Policy

Care in the field: adult anaphylaxis for paramedics

Matt Wilkinson-Stokes BP, is a postgraduate student and paramedic¹; Desiree Rowland BP is a paramedic¹; Maddison Spencer BP is a paramedic¹; Sonja Maria PhD, GCClinED, GCLTHE, BClinPrac(Para) is a Senior Lecturer in paramedicine²; Marc Colbeck BHLthSc, MA, is a critical care paramedic, Senior Lecturer and Clinical Coordinator in Paramedicine¹

Affiliations:

¹Australian Catholic University, School of Nursing, Midwifery and Paramedicine, Queensland

²Charles Sturt University, Bathurst, New South Wales

<https://doi.org/10.33151/ajp.18.916>

Abstract

This paper presents an overview of the definition, clinical features, epidemiology, classification, pathophysiology, evaluation and risk assessment and treatment pharmacodynamics of anaphylaxis from the perspective of Australasian paramedic practice.

Keywords:

anaphylaxis; paramedic

Corresponding Author: Matt Wilkinson-Stokes, matt.wilkinson-stokes@outlook.com

Background

Anaphylaxis is a systemic inflammatory response mediated by the degranulation of granulocytes and subsequent release of inflammatory mediators (1-3). This is most commonly caused by a hypersensitive immunologic response to an antigen; however, it may also be caused by direct granulocyte lysis (1,3). Key features of anaphylaxis include an exposure to a known or suspected antigen and hyperacute onset with two types of multi-system features present, either:

1. integumentary with any of respiratory, cardiovascular and gastrointestinal; or
2. isolated signs of hypotension, bronchospasm or upper airway obstruction where anaphylaxis is considered possible (2,4,5).

Clinical features

Anaphylactic reactions can present in a myriad of ways after exposure to a known or possible antigen. Over a period of minutes to hours the patient may present with a combination of:

- integumentary compromise, including urticaria, itching and flushing of the skin, rash, and angioedema to the upper respiratory tract and face (90% of episodes)
- respiratory compromise, including wheeze, stridor and dyspnoea (85% of episodes)
- gastrointestinal compromise, including nausea, diarrhoea and emesis (45% of episodes)
- cardiovascular symptoms, including hypotension, tachycardia, altered consciousness and syncope (45% of episodes) (6).

It is important to note that angioedema can further present on any part of the integument (6).

Epidemiology

Allergic diseases will affect around one-in-three Australians in their lifetime with approximately 20% of the population, or 4 million Australians, currently living with at least one allergic disease (7,8). It is estimated that anaphylaxis occurs in around 0.2% of children and 3% of adults (8).

The Australasian Society of Clinical Immunology and Allergy (ASCI) reported that food-induced anaphylaxis doubled from 2003 to 2013, with children aged 4 years and younger having the highest hospital admission rates (7). Death from anaphylaxis is rare, with the Australian Bureau of Statistics recording 324 deaths from 1997 to 2013 (8). Drug-induced anaphylactic deaths increased 3-fold from 2003 to 2013 (7).

Over three-quarters of anaphylaxis cases are triggered by three causes: adverse drug reaction, insect envenomation (of which approximately three-quarters are bee stings), and food ingestion (9,10). Of the remaining quarter of cases, approximately one-quarter have a known cause, with the remaining three-quarters being idiopathic (9,10). Based on this epidemiological data it is predicted that by 2050 the number of Australians affected by allergic diseases will increase by 70% to approximately 7.7 million people – and it is therefore likely to become an increasingly frequent element of paramedic practice

(7). However, it is important to note that this data can vary significantly as the definitions of anaphylaxis are inconsistent both nationally and globally, there are irregularities between study designs and sampling populations, different antigens can cause different presentations, and those cases presenting to the hospital emergency department can be misdiagnosed or unrecognised (11). This lack of harmonisation hinders the compiling of accurate nationwide epidemiological data on anaphylaxis.

Classification

The World Allergy Organization describes anaphylaxis as being either immunologic, non-immunologic, or idiopathic (12). Immunological reactions (commonly known as allergic reactions) consist of both immunoglobulin-E (IgE) mediated reactions and non-IgE mediated reactions. IgE mediated reactions occur on re-exposure to an antigen with previous IgE antibody priming of granulocyte receptors, and most commonly arise from medications, venom, food, pollens and latex (1-3,13). A blood test can detect the levels of IgE present to confirm the presence of an allergy (8). Non-IgE mediated reactions involves other components of the immune system, and are commonly triggered by intravenous immunoglobulin and radiocontrast media (13).

