

Northumbria Research Link

Citation: Curry, Sam (2021) Managing anaphylaxis in adults. British Journal of Nursing, 30 (19). pp. 1118-1122. ISSN 0966-0461

Published by: Mark Allen Publishing

URL: <https://doi.org/10.12968/bjon.2021.30.19.1118>
<<https://doi.org/10.12968/bjon.2021.30.19.1118>>

This version was downloaded from Northumbria Research Link:
<http://nrl.northumbria.ac.uk/id/eprint/47692/>

Northumbria University has developed Northumbria Research Link (NRL) to enable users to access the University's research output. Copyright © and moral rights for items on NRL are retained by the individual author(s) and/or other copyright owners. Single copies of full items can be reproduced, displayed or performed, and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided the authors, title and full bibliographic details are given, as well as a hyperlink and/or URL to the original metadata page. The content must not be changed in any way. Full items must not be sold commercially in any format or medium without formal permission of the copyright holder. The full policy is available online: <http://nrl.northumbria.ac.uk/policies.html>

This document may differ from the final, published version of the research and has been made available online in accordance with publisher policies. To read and/or cite from the published version of the research, please visit the publisher's website (a subscription may be required.)

British Journal of Nursing
Managing anaphylaxis in Adults
 --Manuscript Draft--

Manuscript Number:	
Full Title:	Managing anaphylaxis in Adults
Short Title:	
Article Type:	Clinical review
Keywords:	5 Key words: - Anaphylaxis - Allergies - Hypersensitivity - Hypotension - Angioedema
Corresponding Author:	Sam Curry, BSc (Hons) Northumbria University - Coach Lane Campus Newcastle Upon Tyne, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Northumbria University - Coach Lane Campus
Corresponding Author's Secondary Institution:	
First Author:	Sam Curry, BSc (Hons)
First Author Secondary Information:	
Order of Authors:	Sam Curry, BSc (Hons) Clinical Skills Tutor Northumbria University Newcastle. Sam
Order of Authors Secondary Information:	
Abstract:	Anaphylaxis is a severe and potentially life-threatening allergic reaction. The subsequent recognition and treatment of anaphylaxis remains complex and an area of continued professional development for healthcare professionals. Consequently, prompt recognition of anaphylaxis and subsequent treatment and management by the multi-disciplinary team including nurses and allied healthcare professionals is key as this increases the patient's chances of survival and limits them suffering co-morbidities. Providing a contemporary evidenced based clinical discussion on managing anaphylaxis will enable healthcare professionals to provide safer patient care.
Suggested Reviewers:	
Additional Information:	
Question	Response
Please enter the word count of your manuscript excluding references and tables	1851

Title: Managing anaphylaxis in Adults

Author: Sam Curry – Clinical Skills Tutor, Northumbria University, Newcastle.

sam4.curry@northumbria.ac.uk

Word Count: 2539

Abstract:

Anaphylaxis is a severe and potentially life-threatening allergic reaction. The subsequent recognition and treatment of anaphylaxis remains complex and an area of continued professional development for healthcare professionals. Consequently, prompt recognition of anaphylaxis and sequent treatment and management by the multi-disciplinary team including nurses and allied health professionals is key as this increases the patient's chances of survival and limits them suffering co-morbidities. Providing a contemporary evidenced based clinical discussion on managing anaphylaxis will enable healthcare professionals to provide safer patient care.

5 Key words: - Anaphylaxis – Allergies – Hypersensitivity – Hypotension – Angioedema

Anonymous Manuscript

Anaphylaxis is defined by the World Allergy Organization Anaphylaxis Guidance (2020) as being: "*A serious multi-systemic hypersensitivity reaction that is usually rapid in onset and may result in death*". According to Turner et al. (2019), severe anaphylaxis is characterised by potentially life-threatening compromise in airway, breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present. Anaphylactic reactions can be fatal within minutes. It is therefore essential that healthcare professionals recognise the signs and symptoms of a reaction and implement the correct treatment immediately (Resus Council United Kingdom, 2021). The aim of this article therefore is to discuss the immediate management and post management of a patient suffering an anaphylactic reaction.

