

Are ACE Inhibitors and Beta-blockers Dangerous in Patients at Risk for Anaphylaxis?



Christopher A. Coop, MD^a, Rebecca S. Schapira, DO^a, and Theodore M. Freeman, MD^b San Antonio, Tex

The objective of this article is to review the available studies regarding angiotensin converting enzyme (ACE) inhibitors and beta-blockers and their effect on patients at risk for anaphylaxis. A literature search was conducted in PUBMED to identify peer-reviewed articles using the following keywords: anaphylaxis, ACE inhibitor, beta-blocker, food allergy, radiocontrast media, venom allergy, skin testing, and immunotherapy. Some studies show an increased risk of anaphylaxis in patients who are taking ACE inhibitors and beta-blockers, whereas others studies do not show an increased risk. For venom immunotherapy, there are more data supporting the concomitant use of beta-blockers and ACE inhibitors in the build-up and maintenance phases. Most of the medical literature is limited to case reports and retrospective data. Prospective controlled trials are needed on this important topic. For those patients at risk of anaphylaxis who lack cardiovascular disease, it is recommended to avoid beta-blockers and possibly ACE inhibitors. However, for those patients with cardiovascular disease, beta-blockers and ACE inhibitors have been shown to increase life expectancy. Consideration should be given for the concomitant use of these medications while patients are receiving venom immunotherapy. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1207-11)

Key words: Anaphylaxis; ACE inhibitor; Beta-blocker; Food Allergy; Radiocontrast media; Venom allergy; Skin testing; Immunotherapy

Anaphylaxis is a severe, life-threatening manifestation of a systemic immediate hypersensitivity reaction that necessitates prompt medical intervention.¹ The most common causes of anaphylaxis are food and medications; however, Hymenoptera stings, radiocontrast media (RCM), and iatrogenic procedures

such as skin testing, allergy challenges, and immunotherapy are implicated among various other triggers.² Patients taking antihypertensive medications, specifically angiotensin converting enzyme (ACE) inhibitors or beta-blockers, represent a population in whom a possibly increased risk for anaphylaxis has been debated.³

Although the lifetime prevalence of anaphylaxis in the general population is estimated to be approximately 7% and possibly up to 10% to 12%, the prevalence of anaphylaxis in patients taking ACE inhibitors and beta-blockers is unknown.⁴ This presents a clinical conundrum to the physician and can limit efficacious diagnostic and management options for allergic disorders to many patients. This article summarizes the mechanisms of action of ACE inhibitors and beta-blockers in relation to the pathophysiology of anaphylaxis. It presents key arguments with available data regarding food allergy, RCM administration, venom allergy, skin testing, and immunotherapy in patients taking these select antihypertensive medications.

MECHANISM OF ACTION: ANAPHYLAXIS, ACE INHIBITORS, AND BETA-BLOCKERS

Anaphylaxis is classically initiated by allergen cross-linking of IgE on mast cells and basophils, leading to degranulation and release of histamine, tryptase, chymase, platelet-activating factor, prostaglandins, and leukotrienes.^{5,6} Release of these mediators activates inflammatory pathways, including the complement and kallikrein-kinin systems and the clotting cascade. Histamine release, in particular, causes vasodilation leading to increased vascular permeability and decreased peripheral vascular resistance.² Decreased peripheral vascular resistance leads to activation of the renin-angiotensin system, a compensatory mechanism blocked by ACE inhibitors, thus theoretically leading to intensified anaphylaxis. Histamine release also increases cardiac rate, cardiac contractility, and bronchoconstriction.^{2,5} Therefore, it is suggested that beta-blockers mask cardiac signs of anaphylaxis and lead to unopposed alpha-adrenergic activity, causing severe bronchoconstriction. Furthermore, management of anaphylaxis with concomitant beta-blocker use is complicated by the possibility of a blunted response to epinephrine and/or inhaled bronchodilators.⁷ Also animal studies suggest that ACE inhibitors and beta-blockers together may enhance mast cell priming.⁸

Nitric oxide also plays a role in anaphylaxis. Nitric oxide can inhibit the release and effects of catecholamines. It causes vasodilation by increasing the activation of guanylyl cyclase that can result in smooth muscle relaxation via cyclic guanosine monophosphate.⁹ Methylene blue is an inhibitor of guanylyl cyclase and has been used as a treatment for refractory anaphylaxis.¹⁰ There is evidence that glucagon is also helpful in refractory anaphylaxis especially for patients on beta-blockers. Glucagon

^aDepartment of Allergy and Immunology, Wilford Hall Ambulatory Surgical Center, San Antonio, Tex

^bSan Antonio Asthma and Allergy Clinic, San Antonio, Tex

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Air Force or the Department of Defense.