Non-immunological mechanisms differ by having directly mediated granulocyte lysis; however, in practice this can be difficult to distinguish, as patients present clinically identical to those with immune-mediated reaction (14). Non-immunological triggers include the direct effect of opiates and other drugs, physical factors such as exercise, cold and heat, and genetic factors, all of which may affect granulocyte ability to activate and proliferate (13).

Lastly, idiopathic anaphylaxis is diagnosed when the underlying cause of anaphylaxis is unable to be identified. Formal diagnosis requires both obtaining a detailed history and performing extensive diagnostic evaluations including skin-prick tests, serum tryptase and c-kit mutation (15).

Pathophysiology

Anaphylaxis is a systemic inflammatory response, most commonly triggered by re-exposure to an antigen with previous IgE antibody priming of granulocyte receptors (1-3). This begins degranulation of primed granulocytes (mast cells, eosinophils, basophils and neutrophils) and release of inflammatory mediators (including histamine, mast cell tryptase, interleukins and other cytokines, prostaglandin, and others), leading to a systemic inflammatory response (1-3). Less commonly, it can be triggered by direct degranulation from opioids, contrast dye and other substances (3). In both pathways, the cascade of inflammatory mediators leads to further degranulation, precipitating rapid and widespread inflammation (1-3). Histamine additionally acts as a neurotransmitter, stimulating the vomiting centre in the medulla to initiate nausea and emesis (16). Finally, mast cell mediators may destabilise atherosclerotic plaque, increasing the likelihood of concomitant myocardial infarction (17,18).

Decreased vasomotor tone lowers venous return, resulting in reduced preload that can diminish cardiac output (3). Extravasation can be profound and rapid, with up to 35% of the vascular volume transferring to the extravascular space within 10 minutes (19). Together, these effects cause a combined distributive (from vasodilation) and relative hypovolaemic (from extravasation) shock, with elements of cardiogenic (from myocardial depression) shock; the exact phenotype will vary depending on the patient (3,20-22). Bronchoconstriction, mucus plugging and bronchial oedema can obstruct the airway, inhibiting exhalation, reducing tidal volume and leading to gas trapping, increased intrathoracic pressure and hypercarbia (3). This is exacerbated by angioedema and laryngeal oedema, ultimately leading to respiratory failure (3). Hypoxic arrest is the most common cause of mortality in anaphylaxis, with shock-induced cardiac arrest being less common, while disseminated intravascular coagulopathy and associated adrenaline overdose are rare causes (23,24).

Evaluation and risk assessment

Due to the potential severity of harm from delayed treatment, anaphylaxis should be a primary consideration in the differential diagnosis of all patients presenting with rapid onset hypotension or respiratory compromise, especially when coupled with exposure to a known or suspected antigen. Paramedics should bear in mind that the effectiveness of auscultation in determining respiratory compromise was brought into question in a 2020 meta-analysis which found that pulmonary auscultation had poor predictability, with a sensitivity for wheeze in obstructive airway disorders of only 26% (25); paramedics should therefore be mindful that potentially up to three-quarters of patients with obstructive airway disorders, as found in anaphylaxis, will not present with discernable wheezes during auscultation, de-emphasising the importance of wheezes as a 'necessary' finding for diagnosing anaphylaxis. Paramedics should also be aware that hypotensive shock can occur without any cutaneous or respiratory manifestations, and patients with exposure to a known allergen should be closely monitored (19).

Anaphylaxis can be biphasic in nature, and paramedics should remember that in approximately 5–20% of cases symptoms return after apparent resolution; this normally occurs within 12 hours after the initial reaction has resolved without further exposure to the trigger, but may be delayed with an asymptomatic period of up to 72 hours (26,27).

Differential diagnosis

There are many conditions that present with signs and symptoms similar to those of anaphylaxis. They can be grouped as either respiratory, cardiac, neurological, flush syndromes, shock, non-organic diseases, histamine-mediated or psychological (28-30). These are summarised in Table 1.

Treatment variations

Australasian paramedics treat anaphylaxis by focussing on 'basic cares' (airway, breathing, circulatory and disability management,

including oxygen as appropriate) as well as by using the following medications, as required: adrenaline, salbutamol, ipratropium bromide, corticosteroids, antihistamines, glucagon and vascular volume expanders.

