested and geographical region. Anaphylaxis is not predictable. A retrospective, multicentre survey of 1635 children and adolescents undergoing a hospital-based peanut food OFC demonstrated an 11% anaphylaxis rate in this group, which is in line with previously reported rates of adrenaline use in 9%-11% of OFC. Fatal anaphylaxis due to food is rare, and until recently, no cases of fatal anaphylaxis had been reported during hospital-based OFC. However, two recent deaths have been reported in the context of OFC conducted in specialist centres: a 3-year-old boy following a baked milk OFC in the USA, and an 11-year-old boy who died after a peanut OFC. The risk of severe anaphylaxis during OFC conducted under medical supervision must therefore be recognized. In this paper, we present four cases of severe anaphylaxis during hospital-based OFC that were refractory to initial treatment and discuss the management approach to these cases.

### METHODS

This paper is based on four paediatric cases of severe anaphylaxis during hospital-based food challenge that were refractory to initial treatment, between 2018 and 2019 in the South-East of England. Informed consent was obtained from the families for this report. Data on the indications for challenge, challenge procedure, nature of the reaction, treatment given and response to therapy were collected from the chart of each patient.

### RESULTS

#### 3.1 Case 1

A 17-year-old Caucasian male with isolated peanut allergy and index reaction at age 1 year (hives and facial angioedema after eating peanut butter). He had since avoided peanut, with no further reactions. He had been prescribed fluticasone/salmeterol inhaler for asthma but was non-compliant although this did not cause him significant symptoms and baseline spirometry was within normal range. Allergy testing at most recent follow-up was consistent with PR10 sensitization and declining levels of IgE against seed storage proteins, suggesting that true peanut allergy may have resolved and been replaced by pollen food allergy syndrome (see Table 1). An OFC was therefore undertaken to clarify his diagnosis prior to transitioning to adult services, given his decision not to carry adrenaline auto-injector on the basis that he could not remember experiencing a reaction.

Five minutes after the second dose (0.16 g peanut protein), he developed urticaria and rhinitis, followed by wheezing and chest tightness. Despite prompt treatment with a 500 mcg IM adrenaline auto-injector (Emerade, Bausch and Lomb) administered by a specialist nurse, his symptoms progressed with worsening bronchoconstriction, hypoxia (oxygen saturations 91% in room air), tachycardia and a widened pulse pressure. He was kept in a semi-recumbent position and received a further three doses of 500 mcg IM adrenaline by auto-injector over the following 20 minutes (alternating limbs for administration), IV hydrocortisone and chlorphenamine, 500 ml of intravenous saline and nebulized salbutamol. Despite this, the bronchospasm persisted with ongoing tachycardia. At 40 minutes after onset, a peripheral adrenaline infusion of 0.1 mcg/kg/min was commenced via a large-bore peripheral cannula. He responded rapidly and was then transferred to the paediatric intensive care unit (PICU) where he was weaned off the infusion over the following 6 hours. He was discharged the following day.

#### 3.2 Case 2

A 15-year-old teenage male of Afro Caribbean origin, with multiple allergies to cow’s milk, egg, peanut, cashew, pistachio and shrimp. He was prescribed a regular budesonide/formoterol inhaler, and his asthma was well-controlled with minimal breakthrough symptoms. He had experienced previous anaphylaxis at age 10 years to an unknown trigger (possibly nut/egg contamination) which was treated with IM adrenaline. During his most recent clinic review, he reported he was eating significant quantities of rice cakes containing milk. Based on this history and clinical testing (Table 1), he was booked to undergo a baked milk OFC to assess tolerance to baked milk.

