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TREATMENT OF ANAPHYLAXIS AND MODIFICATIONS DURING COVID-19

BACKGROUND

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and is potentially life-threatening.[1,2] The lifetime prevalence of anaphylaxis is between 1.6 to 5.1% with the largest number of incident cases among children and adolescents.[3–5] Most episodes of anaphylaxis are immunoglobulin- E (IgE) mediated with foods, medications and stinging insects being the most common triggers.[6] While various definitions of anaphylaxis exist,[2,7–9] most rely on two body systems being affected, with some combination of cutaneous, respiratory, gastrointestinal and/or cardiac symptoms. Cutaneous symptoms are by far the most common, reported in over 80% of anaphylaxis, followed by respiratory then gastrointestinal involvement.[1]

Food allergy is one of the most common chronic conditions of childhood, directly impacting up to 10% of children and indirectly up to 50% of the population.[10–12] It is the most common cause of anaphylaxis in children.[6] Anaphylaxis is less common in infants than it is in children.[13] While anaphylaxis can be life-threatening, the risk of fatal anaphylaxis is about 1 in 10 million (this is equivalent to being struck by lightning).[14] While it is essential that anaphylaxis be recognized and managed, the risk of fatality is very low. Factors that increase the risk of anaphylaxis severity and/or fatality include comorbidities, such as asthma, mastocytosis, hyperdynamic states including exercise and infection, concurrent medication use (i.e. ACE inhibitors), and age where increased risk taking behavior is common (i.e. in adolescents).[1,15]

Investigations at the time of an anaphylactic reaction include plasma histamine and/or serum tryptase levels, although neither is specific for anaphylaxis.[1] If food allergy is suspected as a trigger of anaphylaxis, subsequent skin prick testing (SPT) and/or food-specific IgE (sIgE) can be measured. However, while SPT and food-specific IgE testing are highly sensitive (from 70-90%), the specificity of testing remains low (less than 50%).[1,2] The rate of false positive tests is up to 40%.[16] As a result, food allergy testing is diagnostic within the context of the presenting anaphylactic history. An allergy skin test (AST) should be performed when a convincing clinical history of allergen induced anaphylaxis is present.[17]

Biphasic anaphylaxis is defined as recurrent symptoms occurring 1 to 72 hours after resolution of the initial reaction (although often within 8 hours) and occurs in 1-20% of patients.[1,15,18,19] Risk factors for biphasic anaphylaxis include more severe initial symptoms, the requirement of more than one dose of epinephrine for recovery, unknown trigger for anaphylaxis, and medication-induced anaphylaxis in the pediatric population.[15]

MANAGEMENT OF ANAPHYLAXIS

Guidelines uniformly recommend epinephrine as first-line therapy in anaphylaxis.[1] Beneficial and life-saving mechanisms of epinephrine include reduction in laryngeal angioedema, cardiac inotropic and chronotropic effects, bronchodilation, and vasoconstriction.[1,16,20] Delay in the use of epinephrine has been associated with increased morbidity and mortality.[21] Despite this, epinephrine autoinjectors are often underutilized both in incidence and within ideal timing of anaphylaxis.[22]

Anyone with a history of anaphylaxis should receive education that includes allergen avoidance, early and appropriate recognition of the signs and symptoms of anaphylactic reaction with appropriate referral to a consulting allergist.[1,15] An epinephrine autoinjector should always be prescribed with education around its proper use and technique. A possible exception to the prescription of an epinephrine autoinjector is if the known trigger was a medication, in which case deferral of this prescription may be possible pending allergy evaluation.[15] A medical alert band is strongly advised in medication-induced anaphylaxis.

Antihistamines (AH1) are often erroneously used in place of epinephrine in the treatment of anaphylaxis. Their role remains as second or third-line therapeutic options in anaphylaxis guidelines.[23] Antihistamines do not relieve upper or lower airway obstruction, shock or hypotension and their onset of action ranges from 1-3 hours.[1] Early AH1 use often delays the use of epinephrine, which is associated with increased risk of anaphylaxis fatality.[24] In addition, there are significant safety concerns with the use of first-generation sedating antihistamines (such as diphenhydramine) which can be associated with somnolence, sedation, or a paradoxical stimulatory response in children.[25] This effect may actually mask worsening anaphylaxis, which can be associated with central nervous system effects.[1] In adolescents and adults, first generation antihistamines have been associated with poor sleep quality, decreased school and work performance, automobile and boat accidents, cardiac toxicity, and are known drugs of abuse.[26] In contrast, second and third generation H1-antihistamines have much fewer adverse effects and a faster onset of action than first generation antihistamines.[26]