Adrenaline is the fundamental agent for treatment of anaphylaxis, as it is uniquely suited to offset the respiratory and perfusion compromise: agonism of alpha-1 receptors causes peripheral vasoconstriction, improving central organ perfusion; agonism of beta-1 receptors causes positive inotropy, chronotropy and dromotropy, improving cardiac output and perfusion; and agonism of beta-2 receptors induces bronchodilation, offsetting obstructive gas trapping and improving tidal volume and oxygenation (31). Furthermore, agonism of beta-2 receptors on mast cells reduces degranulation, minimising release of inflammatory mediators (32-34). Finally, adrenaline agonises alpha-2 receptors and beta-3 receptors to decrease insulin, increase glucagon and increase lipolysis, all of which beneficially increase blood glucose (31,35).

Salbutamol is an adrenergic agonist with preference for beta-2 receptors, inducing bronchodilation and in turn improving ventilation and reducing intrathoracic pressure, and is recommended by some sources as an adjunct to adrenaline (21).

Ipratropium bromide is a cholinergic antagonist via blockade of muscarinic cholinergic receptors (36). Blocking cholinergic receptors decreases the production mucus and of cyclic guanosine monophosphate (cGMP), leading to relaxation of the bronchial smooth muscles, improving ventilation and reducing intrathoracic pressure (36,37). Ipratropium bromide also acts synergistically within cells to increase the effectiveness of beta agonists (36).

Corticosteroids bind to glucocorticoid or mineralcorticoid receptors, inducing a wide range of changes including reduced inflammation and immunosuppression (38). A large-scale systematic review in 2017 showed a lack of evidence for corticosteroids in reducing anaphylaxis severity and preventing a biphasic episode (39).

The mechanism of the antihistamines carried by Australasian paramedics is antagonism of H1 histamine receptors on granulocytes present in the endothelium and in smooth muscle, causing mild relief for itch and urticaria; however, they offer no benefit from a respiratory or circulatory standpoint (21). Antihistamines have been shown by Cochrane review to have no proven benefit in anaphylaxis; despite this, some experts state it is reasonable to administer antihistamines as a symptom control adjunct and prophylactically during early state non-anaphylactic allergies (21,40,41).

Glucagon activates glucagon receptors in the myocardium, increasing cAMP via several mechanisms, which in turn stimulates the inward 'funny' current (increasing pacemaker rate), increases pacemaker calcium release from the sarcoplasmic

Table 1. Differential diagnoses of adult anaphylaxis (28-30)

