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14 **Refractory anaphylaxis during in-hospital food challenges: case series and proposed**
15 **management**

16

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37 GR is current chairperson of the EAACI Anaphylaxis Guideline Committee.

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42

43 **Abstract**

44 **Background**

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

49 **Objective**

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

53 **Methods**

54 We present 4 patients who all experienced severe life-threatening anaphylaxis, refractory to
55 intramuscular adrenaline treatment, during supervised oral food challenges. Patient data were collected
56 from contemporaneous notes and patient consent was obtained.

57 **Results**

58 In all 4 cases, the anaphylaxis reactions were amenable to treatment with low dose intravenous
59 adrenaline, with no reported adverse effects.

60 **Conclusion and clinical relevance**

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

66

67

69 Introduction

70 Anaphylaxis is a “serious systemic hypersensitivity reaction that is usually rapid in onset and may cause
71 death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or
72 the circulation, and may occur without typical skin features or circulatory shock being present” (1). Based
73 on 10 European studies the incidence of anaphylaxis is around 1.5-7.9 per 10000 person years, with a
74 prevalence of 0.3% (2). Hospitalisations due to anaphylaxis have increased over the past 2 decades but
75 fatal anaphylaxis is very uncommon and the rate of fatal food anaphylaxis has not increased over the
76 same time period (3)

77 Oral food challenges (OFC) are a key tool to confirm the diagnosis or resolution of food allergy (4).

78 Anaphylaxis during OFC is not uncommon, and rates vary by patient age, food tested and geographical
79 region. Anaphylaxis is not predictable (5). A retrospective, multicentre survey of 1635 children and
80 adolescents undergoing a hospital-based peanut food OFC demonstrated an 11% anaphylaxis rate in this
81 group (6), which is in line with previously reported rates of adrenaline use in 9-11% of OFC (7, 8). Fatal
82 anaphylaxis due to food is rare (9) and until recently, no cases of fatal anaphylaxis had been reported
83 during hospital-based OFC. However, two recent deaths have been reported in the context of OFC
84 conducted in specialist centres: a 3-year-old boy following a baked milk OFC in the USA (10), and an
85 11-year-old boy who died after a peanut OFC (11). The risk of severe anaphylaxis during OFC conducted
86 under medical supervision must therefore be recognized. In this paper, we present 4 cases of severe
87 anaphylaxis during hospital-based OFC that were refractory to initial treatment and discuss the
88 management approach to these cases.

89 Methods

90 This paper is based on 4 paediatric cases of severe anaphylaxis during hospital-based food challenge that
91 were refractory to initial treatment, between 2018 and 2019 in the South-East of England. Informed
92 consent was obtained from the families for this report. Data on the indications for challenge, challenge
93 procedure, nature of the reaction, treatment given and response to therapy was collected from the chart
94 of each patient.

95 Results

96 Case 1

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

106 Five minutes after the second dose (0.16g peanut protein) he developed urticaria and rhinitis, followed by
107 wheezing and chest tightness. Despite prompt treatment with a 500mcg IM adrenaline auto-injector
108 (Emerade, Bausch and Lomb) administered by a specialist nurse, his symptoms progressed with worsening
109 bronchoconstriction, hypoxia (oxygen saturations 91% in room air), tachycardia and a widened pulse
110 pressure. He was kept in a semi-recumbent position and received a further 3 doses of 500mcg IM
111 adrenaline by auto-injector over the following 20 minutes (alternating limbs for administration), IV
112 hydrocortisone and chlorphenamine, 500 ml of intravenous saline and nebulized salbutamol. Despite this,
113 the bronchospasm persisted with ongoing tachycardia. At 40 minutes after onset, a peripheral adrenaline
114 infusion of 0.1mcg/kg/min was commenced via a large bore peripheral cannula. He responded rapidly and
115 was then transferred to the paediatric intensive care unit (PICU) where he was weaned off the infusion
116 over the following 6 hours. He was discharged the following day.

117 Case 2

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

125 He completed the full challenge protocol (1.37 grams milk protein baked into a muffin). Thirty minutes
126 later, he experienced chest tightness and self-administered his salbutamol inhaler prior to informing the
127 supervising nurse. He immediately received 500mcg IM adrenaline via needle and syringe, oral cetirizine

128 and prednisolone, nebulised salbutamol, and high flow oxygen. Despite this he continued to experience
129 significant dyspnoea and was treated with a further two 500mcg doses of IM adrenaline (also via needle
130 and syringe) with no improvement. He was given an intravenous adrenaline bolus of 10 micrograms of
131 adrenaline (equivalent to 0.17mcg/kg) over five minutes with immediate benefit. No further adrenaline
132 was required, and he was discharged the following day.