Epidemiology of anaphylaxis:

Prevalence and Incidence

Anaphylactic episodes are increasing within the UK, with growing numbers of people presenting to hospitals. Between 2018-2019 data revealed that there were 5534 hospital admissions due to anaphylactic shock in adult patients, and 4482 hospital admissions in 2015-16 (NHS Digital, 2019). Outside of the UK Yu and Lin (2018) carried out a review of the studies on anaphylaxis and found a lifetime prevalence of anaphylaxis estimated to be at 0.05% in the United States and 3% in Europe. Yu and Lin within their review article (2018) states that several studies have suggested an

increase within admissions to hospital and patients presenting to emergency departments suffering from anaphylaxis within the United States and Europe. Subsequently, there does appear to be much variation within the statistics regarding anaphylaxis as a recent systematic review by the European Academy of Allergy and Clinical Immunology food allergy and Anaphylaxis- Group estimated that the incidence rate for all cause anaphylaxis to be 1.5 to 7.9 per 100,000 of the European population (Panesar et al., 2013). The data also indicated that an estimated 1-300 people are at risk of suffering an anaphylactic reaction throughout their lifetime within European populations (Panesar et al., 2013). These figures are suggested to be somewhat lower in Europe compared to the United States, but this may just be because of the criteria needed when diagnosing anaphylaxis in each country (RCUK, 2021).

Baseggio et al. (2021), also carried out a systematic review of the data and regarding food related anaphylaxis found that European populations had a higher prevalence of food related anaphylaxis with crustaceans and Cow's milk being the predominant cause, compared with South Asian populations where the main cause was fish and crustaceans induced anaphylaxis although any particular food/substance dependent on geographical location could potentially cause anaphylaxis, this is why differential food allergens must be labelled on foods worldwide depending on the demographics of their population. Baseggio et al. (2021), review of the data also showed that children in Europe and Asia had an increased risk of anaphylaxis compared with adults.

Mortality

Overall prognosis for anaphylaxis is good within the UK when prompt presentation to hospital and recognition of the condition is undertaken within the hospital setting (Turner et al., 2015). Statistically, there is approximately one per million annually that die from an anaphylactic reaction covering food, venom and medication induced anaphylaxis within the UK (Turner et al., 2017). The risk of death increases depending on a patient's co-morbidities such as asthma, which is associated with an increased risk of death, it has also been stated that healthcare professionals that have not had much exposure to patients suffering an anaphylactic reaction might mistake it for an Asthma attack which can delay the use of adrenaline which is linked to poorer patient outcomes (Pumphrey and Gowland, 2007).

Triggers

Any food or medication can cause anaphylaxis, but the majority are well described, but one-third of reactions are described as idiopathic where a trigger can't be determined, or another immunological response is the causation (Turner et al., 2015). Teenagers and young adults up to the age of 30 years are most at risk from a fatality due to anaphylaxis, but regarding a fatal reaction due to medication the elderly had an increased risk (Baseggio et al., 2021; Turner et al., 2015). This has been attributed to greater co-morbidities involving cardiac function and polypharmacy which is known to affect this population, such as the use of Angio-tension Converting Enzyme (ACE) inhibitors which can be detrimental to someone suffering an anaphylactic reaction (Tejedor-Alonso et al., 2019.)

	Anaphylaxis (all severities)	Fatal anaphylaxis
Foods	<p>Commonest triggers:</p> <ul style="list-style-type: none"> - Peanut - Tree nuts - Cow's milk <p>Accounts for 35% of hospital admissions coded as anaphylaxis (Baseggio et al., 2021).</p>	<p>Commonest triggers according to, Baseggio et al. (2021):</p> <ul style="list-style-type: none"> - Peanut or tree nuts 50% - Cow's milk (11% of total, 26% in children - 19% of anaphylaxis related deaths (Turner et al., 2015).
Medications	<p>Commonest triggers are anti-biotics and chemotherapy drugs.</p> <p>Commonest triggers in perioperative setting, according to Harper et al. (2018):</p>	<p>Commonest triggers according to Pumphrey (2004):</p> <ul style="list-style-type: none"> - NMBA's (32%) - Antibiotics (27%) including penicillin (11%) and