Asthma	Respiratory symptoms such as wheezing, coughing and shortness of breath may occur from asthma or anaphylaxis. In asthma, pathology is usually limited to the respiratory system, and there is the absence of cutaneous and digestive findings, with hypotension only presenting late and subsequent to increased intrathoracic pressure physically compressing the heart and reducing venous return. Anaphylaxis is usually triggered by exposure to a specific (and often, known) antigen. Asthma is chronic with progressive onset, whereas a sudden onset of symptoms in a previously well patient is suggestive of anaphylaxis. Determining a previous history of asthma or anaphylaxis will aid in differentiation
Urticaria	Cutaneous purpura may occur from urticaria, as well as in anaphylaxis. In urticaria, pathology is limited to the integumentary system, and consequently there is the absence of respiratory, digestive, and circulatory findings
Hereditary angioedema	Both hereditary angioedema and anaphylaxis can develop oedema in the deep cutaneous or mucosal tissue of the face, arms, legs, genitalia, tongue and larynx – the latter of which may lead to asphyxia. It can also affect the bowel wall, which may cause abdominal pain, emesis, and diarrhoea. Hereditary angioedema can be differentiated based on the absence of urticaria, hypotension, and history of antigen exposure. These patients do not respond to adrenaline, glucocorticoids, or antihistamines
Severe sepsis	Both severe sepsis and anaphylaxis may trigger shock. An absence of previous allergic reactions, dysthermia (usually hyperthermia, however hypothermia is also possible), other signs of infection (especially if profound), a relatively slower onset of symptoms (although sepsis can present acutely), and a lack of recent specific antigen exposure all suggest sepsis
Cardiogenic shock	Both cardiogenic causes and anaphylaxis may trigger shock. Patient risk factors for coronary artery disease, previous angina episodes, absence of a recent antigen exposure, and typical cardiac signs and symptoms such as positive electrocardiograph findings and pulmonary oedema all suggest cardiogenic pathology
Hypovolaemic shock	Anaphylaxis can cause hypovolaemic shock secondary to intravascular fluid shifts. However, other causes may result in absolute or relative hypovolaemia, including heat exposure, diaphoresis, haemorrhage, emesis, and diarrhoea. History taking can help rule out other causes of hypovolaemia such as gastrointestinal bleeding or a ruptured ectopic pregnancy
Stroke	Neurological symptoms such as syncope or altered consciousness may occur from stroke or anaphylaxis. In stroke, pathology is usually limited to the neurological system (and possibly other systems leading to the stroke, such as the cardiovascular system in the case of atrial fibrillation). There is often an absence of cutaneous and digestive findings, along with a positive stroke test
Vasovagal syncope	Syncope and hypotension may occur from vasovagal causes or anaphylaxis. An absence of cutaneous oedema, flushing rather than pallor, absence of allergic history, and early presentation of bradycardia instead of tachycardia all suggest vasovagal syncope
Panic disorder	Both panic disorder and anaphylaxis may present with anxiety, tremor, diaphoresis, globus sensation, paresthesia, nausea, and emesis. An absence of angioedema and hypotension suggest panic disorder
Vocal cord dysfunction syndrome	Both anaphylaxis and involuntary adduction of the vocal cords while inspiring can lead to dyspnoea, coughing, inspiratory stridor, or expiratory wheeze. An absence of mucosal signs, digestive findings, hypotension, and antigen exposure all suggest vocal cord dysfunction
Food poisoning	Both anaphylaxis and food poisoning may present with abdominal pain or cramps, nausea, emesis, and diarrhoea, usually a few hours post ingestion of food. A patient history of GI conditions (including mild allergies such as celiac or lactose intolerance), the absence of cutaneous and respiratory signs, and the absence of exposure to a possible antigen all suggest food poisoning
Peri-menopausal hot flushes	Both hot flushes and anaphylaxis can present with cutaneous erythema to the face. In peri-menopausal flush, the signs appear several times a day and last for 4-5 minutes, resolving spontaneously (spontaneous resolution will not occur in anaphylaxis). These symptoms, in conjunction with the absence of respiratory tract symptoms and hypotension, as well as the absence of exposure to a possible antigen suggests peri-menopausal flush

reticulum (increasing pacemaker rate), and enhances calcium-induced-calcium-release (increasing contractility) (42). Cumulatively, these effects are thought to increase inotropy and chronotropy; however, there remains debate as to if glucagon truly acts as an inotrope (42). Additionally, glucagon has antibronchospastic properties (43).

Volume fillers allow some restoration of isotonic vascular volume, and have the benefit of being cheap and portable; however, they have multiple risks, including fluid overload, inducing acidosis, reducing haematocrit (potentially causing dilutional anaemia), causing thrombocytopenia and causing leukopenia (44,45).

Summary

Anaphylaxis is a common emergency condition in the Australasian paramedic clinical context. A solid understanding of the characteristics, presentation, differential diagnosis and treatment of anaphylaxis is essential for safe clinical practice. This paper presents a focussed review of this condition appropriate for students and practising paramedics in Australasia.

Funding

The authors have not received funding for the production of this manuscript.

Competing interests

The authors declare no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement.