133 Case 3

134 An 11 year old Caucasian female underwent double-blind, placebo-controlled, food challenge (DBPCFC) to
135 peanut, as part of a research study. She had a history of prior anaphylaxis at age 3 years (generalised
136 urticaria and wheeze, approximately 15 minutes after ingestion of breakfast cereal containing peanut),
137 which responded to IM adrenaline and salbutamol nebuliser. Her asthma was well controlled on a daily
138 fluticasone/salmeterol inhaler.

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

155 Case 4

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

159 Two minutes after her fifth dose (100mg peanut protein, cumulative dose 144mg), she developed
160 abdominal pain and throat tightness. She was noted to have some throat clearing but her peak flow
161 remained normal and she had no wheeze. Twenty minutes later, she developed bilateral, biphasic
162 wheezing and was given 500mcg IM adrenaline (Emerade, Bausch and Lomb) and salbutamol (10 puffs via
163 spacer). 500ml of normal saline was commenced over 30 minutes. However, she had minimal response to
164 treatment, with worsening dyspnoea and progressive truncal urticaria. A further 2 doses of IM adrenaline
165 (500mcg) were given while an intravenous adrenaline infusion was set-up. This was commenced 20
166 minutes following the initial IM adrenaline dose, at (0.17mcg/kg/min). Within 2 minutes, her inspiratory
167 effort had normalised although she still had some expiratory wheeze which settled within 10 minutes.
168 Blood pressure was normal throughout. The infusion was weaned over the following 3 hours and she was
169 transferred to the ward for overnight observation.

170 Discussion

171 National and international guidelines recommend the administration of intramuscular adrenaline for
172 initial management of anaphylaxis (12-14). Despite this, adrenaline remains significantly underused, both
173 in the community (15), but also in hospital (16) and even in simulated scenarios errors frequently occur
174 (17). There are, unsurprisingly, no randomized controlled on the use of adrenaline for anaphylaxis, and
175 recommendations are based on observational data, consensus opinion and pharmacological effect (14,
176 18, 19). Adrenaline should be administered intramuscularly to the antero-lateral thigh, using 1:1000
177 adrenaline at a dose of 0.01ml/kg (maximum dose 500mcg or 0.5ml of 1:1000). Alternatively, fixed doses
178 based on age and weight can be used for greater ease (12, 13). Intramuscular adrenaline works best if
179 used promptly, before anaphylaxis has had time to progress (20) and it has an excellent safety profile (12,
180 13, 21). Transient effects after IM adrenaline administration include pallor, tremor, dizziness, palpitations
181 and headache; these indicate that a therapeutic dose has been given (14).

182 Around 10% of patients who use IM adrenaline for food-induced anaphylaxis continue to experience
183 anaphylaxis requiring at least one further dose to alleviate symptoms (15, 22). All of our patients
184 experienced life-threatening anaphylaxis, with prominent lower respiratory tract involvement
185 (bronchoconstriction). All four were teenagers, an age group known to be at higher risk of fatal reactions

186 (23, 24). They also had asthma, a common feature in fatal food-induced anaphylaxis, affecting up to 75%
187 of cases (23, 24). Of note, they demonstrated worsening of symptoms despite multiple doses of IM
188 adrenaline, thus it is possible that these patients might have suffered a fatal outcome had their reactions
189 occurred out of hospital (25).

190 Intramuscular adrenaline administration alone is not a guarantee of anaphylaxis reversal: in fact, one third
191 of fatalities due to food-anaphylaxis in the UK receive timely adrenaline and yet still die (26-28). Given the
192 available data from venom-induced anaphylaxis (29), it is likely that this reflects a need for more intensive
193 adrenaline administration – beyond that achievable with adrenaline autoinjectors – together with
194 intravenous fluids. A further concern is the limited impact of intramuscular adrenaline on cardiovascular
195 function during anaphylaxis, in contrast to the significant beneficial effects on respiratory symptoms (30).
196 Therefore, patients requiring more than two doses of IM adrenaline are likely to require an adrenaline
197 infusion (12, 13).