	<ul style="list-style-type: none"> - Antibiotics (47%) - Co-amoxiclav (23%) - Teicoplanin (18%) - Neuromuscular blocking agents (NMBAs) (33%) - Chlorhexidine (9%) - Accounts for 17% of hospital admissions coded as anaphylaxis (Turner et al., 2015). 	<ul style="list-style-type: none"> Cephalosporins (12%). - Contrast media (11%) - Non-steroidal anti-inflammatory drugs (6%) - 39% of anaphylaxis related deaths (Turner et al., 2015).
Insect stings	6.5% of anaphylaxis coded hospital admissions (Turner et al., 2015).	14% of anaphylaxis-related deaths (Turner et al., 2015).

Table 1. Causation of UK anaphylaxis cases (RCUK, 2021).

Pathophysiology

Anaphylaxis is a type 1 hypersensitivity – IgE – mediated mast cell degranulation reaction (Delves et al., 2017). This reaction is categorised by constriction of the bronchioles and bronchi, contraction of smooth muscle and dilatation of the capillaries with multi-systematic involvement (Delves et al., 2017).

In anaphylaxis the immune system reacts to antigens (allergens) that the body has been exposed to and mounts an immune response. These antigens can be anything from food substances to medications and bee venom (Helbert, 2017). The antigen helps to generate a specific antibody called an IgE where the allergen binds to the site (Abbas et al., 2018).

The first cell within this process is an antigen presenting cell that absorbs the allergen and then presents it on its cell surface receptors and communicates its findings to the immune system. A T-helper cell is then dispatched which has been through a strenuous maturation process enabling them to respond to the allergen, the T-helper cell then binds with the antigen presenting cell (Nadeau et al., 2012).

The T-helper-cell then communicates with the immune system stating there is a problem triggering the involvement of a B-cell (Galli and Tsai., 2010). The B-cell then attaches the allergens to its cell surface receptors and starts making IgA and IgB but not IgE (Mangan et al., 2004).

The T-cell then communicates with the B-cell through a chemical messenger called a cytokine and tells it to switch to making IgE, these IgE antibodies are then released

and attach to immune cells called Mast and Basophils cells through cross linking, these cells both produce an inflammatory agent called histamine. It is also important to note that through degranulation there can be an immediate release of histamine stored within the Mast and Basophil cell, therefore creating the physiological effects of anaphylaxis (Kraft and Kinet., 2007).

Management of anaphylaxis

Recognition:

Anaphylaxis is likely if a patient is exposed to an allergen (trigger) that they are known to be allergic to, then suddenly deteriorates rapidly usually within minutes or in some instances a delayed reaction can manifest. These usually rapidly developing symptoms can consist of progressing skin changes and potentially airway/breathing or circulatory problems. The reaction is usually unexpected, and the patient will have a sense of impending doom such as feeling as if they are dying (ASCIA, 2020).

Anaphylaxis is likely when all three criteria are met (RCUK, 2021):

- Sudden onset and rapid progression of symptoms.
- Life-threatening airway and/or breathing and/or circulation problems.
- Skin and/or mucosal changes (flushing, urticaria, angioedema).

The following evidence supports the diagnosis (past medical history):

- Patient exposure to a known allergen for example known antibiotic or food substance.

It is crucial to consider:

- Skin or mucosal changes alone are not a sign of anaphylaxis and can be absent in 20% of patients (some may present only with hypotension).
- Gastrointestinal symptoms have also been noted (e.g. vomiting/nausea, abdominal pain and diarrhoea).

Life threatening features include:

Airway problems:

- Airway swelling including throat and tongue (pharyngeal/laryngeal oedema).
- Hoarse voice
- Stridor

Breathing problems:

- Wheeze
- Shortness of breath
- Hypoxia resulting in confusion
- Cyanosis
- Respiratory arrest
- Exacerbation of life-threatening asthma

Circulatory problems:

- Signs of shock
- Tachycardia
- Hypotension
- Decreased Glasgow coma score
- Myocardial ischaemia
- Cardiac arrest

Disability:

- Decreased neurological status
- Central nervous system effects
- Confusion
- Agitation
- Loss of consciousness
- Anxiety
- Gastrointestinal symptoms: abdominal pain, vomiting, incontinence

