

Anaphylaxis: Recognizing Risk and Targeting Treatment



David B.K. Golden, MD *Baltimore, Md*

“Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.”¹ The imminent risk of death is inherent in the fear of anaphylaxis that has grown among our patients and their caregivers. A better understanding of the mechanisms of anaphylaxis may, in the future, provide better ways to disarm the ticking mast cell. For now, we can provide better guidance to those at risk for anaphylaxis to help prevent both alarmism and complacency. Ideally, we would direct greater concern and intervention to prevent severe reactions to those at greatest risk. However, the avoidance of unnecessary prescription of epinephrine and the associated impairment in quality of life in those at low risk is also a worthy goal. Such risk stratification is dependent on the identification of clinical and laboratory markers of risk. Discussion of the stratification of risk of anaphylaxis, and its implications for the prescription of epinephrine autoinjectors (EAI) or immunotherapy, is a core issue in the most recent updates of the Practice Parameters on Anaphylaxis and on Insect Sting Allergy.^{2,3} There is still no specific test that can reliably predict the outcome of allergen exposure in a sensitized individual. However, research can help us identify markers that should guide our shared decision making with affected patients. Many of the articles in this issue of *JACI: In Practice* help us to frame and address these questions and the unmet needs in research and clinical care.

Should patients really worry about dying? Just how high is the chance of death from an anaphylactic reaction? Estimates of anaphylaxis-related mortality have been between 0.5 and 5.5 per million population, with death reportedly occurring in 0.3% to 2% of patients experiencing severe anaphylactic reactions. In a Clinical Commentary review in this theme issue of the journal, Turner et al⁴ present a unique look into the details of the published studies on fatal anaphylaxis, revealing variation in the outcomes and relative risk with different causes and in different settings. They also put everything into perspective in their figures showing the relative risk of death from a variety of causes. It seems the chance of dying during an anaphylactic reaction is not 1% to 2% as previously thought, but at least one order of

magnitude less. The risk is never zero. It is often difficult for patients, caregivers, and physicians to decide whether the risk is at an acceptably low level to forego the potential intervention (such as prescription of an EAI or immunotherapy). In this regard, putting the risk in perspective may alleviate some of the anxiety and facilitate the decision making.

Biphasic anaphylaxis has been associated with fatal and near-fatal reactions. It would certainly be of interest to know of any way to prevent biphasic reactions. In this issue, Alqurashi and Ellis⁵ give us a comprehensive analysis of the literature regarding prevention of biphasic reactions in their Clinical Commentary review. Until the 1980s it was considered inappropriate to give steroids for the treatment of anaphylaxis. It was only the recognition of late-phase inflammatory allergic reactions in the skin and airways that led to the belief, by extrapolation, that this must be the mechanism of biphasic anaphylaxis and therefore could be prevented by early administration of steroids. As pointed out by Alqurashi and Ellis, there has been minimal evidence to support this practice, and it is not recommended in the Practice Parameters.^{2,3} Notably, early use of epinephrine has proven to be the best way to avert a biphasic response and fatal anaphylaxis.⁶

We are also reminded of the role of the mast cell in life-threatening anaphylaxis in the Grand Rounds Review by Lei et al,⁷ which highlights the progress in the diagnosis and management of mast cell disorders. This case provides insight on the range of medications used in these patients. The difficulty in controlling symptoms in these patients, who are at risk for anaphylaxis every day, underscores the need to develop more definitive therapy. Mastocytosis is itself a risk factor for severe anaphylaxis, but the characteristics described by Gulen et al⁸ in this issue may help to distinguish those at greatest risk. The most common cause of anaphylaxis in patients with indolent systemic mastocytosis is insect stings (particularly yellow jacket). Vos et al⁹ describe in this issue a population of patients with mastocytosis in which more than 50% of those who were stung had a systemic reaction. More importantly, 97% of those who were stung experienced at least one severe or very severe reaction, and 91% of those who were subsequently resting had another systemic reaction. Of note is that asymptomatic sensitization is uncommon in patients with mastocytosis: 83/89 (93%) of those who were stung and had positive tests for venom-specific IgE had a systemic reaction to a sting. The authors recommend testing all patients with mastocytosis for venom allergy.