Received for publication February 17, 2017; revised April 21, 2017; accepted for publication April 26, 2017.

Available online May 25, 2017.

Corresponding author: Theodore M. Freeman, MD, San Antonio Asthma and Allergy Clinic, 5282 Medical Dr Suite 500, San Antonio, TX 78229. E-mail: TFree95900@aol.com.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.04.033>

Abbreviations used

ACE-Angiotensin converting enzyme

RCM-Radiopaque media

activates adenylyl cyclase directly and can bypass the beta blockade.^{11,12} Additionally, higher doses of epinephrine may be needed to overcome the beta blockade for refractory anaphylaxis; however, beta-blockers prevent vasodilation, leaving unopposed alpha vasoconstriction that may result in a hypertensive reaction.^{12,13}

ANAPHYLAXIS IN GENERAL

There is some medical literature suggesting that patients taking beta-blockers or ACE inhibitors are at an increased risk of anaphylaxis. Jacobs et al¹⁴ reported on 2 patients who developed anaphylaxis while taking propranolol, a beta-blocker. Both of these patients developed hypotension and were refractory to epinephrine. The authors stated that propranolol can be implicated as a potentiating factor in anaphylaxis because of its antagonistic action on the beta-adrenergic sympathetic system.

A publication in 1983 documented 5 patients who had refractory anaphylaxis while taking propranolol.¹⁵ Another case described a case of fatal bronchospasm and anaphylaxis in a patient using beta-blocker (timolol) eye drops.¹⁶ Finally, Hayhoe et al¹⁷ described a 42-year-old woman who had severe anaphylaxis from labetalol use. She had persistent bradycardia, elevated tryptase levels, and hypotension that was refractory to epinephrine and norepinephrine. Eventually she responded to enoximone that is a nonadrenergic inotrope.

An article by Lee et al¹⁸ was published evaluating risk factors for anaphylaxis severity, organ system involvement, and hospitalization in emergency department patients. Of the 302 patients with anaphylaxis, 55 patients had syncope, hypoxia or hypotension, 57 patients required hospitalization, and 139 patients had 3 or more organ system involvement. Beta-blocker, ACE inhibitor, and diuretic use were significant risk factors of anaphylaxis for multiorgan systemic involvement and hospitalization.

FOOD ALLERGY

A case of severe anaphylactic shock from walnuts and pine nuts occurred in an 87-year-old woman who was taking ramipril, an ACE inhibitor.¹⁹ The authors suggested from this case that ACE inhibitors may exacerbate the severity of anaphylactic reactions in patients with food allergies. There was a publication in 2015 of 2 patients with food pollen allergy syndrome who developed severe angioedema while taking lisinopril, another ACE inhibitor.²⁰ It was postulated that the ACE inhibitor contributed to its reactions to apple, jackfruit, and cashew nuts. Summers et al²¹ collected information on patients with peanut and tree nut allergic reactions and found that patients with serum ACE concentrations < 37.0 mmol/L had an increased risk of severe pharyngeal edema. None of these patients were taking ACE inhibitors.

Because of the potential risk of anaphylaxis with beta-blockers, TenBrook et al²² published an article evaluating whether beta-blockers should be given to patients with heart disease who have peanut-induced anaphylaxis using a Markov model. A meta-analysis and literature review were used to estimate the

model parameters. The results showed that beta-blockers increased the life expectancy of patients at risk for peanut-induced anaphylaxis and cardiovascular disease. The patients who had a myocardial infarction had an increased life expectancy of 9.4 months, and the patients with congestive heart failure had an increased life expectancy of 17.4 months. Thus, in patients with cardiovascular disease, beta-blockers can increase life expectancy despite having food allergies.