Exposure:

- Patchy erythema or generalised rash
- Skin and mucosal membrane changes
- Urticaria
- Angioedema of deeper tissues: eyelids, lips, tongue, throat

Initial treatment

Initial treatment will vary depending on the setting and skills/equipment available at the time. Initial treatment should always consist of stopping an infusion of antibiotics or other medication if this is thought to be the cause and administering [1:1000] IM adrenaline (will reduce airway swelling and increase blood pressure) as soon as possible. Then the ABCDE approach should be implemented and treatment commenced throughout the protocol as it arises. When available full monitoring should be applied including pulse oximetry, non-invasive blood pressure and a minimum of a 3 lead ECG (ASCIA, 2020).

Patients with breathing problems should be sat up. If a patient has low blood pressure and breathing is not compromised, lie the patient flat with their legs elevated to help increase blood pressure. Allowing the patient to stand may lead to the patient suffering a cardiac arrest, if a patient does go into cardiac arrest perform cardiopulmonary resuscitation immediately (Lott et al., 2021).

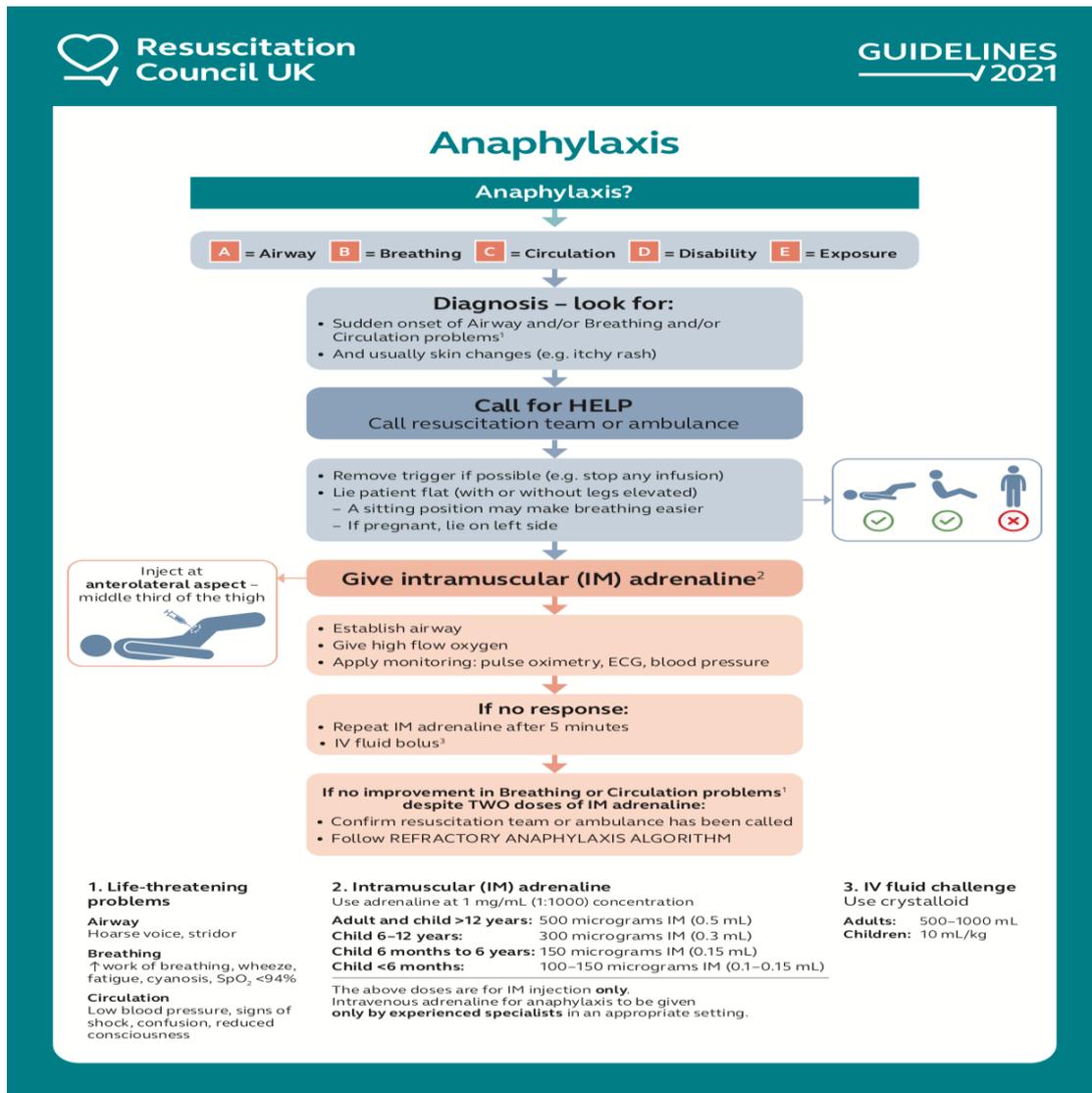


Figure 2: Initial treatment of anaphylaxis (RCUK, 2021).

Drugs used within the initial treatment of anaphylaxis

There are only a limited number of drugs used within the treatment of anaphylaxis. The most important being [1:1000] adrenaline (epinephrine) as evidence shows the prompt administration of this drug within patients suffering an anaphylactic reaction within the early stages correlated with a better clinical outcome (Sheik et al., 2009).

Drugs used initially according to the RCUK (2021):

- [1:1000] IM Adrenaline (repeat after 5 minutes if no change).
- [1:1000] IV Adrenaline (used only by experienced specialists in a critical care setting).
- Nebulised adrenaline for upper respiratory oedema (after IM/IV Adrenaline).
- Oxygen high flow (give soon as available).
- Intravenous fluids (hypotension and severe anaphylaxis): establish IV access then give 10mL/Kg in a child and 500-1000 mL in an adult using initially non-glucose containing crystalloids i.e. Hartmann's. If further fluid doses are needed a non-glucose containing crystalloid should be used. If needed use IO route.
- Antihistamines and steroids are not recommended in the initial treatment.