The best way to prevent fatal anaphylaxis is to reduce or eliminate the cause of the problem. The rise and fall of latex allergy provides important lessons in this regard. The Clinical Commentary review by Kelly and Sussman¹⁰ takes us through many of the important steps in the development of latex allergy as a clinical problem, and how cooperation at many levels can

Division of Allergy and Clinical Immunology, Johns Hopkins University, Baltimore, Md

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Corresponding author: David B.K. Golden, MD, Division of Allergy and Clinical Immunology, Johns Hopkins University, 7939 Honeygo Blvd, Suite 219, Baltimore, MD 21236. E-mail: dgolden1@jhmi.edu.

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TABLE I. Factors that increase the risk for severe, near-fatal, or fatal anaphylaxis

Delay in use of epinephrine
Severity of reaction
Absence of urticaria
Biphasic reaction
β-Blockers/ACEI
Age >65
Cardiovascular or pulmonary disease
Medication as a trigger
Uncontrolled asthma
Elevated tryptase/mast cell disorder
PAF-AH deficiency

ACEI, Angiotensin converting enzyme inhibitors; PAF-AH, platelet activating factor acetyl-hydrolase.

thwart a potential epidemic. The early epidemiologic observations helped to focus preventative efforts on the highest risk individuals, but it took more than a decade of work to effect changes in the workplace, in the products, and in the clinic. The success of this effort is testimony to the dedication of clinicians, scientists, and regulators who did not take no for an answer.

The risk of severe anaphylaxis has been associated with a number of other factors that should be recognized and avoided whenever possible. Table I shows some of the factors known to increase the risk for severe and potentially fatal anaphylaxis. Beta-blockers (BB) and angiotensin converting enzyme inhibitors (ACEI) have been reported to increase the risk of a severe reaction.^{3,11} There has been some controversy and conflicting reports regarding the relative risk associated with BB and ACEI.² Coop et al¹² have compiled a comprehensive Clinical Commentary review of the evidence in an effort to provide guidance to the clinician. In the case of immunotherapy as a cause of anaphylaxis, it is possible that ACEI and BB could increase the chance that a systemic reaction might be severe, even if they do not increase the frequency of systemic reactions. There is relatively low risk of using these medications during maintenance immunotherapy, in part because the frequency of systemic reactions is very low during maintenance treatment.

Epinephrine remains the mainstay of treatment for anaphylaxis, and early use of epinephrine can prevent biphasic reactions and fatal reactions.^{6,13} There have always been barriers to the prescription and appropriate use of EAI. Wasserman et al¹⁴ review the most recent reports in their Clinical Commentary, finding little progress in these areas. Even after a prescription is given and filled (2 of the biggest barriers), patients use the device in less than 20% of incidents where it should have been used. There are also some new concerns for the effective use of EAI. Optimal delivery of the drug is intramuscular in the anterolateral thigh, but this is not always achieved for numerous reasons. The depth of delivery depends not only on needle length, but also on the degree of compression, force of ejection of the solution from the needle tip, and the thickness of subcutaneous tissue. There have been reports of the needle striking bone, of ineffective administration possibly due to subcutaneous delivery, and of marked local tissue trauma resulting from the needle held in the leg of a squirming child for the recommended number of

seconds. Recent studies have identified the need for both shorter and longer needle lengths.^{15,16}

Is the EAI the best way to prevent fatal anaphylaxis? For many patients, caregivers, and prescribers, the threshold for prescribing an EAI is very low because even a 1 in 1000 chance of anaphylaxis is considered by many to be a reason to put an EAI in every pocket. The threshold of symptoms that warrant the use of the device is also very low because of the fear of fatal anaphylaxis.¹⁷ It is interesting that despite these observations, prescription of an EAI and appropriate use of the device both occur at very low rates in the community and in the emergency department. As discussed by Wasserman et al,¹⁴ these problems are not yet improving. Patients and doctors remain confused, resulting in wide variation in the information given to patients. There is clearly a need to identify the markers and predictors of severe anaphylaxis that can guide the decision on which patients, and which reactions, should be treated promptly with epinephrine injection.