References

1. Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. *J Allergy Clin Immunol* 2017;140:335-48. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S0091674917310205>
2. Simons FER, Arduso LRF, Bilò MB, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J* 2014;7:9. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S1939455119302406>
3. Kemp SF. Pathophysiology of anaphylaxis. In: Kelso JM, Feldweg AM, editors. *UpToDate*. Waltham, MA: UpToDate; 2020.
4. Australasian Society of Clinical Immunology and Allergy. Anaphylaxis 2019. Available at: www.allergy.org.au/patients/about-allergy/anaphylaxis
5. Jimenez-Rodriguez T, Garcia-Neuer M, Alenazy LA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. *J Asthma Allergy* 2018;11:121-42. Available at: www.dovepress.com/anaphylaxis-in-the-21st-century-phenotypes-endotypes-and-biomarkers-peer-reviewed-article-JAA
6. Campbell RL, Kelso JM. Anaphylaxis: acute diagnosis. In: Walls RM, Feldweg AM, editors. *UpToDate*. Waltham, MA: UpToDate; 2020.
7. Australasian Society of Clinical Immunology and Allergy. Allergy and Immune Diseases in Australia (AIDA) Report 2013. Balgowah, Australia; 2013.
8. House of Representatives Standing Committee on Health Aged Care and, Sport. Walking the allergy tightrope: addressing the rise of allergies and anaphylaxis in Australia. 2020. Available at: www.allergy.org.au/images/docs/Walkingtheallergytightrope.pdf
9. Turner PJ, Jerschow E, Umasunthar T, et al. Fatal anaphylaxis: mortality rate and risk factors. *J Allergy Clin Immunol Pract* 2017;5:1169-78. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S2213219817305159>
10. Xu YS, Kastner M, Harada L, et al. Anaphylaxis-related deaths in Ontario: a retrospective review of cases from 1986 to 2011. *Allergy Asthma Clin Immunol* 2014;10:38. Available at: <https://aacijournal.biomedcentral.com/articles/10.1186/1710-1492-10-38>
11. Tanno LK, Bierrenbach AL, Simons FER, et al. Critical view of anaphylaxis epidemiology: open questions and new perspectives. *ibid.* 2018;14:12. Available at: <https://aacijournal.biomedcentral.com/articles/10.1186/s13223-018-0234-0>
12. Turner PJ, Worm M, Ansotegui IJ, et al. Time to revisit the definition and clinical criteria for anaphylaxis? *World Allergy Organ J* 2019;12:100066. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S1939455119312207>
13. LoVerde D, Iweala OI, Eginli A, Krishnaswamy G. Anaphylaxis. *Chest* 2018;153:528-43. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S0012369217313326>
14. Montañez MI, Mayorga C, Bogas G, et al. Epidemiology, mechanisms, and diagnosis of drug-induced anaphylaxis. *Front Immunol* 2017;8. Available at: <http://journal.frontiersin.org/article/10.3389/fimmu.2017.00614/full>
15. Fenny N, Grammer LC. Idiopathic anaphylaxis. *Immunol Allergy Clin North Am* 2015;35:349-62. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S0889856115000053>
16. Denholm L, Gallagher G. Physiology and pharmacology of nausea and vomiting. *Anaesth Intensive Care Med* 2018;19:513-6. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S1472029918301541>
17. Bot I, Shi G-P, Kovanen PT. Mast cells as effectors in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2015;3:265-71. Available at: www.ahajournals.org/doi/10.1161/ATVBAHA.114.303570
18. Lagraauw HM, Wezel A, van der Velden D, Kuiper J, Bot I. Stress-induced mast cell activation contributes to atherosclerotic plaque destabilization. *Sci Rep* 2019;9:2134. Available at: www.nature.com/articles/s41598-019-38679-4
19. Mali S, Jambure R. Anaphylaxis management: current concepts. *Anesth Essays Res* 2012;6:115. Available at: www.aeronline.org/text.asp?2012/6/2/115/108284
20. Marone G, Genovese A, Varricchi G, Granata F. Human heart as a shock organ in anaphylaxis. *Allergo J Int* 2014;23:60-6. Available at: <http://link.springer.com/10.1007/>