Second line drug treatments:

- Antihistamine use (H₁-antihistamine) is recommended as a second line treatment for anaphylaxis even though the evidence is weak. Corticosteroids such as hydrocortisone can help shorten reactions and prevent reoccurrence.

Investigations

- Document acute clinical features of presentation i.e., rapid onset, ABCDE involvement.
- Record the time of onset.
- Record circumstances immediately before symptoms (may help to identify trigger).

- Take a time recorded mast cell tryptase blood sample after emergency treatment, then another 1-2 hours after the first but no later than 4 hours. On referral to the specialist allergy clinic, they may need to repeat this test.
- Observations for at least 6-12 hours from onset of symptoms in adults. Children should be admitted for observation.

Discharge and follow up

- Discharge should only be initiated after a senior clinician has reviewed the patient.
- All patients should be offered education on anaphylaxis and what to do in an emergency including how to use an EpiPen (adrenaline) by trained and competent staff.
- Patients should be offered a referral to an allergy clinic for follow up using each Trusts individual referral pathways.

Conclusion

In the UK anaphylactic reactions are increasing. The RCUK emergency guidelines for treating patients suffering from a suspected anaphylactic reaction have been updated recently. The emphasis is on prompt recognition, administration of adrenaline and the ABCDE approach. Treatment all depends on the location of the patient and the equipment/skills available. All patients should be referred to an allergist immediately after suffering an anaphylactic reaction.

Reference List:

Abbas, K.A., Lichtman, H.A & Pillai, S. (2018) *Cellular and molecular immunology*. 9th edn. China: Elsevier.

Australasian Society of Clinical Immunology and Allergy (ASCI) Guideline for the Acute management of anaphylaxis. 2020. Available at:

<https://www.allergy.org.au/hp/papers/acute-management-of-anaphylaxis-guidelines> (Accessed: 17th July 2021).

Baseggio Conrado, A., Ierodiakonou, D., Gowland, M.H., Boyle, R.J. and Turner, P.J. (2021) 'Food anaphylaxis in the United Kingdom: analysis of national data, 1998-2018'. *British Medical Journal*, 2021; 372:n251. BMJ [Online]. doi:<http://dx.doi.org/10.1136/bmj.n251> (Accessed: 25th June 2021).