RADIOCONTRAST MEDIA

Anaphylactoid reactions to RCM have been attributed to the high osmolality of some early contrast media agents. Many of these reactions have been prevented by using low osmolar or iso-osmolar solutions.²³ Lang et al^{24,25} published 2 articles showing that beta-blockers caused increased anaphylactoid reactions in patients receiving RCM. In the first study, of 49 patients having anaphylactoid reactions, exposure to beta-blockers was 27% among patients who had RCM reactions and 12% in matched case controls. In the second study, there were 122 anaphylactoid reactions to RCM and patients taking beta-blockers had an increased odds ratio of 7.67 of having an RCM reaction compared with case controls. A case report described a patient taking a beta-blocker with refractory anaphylactoid shock during coronary angiography.²⁶ The patient was unresponsive to aggressive standard treatment but had clinical improvement on the administration of glucagon.

More recently, Aggarwal et al²⁷ reported that beta-blocker premedication did not increase the frequency of allergic reactions to coronary computed tomography angiography even among patients who had a past history of RCM reactions. The incidence of an allergic reaction in patients who received beta-blockers was 45 of 23,867 (0.19%) compared with those patients who did not receive beta-blockers, which was 9 of 5232 (0.17%). There was no statistical difference between the 2 groups.

VENOM ALLERGY

Awai and Mekori²⁸ in 1984 reported a systemic reaction that was refractory to treatment in a 31-year-old male bee venom allergic patient who was taking propranolol. The authors suggested that beta-blockers should not be used in venom allergic patients. Another case report described a 52-year-old man who had relapsing anaphylaxis after being stung by a bee while taking a beta-blocker (propranolol) and a calcium channel blocker (nifedipine).²⁹

Ruëff et al³⁰ conducted a retrospective study of 206 Hymenoptera venom allergic patients and found that the patients taking ACE inhibitors had an increased risk of severe anaphylaxis to field stings. In contrast to these first 2 reports, Stoevesandt et al³¹ analyzed 657 patients with Hymenoptera venom allergy and found that there was no statistical difference in the severity of venom allergy in patients taking cardiovascular medications versus those patients not taking cardiovascular medications. In this study, 59 patients were taking beta-blockers and 32 patients were taking ACE inhibitors at the time of their field sting. Overall, there is not enough data in the medical literature regarding venom allergy and anaphylaxis. However, unless there is a good medical indication to use these cardiovascular drugs, it may be prudent to avoid beta-blockers and ACE inhibitors in those patients who are venom allergic.

SKIN TESTING

In the anaphylaxis practice parameter, the use of beta-blockers and ACE inhibitors is cited as a relative contraindication to skin testing.³² Unfortunately, there is little evidence evaluating skin testing of patients on ACE inhibitors and beta-blockers. Fung and Kim³³ completed a retrospective study of 191 patients who were taking beta-blockers (190 patients on oral beta-blockers and 1 patient with beta-blocker eye drops) while being skin tested to various allergens. Of the patients being skin tested, 54 had positive percutaneous tests, 14 patients had positive intradermal tests, and 4 patients had percutaneous and intradermal positive skin tests. None of the skin tests resulted in any adverse events. The authors concluded that their data demonstrated the relative safety of skin prick tests to patients on beta-blockers. Nonetheless, this was a small study and the authors recommended larger prospective multicenter studies.

IMMUNOTHERAPY

There is more evidence in the medical literature regarding patients receiving allergen immunotherapy while taking beta-blockers and ACE inhibitors. A case report in 1981 documented anaphylaxis refractory to epinephrine in a patient taking propranolol and receiving a maintenance immunotherapy injection to grass pollen.³⁴ There have been some reports of death of patients receiving immunotherapy while taking beta-blockers or ACE inhibitors. In a study published in 1987, Lockey et al³⁵ reported 2 fatalities of immunotherapy patients who were taking beta-blockers. Reid et al³⁶ published a study with 1 death of a patient taking a beta-blocker while receiving immunotherapy in a survey of allergists from 1985 to 1989. There were 17 reported immunotherapy fatalities during this survey period.