- s40629-014-0007-3
21. Campbell RL, Kelso JM. Anaphylaxis: emergency treatment. In: Walls RM, Randolph AG, Feldweg AM, editors. UpToDate. Waltham, MA: UpToDate; 2020.
 22. Ring J, Beyer K, Biedermann T, et al. Guideline for acute therapy and management of anaphylaxis. *Allergo J Int* 2014;23:96-112. Available at: <http://link.springer.com/10.1007/s40629-014-0009-1>
 23. Lee JK, Vadas P. Anaphylaxis: mechanisms and management. *Clin Exp Allergy* 2011;41:923-38. Available at: <http://doi.wiley.com/10.1111/j.1365-2222.2011.03779.x>
 24. Bock SA. Fatal anaphylaxis. In: Kelso J, Feldweg A, editors. UpToDate. Waltham, MA: UpToDate; 2020.
 25. Arts L, Lim EHT, van de Ven PM, Heunks L, Tuinman PR. The diagnostic accuracy of lung auscultation in adult patients with acute pulmonary pathologies: a meta-analysis. *Sci Rep* 2020;10:1-11.
 26. Tupper J. Anaphylaxis: a review and update. *Can Fam Physician* 2010;56:1009-11.
 27. Lieberman PL. Biphasic and protracted anaphylaxis. In: Kelso JM, Feldweg AM, editors. UpToDate. Waltham, MA: UpToDate; 2020.
 28. Simons FER, Arduoso LRF, Bilò MB, et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011;4:13-37. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S1939455119304132>
 29. Maurer M, Magerl M. Hereditary angioedema: an update on available therapeutic options. *JDDG J der Dtsch Dermatologischen Gesellschaft* 2010;8:663-72. Available at: <http://doi.wiley.com/10.1111/j.1610-0387.2010.07450.x>
 30. Craig T, Pürsün EA, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J* 2012;5:182-99. Available at: www.waojournal.org/content/5/12/182
 31. Ring J, Klimek L, Worm M. Adrenaline in the acute treatment of anaphylaxis. *Dtsch Arzteblatt Online* 2018; Available at: www.aerzteblatt.de/10.3238/arztebl.2018.0528
 32. Kay LJ, Peachell PT. Mast cell beta2-adrenoceptors. In: *Mast Cells in Allergic Diseases*. Basel: KARGER; 2005. p. 145-53. Available at: www.karger.com/Article/FullText/87641
 33. Wood JP. Safety of epinephrine for anaphylaxis in the emergency setting. *World J Emerg Med* 2013;4:245. Available at: www.wjem.com.cn/default/article/index/id/257
 34. Peachell P. Regulation of mast cells by β -agonists. *Clin Rev Allergy Immunol* 2006;31:131-42. Available at: <http://link.springer.com/10.1385/CRIAI:31:2:131>
 35. Sicherer SH. Prescribing epinephrine for anaphylaxis self-treatment. In: Kelso JM, Feldweg A, editors. UpToDate. Waltham, MA: UpToDate; 2020.
 36. Gosens R, Gross N. The mode of action of anticholinergics in asthma. *Eur Respir J* 2018;52:1701247. Available at: <http://dx.doi.org/10.1183/13993003.01247-2017>
 37. Marotta SE, Belchikov Y, Banker K, Marshall PS. Emergency management of acute severe asthma exacerbation in the adult population. *J Asthma Allergy Educ* 2010;1:174-9. Available at: <http://journals.sagepub.com/doi/10.1177/2150129710374232>
 38. Williams DM. Clinical pharmacology of corticosteroids. *Respir Care* 2018;63:655-70. Available at: <http://rc.rcjournal.com/lookup/doi/10.4187/respcare.06314>
 39. Alqurashi W, Ellis AK. Do corticosteroids prevent biphasic anaphylaxis? *J Allergy Clin Immunol Pract* 2017;5:1194-205. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S2213219817303859>
 40. Sheikh A, ten Broek V, Brown SGA, Simons FER. H1-antihistamines for the treatment of anaphylaxis. *Allergy* 2007;62:830-7. Available at: <http://doi.wiley.com/10.1111/j.1398-9995.2007.01435.x>
 41. Kawano T, Scheuermeyer FX, Gibo K, et al. H1-antihistamines reduce progression to anaphylaxis among emergency department patients with allergic reactions. *Zehtabchi S, editor. Acad Emerg Med* 2017;24:733-41. Available at: <http://doi.wiley.com/10.1111/acem.13147>
 42. Hernández-Cascales J. Does glucagon have a positive inotropic effect in the human heart? *Cardiovasc Diabetol* 2018;17:148. Available at: <https://cardiab.biomedcentral.com/articles/10.1186/s12933-018-0791-z>
 43. Insuela DBR, Azevedo CT, Coutinho DS, et al. Glucagon reduces airway hyperreactivity, inflammation, and remodeling induced by ovalbumin. *Sci Rep* 2019;9:6478. Available at: www.nature.com/articles/s41598-019-42981-6
 44. Soong JTY, Soni N. Circulatory shock. *Medicine (Baltimore)* 2013;41:64-9. Available at: <https://linkinghub.elsevier.com/retrieve/pii/S1357303912002812>
 45. Hale AJ, Ricotta DN, Herzig SJ, William JH, Freed JA. A quantitative approach to dilutional anemia. *J Hematol* 2019;8:86-7. Available at: www.thejh.org/index.php/JH/article/view/498