199 Intravenous adrenaline is not without risks, and guidelines suggest its use be limited to “*those experienced*
200 *in the use and titration of vasopressors in their normal clinical practice (e.g., anaesthetists, emergency*
201 *physicians, intensive care doctors).*” (12). However, the protocol suggested by Brown et al (29) and
202 reproduced in Figure 1 forms part of established anaphylaxis management in Australia and Spain, and was
203 used in Cases 3 and 4. In a series of 19 patients treated successfully with this protocol, no adverse
204 reactions were noted related to the intervention (29). The protocol suggested by Brown et al is simple
205 enough to be undertaken within the hospital environment while more experienced support is obtained.
206 After failure to respond to the second dose of adrenaline, an IV infusion should be prepared; in our
207 experience, this can be achieved in under 5 minutes where an emergency box has been prepared in
208 advance. At the same time, large-bore peripheral IV access should be obtained, continuous ECG
209 monitoring established and support from the local anaesthetic or intensive care team sought. We
210 consider an intravenous infusion to be the safest option, given that intravenous adrenaline boluses are
211 associated with greater dosing errors and can contribute to adverse outcomes, including
212 tachyarrhythmias, pulmonary oedema and hypertensive crisis (14, 21, 25, 31).

213 An additional key element in the management of severe anaphylaxis is avoiding an upright posture, which
214 has been associated with fatal events (thought to be due to postural hypotension in the context of an
215 anaphylaxis-induced decrease in venous return, causing sudden circulatory collapse (14, 32)). A
216 recumbent or semi-recumbent posture with legs elevated is preferable (14, 26). It is crucial that in severe

217 reactions, healthcare staff avoid the temptation to move patients to a stabilization/ high dependency area
218 prior to stabilisation. This may entail the setting up of an adrenaline infusion in a clinical area where staff
219 are unfamiliar with its use: this must be addressed in any local protocol, and risk mitigated through staff
220 training and support from critical care areas.

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

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References

1. Turner PJ, Worm M, Ansotegui IJ, El-Gamal Y, Rivas MF, Fineman S, et al. Time to revisit the definition and clinical criteria for anaphylaxis? The World Allergy Organization journal. 2019;12(10):100066.
2. Panesar SS, Javad S, de Silva D, Nwaru BI, Hickstein L, Muraro A, et al. The epidemiology of anaphylaxis in Europe: a systematic review. Allergy. 2013;68(11):1353-61.
3. Turner PJ, Campbell DE, Motosue MS, Campbell RL. Global Trends in Anaphylaxis Epidemiology and Clinical Implications. The Journal of Allergy and Clinical Immunology In Practice. 2020;8(4):1169-76.
4. Bird JA, Leonard S, Groetch M, Assa'ad A, Cianferoni A, Clark A, et al. Conducting an Oral Food Challenge: An Update to the 2009 Adverse Reactions to Foods Committee Work Group Report. The Journal of Allergy and Clinical Immunology In Practice. 2020;8(1):75-90.e17.
5. Roberts G, Allen K, Ballmer-Weber B, Clark A, Crevel R, Dunn Galvin A, et al. Identifying and managing patients at risk of severe allergic reactions to food: Report from two iFAAM workshops. Clinical and Experimental Allergy.. 2019;49(12):1558-66.
6. Arkwright PD, MacMahon J, Koplin J, Rajput S, Cross S, Fitzsimons R, et al. Severity and threshold of peanut reactivity during hospital-based open oral food challenges: An international multicenter survey. Pediatric Allergy and Immunology.. 2018;29(7):754-61.
7. Perry TT, Matsui EC, Conover-Walker MK, Wood RA. Risk of oral food challenges. The Journal of Allergy and Clinical Immunology. 2004;114(5):1164-8.
8. Lieberman JA, Cox AL, Vitale M, Sampson HA. Outcomes of office-based, open food challenges in the management of food allergy. The Journal of Allergy and Clinical Immunology. 2011;128(5):1120-2.
9. Umasunthar T, Leonardi-Bee J, Hodes M, Turner PJ, Gore C, Habibi P, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. Clinical and Experimental Allergy.. 2013;43(12):1333-41.
10. Roberts G. Food challenges, the risks and benefits. Clinical and Experimental Allergy.. 2017;47(9):1106-7.
11. Pouessel G, Beaudouin E, Tanno LK, Drouet M, Deschildre A, Labreuche J, et al. Food-related anaphylaxis fatalities: Analysis of the Allergy Vigilance Network((R)) database. Allergy. 2019;74(6):1193-6.
12. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P, et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Resuscitation. 2008;77(2):157-69.
13. Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014;69(8):1026-45.