Baseggio Conrado, A., Patel, N., Turner, P.J. (2021) 'Global patterns in anaphylaxis due to specific foods: a systematic review' *The Journal Of Allergy And Clinical Immunology*, 21. Science direct [Online]. doi: 10.1016/j.jaci.2021.03.048. Epub ahead of print. (Accessed June 24th 2021).

Cardona, V., Ansotegui, I.J., Ebisawa, M., El-Gamal, Y., Rivas, M.F., Fineman, S., Geller, M., Gonzalez-Estrada, A., Greenberger, P.A., Borges, M.S. and Senna, G. (2020) World allergy organization anaphylaxis guidance 2020. *World Allergy Organization Journal*, 13(10), p.100472. Pubmed

[Online]. doi:<http://doi.org/10.1016/j.waojou.2020.100472> (Accessed: 24th June 2021).

Delves, J.P., Martins, S.J. & Burton, D.R. (2017) *Roitt's essential immunology*. 13th edn. Chichester: Wiley Blackwell.

Harper, N.J.N., Cook, T.M., Garcez, T., Farmer, L., Floss, K., Marinho, S., Torevell, H., Warner, A., Ferguson, K., Hitchman, J. and Egner, W. (2018) Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *British journal of anaesthesia*, 121(1), pp.159-171.

ScienceDirect [Online]. doi:<https://doi.org/10.1016/j.bja.2018.04.014> (Accessed: 24th June 2021).

Helbert, M. (2017) *Immunology for medical students*. 3rd edn. Philadelphia, PA: Elsevier.

Joyce, E.Y. and Lin, R.Y. (2018). 'The epidemiology of anaphylaxis'. *Clinical reviews in allergy & immunology*, 54(3), pp.366-374. Springerlink [online]. Doi: <https://doi.org/10.1007/s12016-015-8503-x> (Accessed: 24th June 2021).

Kraft, S. and Kinet, J.P. (2007) 'New developments in FcεRI regulation, function and inhibition', *Nature Reviews Immunology*, 7(5), pp.365-378.

Nature reviews immunology [Online]. doi: <https://doi.org/10.1038/nri2072> (Accessed: 25th June 2021).

Lott, C., Truhlář, A., Alfonzo, A., Barelli, A., González-Salvado, V., Hinkelbein, J., Nolan, J., Paal, P., Perkins, G., Thies, K., Yeung, J., Zideman, D., Soar, J., Khalifa, G., Álvarez, E., Barelli, R., Bierens, J., Boettiger, B., Brattebø, G., Browne, D., Brugger, H., Darocha, T., Deakin, C., Dunning, J., Hunyadi-Anticevic, S., Koster, R., Lockey, D., Pasquier, M., Schmitz, J. (2021). 'European Resuscitation Council Guidelines 2021: Cardiac arrest in special circumstance's'. *Resuscitation*, 161(1), pp. 152-219. Pubmed [Online]. doi:<https://doi.org/10.1016/j.resuscitation.2021.02.011>. (Accessed: July 28th 2021).

Mangan NE, Fallon RE, Smith P, van Rooijen N, McKenzie AN, Fallon PG. (2004) 'Helminth infection protects mice from anaphylaxis via IL-10-producing B cells', *The Journal of Immunology*, 173 (10) pp. 6346-6356. Pubmed [Online]. doi: 10.4049/jimmunol.173.10.6346 (Accessed: 25th June).

Nadeau KC, Kohli A, Iyengar S, DeKruyff RH, Umetsu DT. (2012) 'Oral immunotherapy and anti-IgE antibody-adjunctive treatment for food allergy', *Immunology Allergy Clinic North America*, 32 (1), pp.111-133. Pubmed [Online]. doi: <https://doi.org/10.1016/j.iac.2011.11.004> (Accessed: 25th June 2021).

National Health Service Digital (2021). Statistics on hospital admissions with the primary diagnosis of anaphylactic shock. Available at: <https://digital.nhs.uk/data-and-information/supplementary-information/2021/statistics-on-hospital-admissions-with-a-primary-diagnosis-of-anaphylactic-shock-and-allergies-with-an-age-breakdown-of-under-18-18-and-over-and-both-by-provider-and-at-national-level>

(Accessed: 23rd June 2021).