Another study over a 12-year period collected data on fatal reactions to immunotherapy and skin testing.³⁷ There were 41 immunotherapy fatal reactions and only 1 patient was found to be taking an ACE inhibitor. None of the patients were taking beta-blockers. Lockey et al³⁸ again published a review article in 2001 reporting that patients on beta-blockers were at risk for systemic reactions and fatalities from allergen immunotherapy.

A study in 2006 by Amin et al³⁹ described a near fatal reaction in a patient taking a beta-blocker and receiving allergen immunotherapy. Interestingly, there were also 2 patients with near fatal reactions who were taking angiotensin receptor blockers while receiving immunotherapy. Bernkopf et al⁴⁰ concluded that ACE inhibitors were independent predictors of the development of systemic reactions during the build-up phase of Hymenoptera venom immunotherapy in 175 patients. Other anecdotal reports of severe anaphylaxis with Hymenoptera venom immunotherapy have been reported in patients taking ACE inhibitors.^{41,42} These patients had anaphylaxis with severe hypotension after administration of a subcutaneous injection of Hymenoptera venom. They were resuscitated and were able to successfully continue venom immunotherapy by either stopping their ACE inhibitor altogether or holding it 24 hours before their venom immunotherapy injection.

In contrast to the prior studies, there have been a number of publications demonstrating that the concomitant use of ACE inhibitors or beta-blockers did not seem to increase the overall incidence of systemic reactions to immunotherapy. Hepner et al⁴³ assessed systemic reactions to immunotherapy over a 1-year prospective study. There were a total of 166 systemic

reactions in 144 patients. Only 1 patient who had a systemic reaction was taking a beta-blocker. White and England⁴⁴ analyzed 79 patients on venom immunotherapy. Seventeen of these patients were also taking an ACE inhibitor during venom immunotherapy for a mean time of 17 months. None of patients taking an ACE inhibitor experienced systemic reactions versus 13 systemic reactions in patients receiving immunotherapy while not taking an ACE inhibitor.

Rank et al⁴⁵ evaluated 29 immunotherapy systemic reactions in a study of 338 immunotherapy patients over a 2-year period. ACE inhibitors and beta-blockers did not increase the odds of having a systemic reaction to subcutaneous allergen immunotherapy. Additional studies of Hymenoptera venom allergic patients while taking beta-blockers and ACE inhibitors were conducted. These studies found that the patients taking cardiovascular medications did not have an increased risk of systemic reactions to build-up venom immunotherapy.⁴⁶

Stoevesandt et al⁴⁷ assessed patients receiving Hymenoptera venom during the build-up phase. There were 90 patients taking ACE inhibitors and 23 patients taking beta-blockers. ACE inhibitors or beta-blockers were not significantly related to the incidence of systemic reactions. Another study of patients on maintenance Hymenoptera venom immunotherapy was published.⁴⁸ Of the 225 patients, 71 were taking an ACE inhibitor and 40 were taking a beta-blocker. Surprisingly, systemic reaction rates were lower in these patients taking an ACE inhibitor or beta-blocker.

Finally, Müller and Haerberli⁴⁹ undertook a prospective study of patients with cardiovascular disease who were taking beta-blockers and receiving venom immunotherapy.⁴⁹ Of the 25 patients on beta-blockers during immunotherapy, 3 (12%) developed systemic reactions, compared with 23 (16.7%) of 117 patients not taking beta-blockers. No severe reactions were reported in the patients taking beta-blockers and receiving venom immunotherapy. The authors concluded that beta-blockers may be indicated in patients with cardiovascular disease who are receiving venom immunotherapy.