He completed the full challenge protocol (1.37 g milk protein baked into a muffin). Thirty minutes later, he experienced chest tightness and self-administered his salbutamol inhaler prior to informing the supervising nurse. He immediately received 500 mcg IM adrenaline via needle and syringe, oral cetirizine and prednisolone, nebulized salbutamol and high flow oxygen. Despite this, he continued to experience significant dyspnoea and was treated with a further two 500 mcg doses of IM adrenaline (also via needle and syringe) with no improvement. He was given an intravenous adrenaline bolus of 10 micrograms of adrenaline (equivalent to 0.17 mcg/kg) over five minutes with immediate benefit. No further adrenaline was required, and he was discharged the following day.
| Case | Age (years) | Food allergies | Co-morbidities | Food challenged, eliciting and cumulative allergen dose | SPT | sIgE (kUA/L) | Key events post-triggering dose (minutes) | Initial treatment | Final treatment |
|------|-------------|----------------|----------------|---------------------------------------------------------|-----|-------------|------------------------------------------|-----------------|----------------|
| 1    | 17          | Peanut         | Asthma (ICS + LABA) | Peanut 7 mm | Peanut 2.33 | Any symptoms: 5 | IM adrenaline 0.5 mg x4, hydrocortisone, chlorphenamine, nebulized salbutamol, fluid bolus, oxygen | 0.1 mcg/kg/min peripheral adrenaline infusion |
|      |             |                |                | Birch pollen 6 mm | Ara h 2 0.47 | Anaphylaxis: 8 | IV adrenaline: 10 | Improving: 50 |
|      |             |                |                |               | Ara h 8 6.7 | IV adrenaline: 40 | Improving: 50 |
|      |             |                |                |               |                |                |               |
| 2    | 15          | Cow’s milk, egg, peanut, cashew, pistachio, shrimp | Asthma (ICS + LSBA), eczema | Baked milk 18 mm | Cow’s milk > 100 | Any symptoms: 30 | IM adrenaline 0.5 mg x3, cetirizine, prednisolone, nebulized salbutamol, oxygen | 10 mcg adrenaline as an IV bolus (equivalent to 0.17 mcg/kg) |
|      |             |                |                | Boiled milk 7 mm |                | Anaphylaxis: 30 | IV adrenaline: 35 | Improving: 65 |
|      |             |                |                |               |                | IV adrenaline: 60 |               |
|      |             |                |                |               |                |                |               |
| 3    | 11          | Peanut         | Asthma (ICS + LABA) | Peanut 5 mm | Peanut> 100 | Any symptoms: 10 | IM adrenaline (0.3 mg x 3), chlorphenamine, nebulized adrenaline and salbutamol, iv fluids, hydrocortisone | 0.17 mcg/kg/min peripheral adrenaline infusion |
|      |             |                |                |               | Ara h 1 41.5 | Anaphylaxis: 160 | IV adrenaline: 220 | Improving: 235 |
|      |             |                |                |               | Ara h 2 > 100 | IV adrenaline: 162 |               |
|      |             |                |                |               | Ara h 3 6.7 | IV adrenaline: 220 |               |
|      |             |                |                |               |                |                |               |
| 4    | 15          | Peanut, tree nuts | Asthma (ICS) | Peanut 15 mm | Peanut> 100 | Any symptoms: 2 | IM adrenaline (0.5 mg x 3), nebulized salbutamol, iv fluid bolus | 0.17 mcg/kg/min peripheral adrenaline infusion |
|      |             |                |                |               | Ara h 1 86.5 | Anaphylaxis: 19 | IV adrenaline: 20 | Improving: 43 |
|      |             |                |                |               | Ara h 2 > 100 | IV adrenaline: 20 |               |
|      |             |                |                |               | Ara h 3 > 100 | IV adrenaline: 40 |               |

Abbreviations: ICS, inhaled corticosteroids; LABA, long acting beta-agonist.
An 11-year-old Caucasian female underwent double-blind, placebo-controlled, food challenge (DBPCFC) to peanut, as part of a research study. She had a history of prior anaphylaxis at age 3 years (generalized urticaria and wheeze, approximately 15 minutes after ingestion of breakfast cereal containing peanut), which responded to IM adrenaline and salbutamol nebulizer. Her asthma was well-controlled on a daily fluticasone/salmeterol inhaler.

During OFC, she developed mild lip oedema, odynophagia and abdominal pain to cumulative 143 mg peanut protein. The challenge was stopped, and she was treated with cetirizine, 500 mL intravenous saline and buscopan. She vomited 60 minutes later, which caused throat tightness and was associated with generalized urticaria. She was given 5 mg iv chlorphenamine. Her symptoms settled, and she fell asleep for 40 minutes. When she awoke, she went to the bathroom and was noted to develop facial flushing. She became sleepy again and was noted to have a soft inspiratory stridor. On auscultation, she has markedly reduced air entry, bilateral biphasic wheeze which worsened despite IM adrenaline administered using an auto-injector 300 mcg (EpiPen, Meda Pharmaceuticals), nebulized adrenaline (4ml of 1:1000) and high flow oxygen. Over the next 50 minutes, she was given 2 further doses of IM adrenaline (10mcg/kg by needle/syringe), iv hydrocortisone, back-to-back nebulized salbutamol while senior PICU input was awaited. She had ongoing severe dyspnoea, with use of accessory muscles but maintained her saturations in high flow oxygen. Given her ongoing respiratory distress, a decision was made by the team to commence a peripheral adrenaline infusion (0.17 mcg/kg/min). Her blood pressure remained normal throughout. Within 30 minutes, her respiratory distress had resolved, and she was able to talk in complete sentences. The infusion was weaned over the following 6 hours, and she was discharged from PICU the next day.

A 15-year-old white Caucasian female with multiple nut allergies (peanut, hazelnut, macadamia) and prior anaphylaxis to peanut requiring 2 doses of IM adrenaline at age 13 years. She had well-controlled asthma (beclomethasone twice daily). She attended hospital for a DBPCFC to peanut, as part of a research study.