National Institute for Health and Clinical Excellence (2020). Anaphylaxis: Assessment to confirm anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic reaction. Available at: <https://www.nice.org.uk/guidance/cg134/evidence/anaphylaxis-full-guideline-pdf-184946941> (Accessed: 20th July 2021).

Panesar, S.S., Javd, S., de Silva, D., Nwaru, B.I., Hickstein, L., Muraro, A., Roberts, G., Worm, M., Bilo, M. B., Cardona, V., Dubois, A. E. J., Dunn Galvin, A., Fernandez-Rivas, S., Halken, S., Lack, G., Niggeman, B., Santos, A.F., Viieg-Beoerstra, B.J., Zokipli, Z. Q., Sheik, A. (2013) 'The epidemiology of anaphylaxis in Europe: a systematic review', *European Journal Of Allergy And Clinical Immunology*, 68(11), pp. 1353-1361. Wiley Online Library [online]. Doi: <https://doi.org/10.1111/all.12272> (Accessed: 24th June 2021).

Pumphrey, R.S. (2004) 'Fatal anaphylaxis in the UK, 1992-2001'. In *Novartis Foundation symposium. (ed.) Anaphylaxis: vol. 257*. Chichester; New York; John Wiley, pp. 116.

Pumphrey, R.S. and Gowland, M.H. (2007) 'Further fatal allergic reactions to food in the United Kingdom, 1999-2006, *Journal of Allergy and Clinical Immunology*, 119(4), pp.1018-1019. Jacionline [Online]. doi: <https://doi.org/10.1016/j.jaci.2007.01.021> (Accessed: 24th June 2021).

Resuscitation Council UK (2021). Emergency treatment of anaphylaxis for healthcare providers. Available at: <https://www.resus.org.uk/library/additional-guidance/guidance-anaphylaxis/emergency-treatment> (Accessed: 23rd June 2021).

Sheikh A, Shehata Y.A, Brown S.G, Simons F.E. (2009) 'Adrenaline for the treatment of anaphylaxis: Cochrane systematic review', *European Journal of Allergy and Clinical Immunology*, 64 (1), pp. 204-212. Wiley Online Library [Online]. doi: <https://doi.org/10.1111/j.1398-9995.2008.01926.x> (Accessed: 25th June 2021).

Tejedor-Alonso, M.A., Farias-Aquino, E., Pérez-Fernández, E., Grifol-Clar, E., Moro-Moro, M. and Rosado-Ingelmo, A. (2019) 'Relationship between anaphylaxis and use of beta-blockers and angiotensin-converting enzyme

inhibitors: a systematic review and meta-analysis of observational studies'. *The Journal of Allergy and Clinical Immunology: In Practice*, 7(3), pp.879-897. ScienceDirect [Online].

doi:<https://doi.org/10.1016/j.jaip.2018.10.042> (Accessed: 24th June 2021).

Turner, P.J., Gowland, M.H., Sharma, V., Ierodiakonou, D., Harper, N., Garcez, T., Pumphrey, R. and Boyle, R.J. (2015) 'Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012'. *Journal of Allergy and Clinical Immunology*, 135(4), pp.956-963.

Turner, P.J., Jerschow, E., Umasunthar, T., Lin, R., Campbell, D.E. and Boyle, R.J. (2017). 'Fatal anaphylaxis: mortality rate and risk factors', *The Journal of Allergy and Clinical Immunology: In Practice*, 5(5), pp.1169-1178.

Turner, P.J., Worm, M., Ansotegui, I.J., El-Gamal, Y., Rivas, M.F., Fineman, S., Geller, M., Gonzalez-Estrada, A., Greenberger, P.A., Tanno, L.K. and Sánchez-Borges, M. (2019). 'Time to revisit the definition and clinical criteria for anaphylaxis?'. *World Allergy Organization Journal*, 12(10), pp.100067. World Allergy Organization Journal [online].

doi:<https://doi.org/10.1016/j.waojou.2019.100066> (Accessed: 23rd June 2021).