For these reasons, prevention of fatal anaphylaxis may be better accomplished by improved education of physicians and patients to recognize the risk factors for severe reactions. This approach might be compared with coronary heart disease, in which real progress in reducing mortality came not from having nitroglycerin in every pocket to ease the acute symptoms, but from education on how to target the patients with greatest risk based on basic and epidemiologic research. There is no replacement for vigilance, and no shortage of examples of unfortunate and preventable outcomes. However, if we can identify those at greatest risk, we can more efficiently prescribe EAI, more specifically treat with epinephrine when a reaction develops, advise immunotherapy when needed, and even prevent or abort epidemics.

REFERENCES

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
2. Golden DBK, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol* 2017;118:28-54.
3. 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.
4. Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: mortality rate and risk factors. *J Allergy Clin Immunol Pract* 2017;5:1169-78.
5. Alqurashi W, Ellis AK. Do corticosteroids prevent biphasic anaphylaxis? *J Allergy Clin Immunol Pract* 2017;5:1194-205.
6. Simons FE, Clark S, Camargo CA. Anaphylaxis in the community: learning from the survivors. *J Allergy Clin Immunol* 2009;124:301-6.
7. Lei D, Akin C, Kovalszki A. Management of mastocytosis in pregnancy: a review. *J Allergy Clin Immunol Pract* 2017;5:1217-23.
8. Gülen T, Ljung C, Nilsson G, Akin C. Risk factor analysis of anaphylactic reactions in patients with systemic mastocytosis. *J Allergy Clin Immunol Pract* 2017;5:1248-55.
9. Vos BJPR, van Anrooij B, van Doormaal JJ, Dubois AEJ, Oude-Elberink JNG. Fatal anaphylaxis to yellow jacket stings in mastocytosis: options for identification and treatment of at risk patients. *J Allergy Clin Immunol Pract* 2017;5:1264-71.
10. Kelly KJ, Sussman G. Latex allergy: Where are we now and how did we get there? *J Allergy Clin Immunol Pract* 2017;5:1212-6.
11. Nassiri M, Babina M, Dolle S, Edenharter G, Rueff F, Worm M. Ramipril and metoprolol intake aggravate human and murine anaphylaxis: evidence for direct mast cell priming. *J Allergy Clin Immunol* 2015;135:491-9.

12. Coop CA, Schapira RS, Freeman TM. Are ACE-inhibitors and beta-blockers dangerous in patients at risk for anaphylaxis? *J Allergy Clin Immunol Pract* 2017;5:1207-11.
13. Ellis AK. Priority role of epinephrine in anaphylaxis further underscored—the impact on biphasic anaphylaxis. *Ann Allergy Asthma Immunol* 2015;115:165.
14. Waserman S, Avilla E, Ben-Shoshan M, Rosenfield L, Adcock AB, Greenhawt M. Epinephrine auto-injectors: new data, new problems. *J Allergy Clin Immunol Pract* 2017;5:1180-91.
15. Kim H, Dinakar C, McInnis P, Rudin D, Benain X, Daley W, et al. Inadequacy of current pediatric epinephrine autoinjector needle length for use in infants and toddlers. *Ann Allergy Asthma Immunol* 2017;118:719-725.e1.
16. Manuyakorn W, Bamrunghaowkasem B, Ruangwattanapaisarn N, Kamchaisatian W, Benjaponpitak S. Optimal needle length for epinephrine pre-filled syringe in children. *Ann Allergy Asthma Immunol* 2017;118:740-741.e1.
17. Turner PJ, DunnGalvin A, Hourihane JOB. The emperor has no symptoms: the risks of a blanket approach to using epinephrine autoinjectors for all allergic reactions. *J Allergy Clin Immunol Pract* 2016;4:1143-6.

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