Antihistamines should never be used in place of epinephrine; if used as an adjunct therapy, non-sedating antihistamines are preferred to first-generation antihistamines. The Canadian Society of Allergy and Clinical Immunology notes that first-generation antihistamines should only be used if absolutely necessary in the treatment of allergic disease and have advocated to have them available only behind the counter in pharmacies.[26]

While oral corticosteroids are often prescribed, there is no evidence that their use prevents a biphasic reaction.[27,28] In fact, some studies suggest that oral steroids can actually increase risk. The Cross-Canada Anaphylaxis Registry found that pre-hospital corticosteroid treatment was associated with an increased risk of intensive care unit/hospital ward admission after adjusting for reaction severity, treatment with epinephrine, sex, age and comorbidities.[29] In this study, a total of 3498 cases of anaphylaxis, of which 80.3% were children, presented to 9 EDs across Canada. Pre-hospital treatment with epinephrine was administered in 31% of cases, whereas antihistamines and corticosteroids were used in 46% and 2% of cases, respectively. Admission to the intensive care unit/hospital ward was associated with pre-hospital treatment with corticosteroids (adjusted odds ratio, 2.84; 95% confidence interval [CI], 1.55, 6.97). In addition, even short-term use of oral steroids can have detrimental effects in children including vomiting, sleep disturbances and behavioral changes as evidenced by a systematic review involving thirty-eight studies of which 22 randomised controlled trials (RCTs) met the inclusion criteria. The studies involved a total of 3,200 children in whom 850 ADRs were reported.[30] Recent 2020 guidance from the Joint Task Force on anaphylaxis management recommend against the use of corticosteroids to prevent biphasic anaphylaxis.[15]

MANAGEMENT OF ANAPHYLAXIS DURING COVID-19

COVID-19 and its impact on healthcare resources, as well as the reallocation of medical services has resulted in changes to care across medicine as a whole, including the management of allergy care such as anaphylaxis.[31] Prior to COVID-19, if an epinephrine autoinjector was used for treatment of anaphylaxis, it was commonly recommended that emergency medical services (EMS) be activated, with the patient transported to the hospital to be monitored in the case of a biphasic reaction.[32,33] During COVID-19, an alternative approach has been outlined which involves at-home monitoring (instead of reflex EMS activation) with epinephrine use.[34] Based on this approach, epinephrine would be administered in the case of a severe allergic reaction, with patients then monitored at home for treatment response.[34] If symptoms resolve, their healthcare provider would be notified non-urgently for routine follow-up. If symptoms either persist or worsen a second dose of epinephrine should be injected and EMS activated. At-home monitoring would only be recommended in those who have a clear understanding of anaphylaxis monitoring, who have at least 2 epinephrine autoinjectors available with good control of comorbidities such as asthma.[34] A review of this alternative approach will be needed to assess outcomes and any adverse reactions and/or delayed access to further anaphylactic care. The decision to monitor at home should only be made in the context of shared decision making, between the healthcare team, patients and their families with agreement of the risks and benefits of this approach.[35] Immediate EMS activation would remain available if there is concern of any further allergy symptoms or lack of familial comfort.[35] A revised anaphylaxis algorithm has been developed that incorporates this at-home monitoring approach during COVID-19 (**Figure 1**).[34]

It has been posited that while this recommendation was designed specifically in the context of COVID-19, and the need to reduce risk of contracting COVID-19 in the ED as well as to reduce the burden on healthcare resources, there may be reason to consider this approach after the pandemic.[35] The rationale for this is multifactorial. Firstly, the requirement for EMS activation has been shown to be a barrier to using an epinephrine autoinjector among families of children with food allergy.[36] Second of all, the practice of automatic EMS activation has not been shown to reduce fatality due to anaphylaxis (only early use of epinephrine has been shown to do that).[35] Finally, the practice of automatic EMS activation has not been shown to be cost-effective (unless there was a very high risk of fatality with the majority of children requiring other additional care while in the ED).[37]

CONCLUSION

While anaphylaxis is relatively common, fatality due to anaphylaxis is exceptionally rare. Epinephrine is uniformly recommended as first-line therapy for the treatment of anaphylaxis. While antihistamines are often used in place of epinephrine they have a secondary or tertiary role in the acute management of anaphylaxis. Antihistamines used as adjunct therapy for cutaneous symptoms, should be from second- or third-generation non-sedating antihistamine categories over first generation antihistamines due to safety profile. While oral steroids are often prescribed to prevent biphasic anaphylaxis evidence is lacking for this approach. Finally, with the impact of the COVID-19 pandemic, recommendations for anaphylaxis management suggest at home epinephrine auto-injector use, and monitoring without reflex EMS activation unless poor response to epinephrine is encountered. The practice of EMS activation has not proven to be cost-effective and may serve as a barrier to epinephrine use. Analysis and data capture of this "at home" modified anaphylaxis treatment plan may result in the long-term reassessment of the management of anaphylaxis in the post-pandemic era as well.