Based on the available evidence, the anaphylaxis practice parameter states that physicians should consider stopping ACE inhibitors for at least 24 hours before administering build-up and maintenance venom immunotherapy injections to prevent severe systemic reactions.³² Also the anaphylaxis practice parameter recommends that beta-blockers should be used with caution in patients receiving immunotherapy.³² However with venom immunotherapy that can be lifesaving, the benefits of immunotherapy outweigh the possible anaphylaxis risk associated with taking a beta-blocker or ACE inhibitor. Therefore, for patients who require a beta-blocker or ACE inhibitor for cardiovascular disease, venom immunotherapy can be prescribed while they are taking their cardioprotective medication.⁵⁰

In regard to aeroallergen immunotherapy that is an elective procedure, a judgment call must be made by the allergist. Conclusive data regarding the use of beta-blockers and/or ACE inhibitors for patients starting or maintaining immunotherapy do not exist. In our practice, typically we allow aeroallergen immunotherapy for patients on ACE inhibitors but not beta-blockers. We do allow patients on beta-blockers with cardiovascular disease to start and maintain venom immunotherapy. In selective cases, aeroallergen immunotherapy may be warranted for patients on beta-blockers. It is recommended that patients on beta-blockers and ACE inhibitors be made aware of their risks of

receiving aeroallergen immunotherapy and appropriate consent should be accomplished.

CONCLUSIONS

Overall, there is not a lot of medical literature evaluating whether patients on ACE inhibitors or beta-blockers are at an increased risk of anaphylaxis. Most of the medical literature is limited to case reports and retrospective data. Initial reports suggested that beta-blockers were dangerous for patients at risk for anaphylaxis and ACE inhibitors were acceptable. More recent data seem to indicate that beta-blockers may be safe for patients at risk for anaphylaxis and perhaps ACE inhibitors are worrisome. Some of this evidence is conflicting and there have not been definitive studies. Ultimately, prospective controlled trials are needed on this important topic. There are data that beta-blockers may mask cardiac signs of anaphylaxis and blunt the response to epinephrine in cases of anaphylaxis. It is recommended to avoid beta-blockers and possibly even ACE inhibitors for those patients at risk of anaphylaxis who lack cardiovascular disease. However, for those patients with cardiovascular disease, beta-blockers and ACE inhibitors have been shown to decrease mortality and increase life expectancy. Consideration should be given for patients with cardiovascular disease and venom immunotherapy to remain on their beta-blockers and ACE inhibitors.⁴⁹ We recommend that these medications be continued for patients who need them on venom immunotherapy.