Two minutes after her fifth dose (100 mg peanut protein, cumulative dose 144 mg), she developed abdominal pain and throat tightness. She was noted to have some throat clearing, but her peak flow remained normal and she had no wheeze. Twenty minutes later, she developed bilateral, biphasic wheezing and was given 500 mcg IM adrenaline (Emerade, Bausch and Lomb) and salbutamol (10 puffs via spacer). 500 ml of normal saline was commenced over 30 minutes. However, she had minimal response to treatment, with worsening dyspnoea and progressive truncal urticaria. A further 2 doses of IM adrenaline (500 mcg) were given, while an intravenous adrenaline infusion was set-up. This was commenced 20 minutes following the initial IM adrenaline dose, at (0.17 mcg/kg/min). Within 2 minutes, her inspiratory effort had normalized although she still had some expiratory wheeze which settled within 10 minutes. Blood pressure was normal throughout. The infusion was weaned over the following 3 hours, and she was transferred to the ward for overnight observation.

National and international guidelines recommend the administration of intramuscular adrenaline for initial management of anaphylaxis.12-14 Despite this, adrenaline remains significantly underused, both in the community,15 but also in hospital16 and even in simulated scenarios errors frequently occur.17 There are, unsurprisingly,
Intravenous adrenaline is not without risks, and guidelines suggest its use be limited to “those experienced in the use and titration of vasopressors in their normal clinical practice (e.g. anaesthetists, emergency physicians, intensive care doctors).” However, the protocol suggested by Brown et al. reproduces in Figure 1 forms part of established anaphylaxis management in Australia and Spain and was used in Cases 3 and 4. In a series of 19 patients treated successfully with this protocol, no adverse reactions were noted related to the intervention. The protocol suggested by Brown et al. is simple enough to be undertaken within the hospital environment while more experienced support is obtained. After failure to respond to the second dose of adrenaline, an IV infusion should be prepared; in our experience, this can be achieved in under 5 minutes where an emergency box has been prepared in advance. At the same time, large-bore peripheral IV access should be obtained, continuous ECG monitoring established and support from the local anaesthetic or intensive care team sought. We consider an intravenous infusion to be the safest option, given that intravenous adrenaline boluses are associated with greater dosing errors and can contribute to adverse outcomes, including tachyarrhythmias, pulmonary oedema and hypertensive crisis.

An additional key element in the management of severe anaphylaxis is avoiding an upright posture, which has been associated with fatal events (thought to be due to postural hypotension in the context of an anaphylaxis-induced decrease in venous return, causing sudden circulatory collapse). A recumbent or semi-recumbent posture with legs elevated is preferable. It is crucial that in severe reactions, healthcare staff avoid the temptation to move patients to a stabilization/high dependency area prior to stabilization. This may entail the setting up of an adrenaline infusion in a clinical area where staff are unfamiliar with its use: this must be addressed in any local protocol, and risk mitigated through staff training and support from critical care areas.

In summary, we report four cases of refractory anaphylaxis successfully treated with low-dose intravenous adrenaline through a peripheral cannula. While IM adrenaline remains the mainstay of first aid management of anaphylaxis, we encourage physicians who routinely perform procedures such as OFC to consider a framework for managing refractory reactions; this should include consideration of a peripheral intravenous adrenaline infusion (according to Figure 1 & Table 2) as a rescue option while specialist critical care support is obtained.

**TABLE 2** Recommendations for management of anaphylaxis refractory to initial IM adrenaline

| Author’s recommendations where anaphylaxis occurs refractory to initial dose of IM adrenaline |
|-----------------------------------------------------------------------------------|
| 1. Call for help |
| 2. Apply high flow oxygen. Do not move the patient but leave in semi-recumbent position. |
| 3. Administer 2nd dose of IM adrenaline at 10 mcg/kg maximum 500 mcg using needle and syringe, into anterolateral thigh (use opposite side to initial IM adrenaline) |
| 4. Apply ECG/HR/BP monitoring |

IV adrenaline infusion (see Figure 1):
- Secure 2 x wide-bore intravenous cannula, for example antecubital fossa.
- Prepare IV adrenaline infusion and initiate as per Figure 1
- Give IV fluids vis second cannula (adrenaline may be ineffective in the absence of adequate fluid resuscitation)
- Seek urgent intensive care or anaesthetic support

**CONFLICT OF INTEREST**

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chairperson of the EAACI Anaphylaxis Guideline Committee. The remaining authors have no COI to declare.

AUTHOR CONTRIBUTION
CA wrote the manuscript, with review and contributions from PT, GR and MEL. SB, AM and SE provided case information.

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