Revised Anaphylaxis Management Algorithm During COVID Pandemic

To be implemented based on the local risk / benefit assessment

Patients with history of severe anaphylaxis such as those who have been intubated and ventilated, or had reactions treated with more than two doses of epinephrine should follow their routine anaphylaxis plan and activate emergency services immediately when anaphylaxis is recognized.

IMPORTANT REMINDER: Anaphylaxis is a potentially life-threatening, severe allergic reaction.
If in doubt, give epinephrine.

SEVERE SYMPTOMS: any of the following

LUNG
Shortness of breath
Wheezing, repetitive cough

HEART
Pale or bluish skin, faintness, weak pulse, dizziness

GUT
Repetitive vomiting, severe diarrhea

THROAT
Tight or hoarse throat, trouble breathing or swallowing

SKIN
Many hives over body, widespread redness

MOUTH
Significant swelling of the tongue or lips

OTHER
Feeling something bad is about to happen, anxiety, confusion

Mild symptoms from <u>more than one</u> system area:
Itchy runny nose, sneezing and/or Itchy mouth and/or few hives, mild itch and /or mild nausea or discomfort

1. INJECT EPINEPHRINE IMMEDIATELY
while seated; have telephone within reach

2. **Notify a housemate or neighbor to help you**
3. **Lay down with legs elevated near the doorway, which should be unlocked or open to allow others to enter and help. Keep children in a position of comfort, to minimize respiratory distress and agitation and risk of aspiration in case of vomiting.**
4. **Administer oral antihistamine, preferably non-sedating (e.g. cetirizine)**
5. **Administer albuterol for respiratory symptoms if prescribed and available**
6. **Monitor symptoms and blood pressure/pulse if possible**

SYMPTOMS DON'T IMPROVE OR WORSEN

Repeat epinephrine injection in 5 minutes or sooner if symptoms escalate rapidly

SEVERE SYMPTOMS DON'T IMPROVE OR WORSEN

Activate Emergency Services *(Call 911)*

SEVERE SYMPTOMS RESOLVE

Continue to monitor for 4-6 hours for the recurrence of symptoms

Be ready to administer treatment if symptoms reappear (biphasic anaphylaxis)

Notify your physician on a non-urgent basis

Replenish emergency medications

Figure 1. Revised anaphylaxis algorithm replacing the standard management protocol during the COVID-19 pandemic ; adapted from Casale et al, 2020

References

1.Simons FER. Anaphylaxis. J Allergy Clin Immunol. 2010;125:S161-81.

2. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel. J Allergy Clin Immunol. 2010;126:S1-58.

3. Lieberman P, Camargo CAJ, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann allergy, asthma Immunol Off Publ Am Coll Allergy, Asthma, Immunol. 2006;97:596–602.

4. Wood RA, Camargo CA, Lieberman P, Sampson HA, Schwartz LB, Zitt M, et al. Anaphylaxis in America: The prevalence and characteristics of anaphylaxis in the United States. J Allergy Clin Immunol [Internet]. 2014;133:461–7. Available from: http://www.sciencedirect.com/science/article/pii/S009167491301302X

5. Shaker MS, Oppenheimer J, Wallace D V, Golden DBK, Lang DM, Lang ES, et al. Making the GRADE in anaphylaxis management: Toward recommendations integrating values, preferences, context, and shared decision making. Ann Allergy Asthma Immunol. 2020;in press.

6. Fischer D, Vander Leek TK, Ellis AK, Kim H. Anaphylaxis. Allergy Asthma Clin Immunol [Internet]. 2018;14:54. Available from: https://pubmed.ncbi.nlm.nih.gov/30263034

7. Simons FER, Ardusso LRF, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J. 2011;4:13–37.

8. 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? World Allergy Organ J. 2019;12:100066.

9. Rüggeberg JU, Gold MS, Bayas J-M, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25:5675–84.

10. Soller L, Ben-Shoshan M, Harrington DW, Fragapane J, Joseph L, St Pierre Y, et al. Overall prevalence of self-reported food allergy in Canada. J Allergy Clin Immunol. 2012;130:986–8.

11. Clarke AE, Elliott S, Pierre YS, Soller L, La Vieille S, Ben-Shoshan M. Temporal Trends in Prevalence of Food Allergy in Canada. J Allergy Clin Immunol Pr. 2019;[epub ahea.

12. Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and Severity of Food Allergies Among US Adults. JAMA Netw open. 2019;2:e185630.

13. Abrams EM, Primeau M-N, Kim H, Gerdts J, Chan ES. Increasing awareness of the low risk of severe reaction at infant peanut introduction: Implications during COVID-19 and beyond. J Allergy Clin Immunol Pract. United States; 2020. p. in press.

14. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal Anaphylaxis: Mortality Rate and Risk Factors. J Allergy Clin Immunol Pr. 2017;5:1169–78.

15. Shaker MS, Wallace D V, Golden DBK, Oppenheimer J, Bernstein JA, Campbell RL, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020;145:1082–123.

16. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. CMAJ. 2016;188:1087–93.

17. Fleischer DM, Chan ES, Venter C, Spergel JM, Abrams EM, Stukus D, et al. A Consensus Approach to the Primary Prevention of Food Allergy Through Nutrition: Guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical. J Allergy Clin Immunol Pr. 2020;in press.

18. Sicherer SH, Simons FER. Epinephrine for First-aid Management of Anaphylaxis. Pediatrics. 2017;139.

19. Lee S, Bellolio MF, Hess EP, Campbell RL. Predictors of biphasic reactions in the emergency department for patients with anaphylaxis. J Allergy Clin Immunol Pr. 2014;2:281–7.

20. Food allergy: a practice parameter. Ann Allergy Asthma Immunol. 2006;96:S1-68.

21. Pumphrey RSH, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. Vol. 119, J Allergy Clin Immunol. United States; 2007. p. 1018–9.

22. Prince BT, Mikhail I, Stukus DR. Underuse of epinephrine for the treatment of anaphylaxis: missed opportunities. J Asthma Allergy. 2018;11:143–51.

23. Simons FER, Ardusso LRF, Bilo MB, Dimov V, Ebisawa M, El-Gamal YM, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. Curr Opin Allergy Clin Immunol. 2012;12:389–99.

24. Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol. 2007/03/14. 2007;119:1018–9.

25. Church MK, Maurer M, Simons FER, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. Allergy. 2010;65:459–66.

26. Fein MN, Fischer DA, O'Keefe AW, Sussman GL. CSACI position statement: Newer generation H(1)-antihistamines are safer than first-generation H(1)-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. Allergy, asthma, Clin Immunol Off J Can Soc Allergy Clin Immunol. 2019;15:61.

27. Alqurashi W, Ellis AK, Ottawa F. Do Corticosteroids Prevent Biphasic Anaphylaxis ? J Allergy Clin Immunol Pract [Internet]. 2017;5:1194–205. Available from: http://dx.doi.org/10.1016/j.jaip.2017.05.022

28. Alqurashi W, Stiell I, Chan K, Neto G, Alsadoon A, Wells G. Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis. Ann Allergy Asthma Immunol. 2015;115:217-223 e2.

29. Gabrielli S, Clarke A, Morris J, Eisman H, Gravel J, Enarson P, et al. Evaluation of Prehospital Management in a Canadian Emergency Department Anaphylaxis Cohort. J Allergy Clin Immunol Pr. 2019;7:2232-2238.e3.

30. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child. 2016;101:365–70.

31. Searing DA, Dutmer CM, Fleischer DM, Shaker MS, Oppenheimer J, Grayson MH, et al. A Phased Approach to Resuming Suspended Allergy/Immunology Clinical Services. J Allergy Clin Immunol Pr. 2020;8:2125–34.

32. Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis--a practice parameter update 2015. Ann Allergy Asthma Immunol. 2015;115:341–84.

33. Simons FER, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015;8:32.

34. Casale TB, Wang J, Nowak-Wegrzyn A. Acute At Home Management of Anaphylaxis During the Covid-19 Pandemic. Vol. 8, J Allergy Clin Immunol Pract. 2020. p. 1795–7.

35. Mack DP, Chan ES, Shaker M, Abrams EM, Wang J, Fleischer DM, et al. Novel Approaches to Food Allergy Management During COVID-19 Inspire Long-Term Change. J Allergy Clin Immunol Pr. 2020;in press.

36. Robinson M, Greenhawt M, Stukus DR. Factors associated with epinephrine administration for anaphylaxis in children before arrival to the emergency department. Ann Allergy Asthma Immunol. 2017;119:164–9.

37. Shaker M, Kanaoka T, Feenan L, Greenhawt M. An economic evaluation of immediate vs non-immediate activation of emergency medical services after epinephrine use for peanut-induced anaphylaxis. Ann Allergy Asthma Immunol. 2019;122:79–85.