14. Simons FE, Arduzzo LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *The World Allergy Organization journal*. 2011;4(2):13-37.
15. Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J, et al. The use of adrenaline autoinjectors by children and teenagers. *Clinical and Experimental Allergy*.. 2012;42(2):284-92.
16. Anagnostou K, Turner PJ. Myths, facts and controversies in the diagnosis and management of anaphylaxis. *Archives of disease in childhood*. 2019;104(1):83-90.
17. Maa T, Scherzer DJ, Harwayne-Gidansky I, Capua T, Kessler DO, Trainor JL, et al. Prevalence of Errors in Anaphylaxis in Kids (PEAK): A Multicenter Simulation-Based Study. *The Journal of Allergy and Clinical Immunology: In Practice*. 2019.
18. Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline for the treatment of anaphylaxis: cochrane systematic review. *Allergy*. 2009;64(2):204-12.
19. Simons FE, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. *The World Allergy Organization journal*. 2015;8(1):32.
20. Bautista E, Simons FE, Simons KJ, Becker AB, Duke K, Tillett M, et al. Epinephrine fails to hasten hemodynamic recovery in fully developed canine anaphylactic shock. *International archives of allergy and immunology*. 2002;128(2):151-64.
21. Campbell RL, Bellolio MF, Knutson BD, Bellamkonda VR, Fedko MG, Nestler DM, et al. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *The Journal of Allergy and Clinical Immunology In Practice*. 2015;3(1):76-80.
22. Ierodiakonou D PN, Chong KW, Yip AG, Bartra J, Boyle RK, Turner PJ. Need for more than 1 dose of adrenaline to treat anaphylaxis: A systematic review and meta-analysis. Abstract presented at the EAACI International Annual Conference; London, UK2020.
23. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal Anaphylaxis: Mortality Rate and Risk Factors. *The journal of allergy and clinical immunology In practice*. 2017;5(5):1169-78.
24. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *The Journal of Allergy and Clinical Immunology*. 2015;135(4):956-63.e1.
25. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clinical and Experimental Allergy*.. 2000;30(8):1144-50.

26. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. *The Journal of Allergy and Clinical Immunology*. 2007;119(4):1018-9.
27. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *The Journal of Allergy and Clinical Immunology*. 2007;119(4):1016-8.
28. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, Kohli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *The Journal of Allergy and Clinical Immunology*. 2016;137(4):1128-37.e1.
29. Brown SG, Blackman KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emergency Medicine Journal*. 2004;21(2):149-54.
30. Ruiz-Garcia M, Hayward C, Tang A, Clark A, Skypala IJ, Durham SR, et al. Effects of Intramuscular Epinephrine on Cardiovascular Parameters during IgE-Mediated Allergic Reactions to Peanut. *Journal of Allergy and Clinical Immunology*. 2016;137(2, Supplement):AB50.
31. Johnston SL, Unsworth J, Gompels MM. Adrenaline given outside the context of life threatening allergic reactions. *BMJ (Clinical research ed)*. 2003;326(7389):589-90.
32. Mullins RJ, Wainstein BK, Barnes EH, Liew WK, Campbell DE. Increases in anaphylaxis fatalities in Australia from 1997 to 2013. *Clinical and Experimental Allergy*. 2016;46(8):1099-110.

Table 1 Patient characteristics. ICS= inhaled corticosteroids. LABA= long acting beta-agonist

Case	Age (years)	Food allergies	Co-morbidities	Food challenged, eliciting and cumulative allergen dose	SPT	slgE (kUA/l)	Key events post triggering dose (minutes)	Initial treatment	Final treatment
1	17	Peanut	Asthma (ICS +LABA)	Peanut Eliciting: 0.16g Cumulative: 0.32 g	Peanut 7mm Birch pollen 6mm	Peanut 2.33 Ara h 2 0.47 Ara h 8 6.7	Any symptoms: 5 Anaphylaxis: 8 IM adrenaline: 10 IV adrenaline: 40 Improving: 50	IM adrenaline 0.5mg x4, hydrocortisone, chlorphenamine, nebulised salbutamol, fluid bolus, oxygen	0.1mcg/kg/min peripheral adrenaline infusion
2	15	Cow's milk, egg, peanut, cashew, pistachio, shrimp	Asthma (ICS + LSBA), eczema	Baked milk Eliciting: 0.68g Cumulative: 1.37g	Milk 18mm Boiled milk 7mm	Cow's milk >100	Any symptoms: 30 Anaphylaxis: 30 IM adrenaline: 35 IV adrenaline: 60 Improving: 65	IM adrenaline 0.5mg x3, cetirizine, prednisolone, nebulised salbutamol, oxygen	10 mcg adrenaline as an IV bolus (equivalent to 0.17mcg/kg)
3	11	Peanut	Asthma (ICS +LABA)	Peanut	Peanut 5mm	Peanut >100 Ara h 1 41.5	Any symptoms: 10 Anaphylaxis: 160	IM adrenaline (0.3mg x 3), chlorphenamine,	0.17mcg/kg/min peripheral

				Eliciting: 0.10g Cumulative: 0.14 g		Ara h 2 >100 Ara h 3 6.78	IM adrenaline: 162 IV adrenaline: 220 Improving: 235	nebulised adrenaline and salbutamol, iv fluids, hydrocortisone	adrenaline infusion
4	15	Peanut, tree nuts	Asthma (ICS)	Peanut Eliciting: 0.10g Cumulative: 0.14g	Peanut 15mm	Peanut >100 Ara h 1 86.5 Ara h 2 >100 Ara h 3 >100	Any symptoms: 2 Anaphylaxis: 19 IM adrenaline: 20 IV adrenaline: 40 Improving: 43	IM adrenaline (0.5mg x 3), nebulised salbutamol, iv fluid bolus	0.17mcg/kg/min peripheral adrenaline infusion

Table 2 Recommendations for management of anaphylaxis refractory to initial IM adrenaline

Table 2: 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 10mcg/kg maximum 500mcg using needle and syringe, into antero-lateral thigh (use opposite side to initial IM adrenaline) 4. Apply ECG/HR/BP monitoring	
<u>IV adrenaline infusion (see Figure 1):</u> • Secure 2 x wide-bore intravenous cannula e.g. 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	

Figure 1 Proposed adrenaline infusion guideline (29)

ADRENALINE INFUSION GUIDELINE FOR ANAPHYLAXIS

1 PREPARATION

- Requires continuous physiological monitoring (**ECG, SpO2, BP 3-5 minutely**)
- Give via an **infusion pump** through a **dedicated line**, or piggybacked with **anti-reflux valves on all other lines** to prevent the adrenaline going back up into another fluid bag instead of into the patient
- BEWARE infusions on the same side as a BP cuff; frequent BP measurements may interfere with the infusion
- FIRST BAG: **1mg adrenaline in 100 mL saline = 0.01mg/mL (1:100,000)**
i.e. **1 mL/kg/Hr gives the equivalent of a 0.01 mg/kg dose over 1 hour (0.17 ug/kg/min)**

2 INITIATION & ADJUSTMENT

- **Start at 0.5-1 mL/kg/Hr** (30-100 mL/Hr in adults) depending on reaction severity:
Moderate severity: 0.5 mL/kg/Hr Severe (hypotensive or hypoxic): 1 mL/kg/Hr
- **Titrate** up or down according to response, aiming for the lowest effective infusion rate
Allow for a short elimination half-life; steady state is reached 5-10 minutes after a change in the infusion rate
- **Tachycardia, tremor, and pallor with a normal or raised blood pressure are signs of adrenaline toxicity:**
Reduce the infusion rate (if toxicity is severe, stop the infusion briefly before recommencing at a lower rate)
- **The safe maximum rate of adrenaline infusion** is unknown, but is probably <1 ug/kg/min (6mL/kg/Hr of the above solution of 1mg in 100 mL).

3 DE-ESCALATION AND CESSATION

- **As the reaction resolves, an infusion that was previously therapeutic can start to have toxic effects:**
Therefore, when features resolve begin reducing the infusion, aiming for around half the starting rate if possible
- 60 minutes after the resolution of all symptoms and signs, wean the infusion over another 30 minutes and stop; watch closely for reaction recurrence

Figure 1 Proposed adrenaline infusion guideline (29)