REFERENCES

- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Health Organization, October 2003. *J Allergy Clin Immunol* 2004;113:832-6.
- Brown SGA, Kemp SF, Lieberman PL. Anaphylaxis. In: Adkinson N, Bochner B, Busse W, et al., editors. *Middleton's Allergy: Principles and Practice*. 8th ed. St Louis: Mosby-Elsevier; 2014. p. 1237-59.
- Munoz-Cano R, Picado C, Valero A, Bartra J. Mechanisms of anaphylaxis beyond IgE. *J Invest Allergol Clin Immunol* 2016;26:73-82.
- Lieberman P, Camargo CA Jr, 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* 2006;97:596.
- Houser S, Weng C, Liu Y. A patient with an allergy emergency. *JAMA Otolaryngol Head Neck Surg* 2015;141:382-5.
- Bochner BS, Lichtenstein LM. Anaphylaxis. *N Engl J Med* 1991;324:1785-90.
- Toogood J. Beta-blocker therapy and the risk of anaphylaxis. *Can Med Assoc J* 1987;136:929-33.
- Nassiri M, Babina M, Dölle 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.
- Evora PR, Simon MR. Role of nitric oxide production in anaphylaxis and its relevance for the treatment of anaphylactic hypotension with methylene blue. *Ann Allergy Asthma Immunol* 2007;99:306-13.
- Bauer CS, Vadas P, Kelly KJ. Methylene blue for the treatment of refractory anaphylaxis without hypotension. *Am J Emerg Med* 2013;31:264.e3-5.
- Zaloga GP, DeLacey W, Holmboe E, Chernow B. Glucagon reversal of hypotension in a case of anaphylactoid shock. *Ann Intern Med* 1986;105:65-6.
- Kemp AM, Kemp SF. Pharmacotherapy in refractory anaphylaxis: when intramuscular epinephrine fails. *Curr Opin Allergy Clin Immunol* 2014;14:371-8.
- Lieberman P, Simons FE. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. *Clin Exp Allergy* 2015;45:1288-95.
- Jacobs RL, Rake GW Jr, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. *J Allergy Clin Immunol* 1981;68:125-7.
- Hannaway PJ, Hopper GD. Severe anaphylaxis and drug-induced beta-blockade. *N Engl J Med* 1983;308:1536.
- Odeh M, Oliven A, Bassan H. Timolol eyedrop-induced fatal bronchospasm in an asthmatic patient. *J Fam Pract* 1991;32:97-8.
- Hayhoe S, Navapurkar V, Conway Morris A. Use of enoximone in management of anaphylaxis complicated by labetalol use [published online October 26, 2015]. *BMJ Case Rep* 2015. <http://dx.doi.org/10.1136/bcr-2015-212432>.
- Lee S, Hess EP, Nestler DM, Athmaram VRB, Bellolio MF, Decker WW, et al. Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis. *J Allergy Clin Immunol* 2013;131:1103-8.
- Moneret-Vautrin DA, Blain H, Kanny G, Bloch Y. Anaphylaxis to walnuts and pine nuts induced by ACE. *Allergy* 1998;53:1233-4.
- Ferastraorau D, Rosenstreich D, Jariwala S. Severe angioedema associated with angiotensin-converting enzyme inhibitor therapy in two patients with pollen-food allergy syndrome. *J Clin Hypertens (Greenwich)* 2015;17:493-4.
- Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol* 2008;121:632-8.
- TenBrook JA Jr, Wolf MP, Hoffman SN, Rosenwasser LJ, Konstram MA, Salem DN, et al. Should beta-blockers be given to patients with heart disease and peanut-induced anaphylaxis? A decision analysis. *J Allergy Clin Immunol* 2004;113:977-82.
- Lieberman P. Anaphylactic reactions to radiocontrast material. *Immunol Allergy Clin North Am* 1992;12:660.
- Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. *Ann Intern Med* 1991;115:270-6.
- Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from radiographic contrast media is associated with both beta-blocker exposure and cardiovascular disorders. *Arch Intern Med* 1993;153:2033-40.
- Javed N, Javed H, Javed S, Moussa G, Wong P, Reza F. Refractory anaphylactoid shock potentiated by beta-blockers. *Cathet Cardiovasc Diagn* 1996;39:383-4.
- Aggarwal A, Smith JL, Chinnaiyan KM, Mehta N, Boura J, Khoury Abdulla R, et al. β -Blocker premedication does not increase the frequency of allergic reactions from coronary CT angiography: results from the Advanced Cardiovascular Imaging Consortium. *J Cardiovasc Comput Tomogr* 2015;9:270-1.
- Awai LE, Mekori YA. Insect sting anaphylaxis and beta-adrenergic blockade: a relative contraindication. *Ann Allergy* 1984;53:48-9.
- Kivity S, Yarchovsky J. Relapsing anaphylaxis to bee sting in a patient treated with beta-blocker and Ca blocker. *J Allergy Clin Immunol* 1990;85:669-70.
- Rueff F, Przybilla B, Biló M, Müller U, Scheipl F, Aberer W, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *J Allergy Clin Immunol* 2009;124:1047-54.
- Stoevesandt J, Hain J, Kerstan A, Trantmann A. Over- and underestimated parameters in severe Hymenoptera venom-induced anaphylaxis: cardiovascular medication and absence of urticaria/angioedema. *J Allergy Clin Immunol* 2012;130:698-704.
- 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.
- Fung IN, Kim HL. Skin prick testing in patients using beta-blockers: a retrospective analysis. *Allergy Asthma Clin Immunol* 2010;6:2.
- Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981;47:35-7.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987;79:660-77.
- Reid MJ, Lockey RF, Turkeltaub PC, Platts-Mills TA. Survey of fatalities from skin testing and immunotherapy 1985-1989. *J Allergy Clin Immunol* 1993;92(Pt 1):6-15.
- Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-36.
- Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol* 2001;87(Suppl 1):47-55.
- Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. *J Allergy Clin Immunol* 2006;117:169-75.
- Bernkopf K, Rönisch H, Spornraft-Ragaller P, Neumeister V, Bauer A. Safety and tolerability during build-up phase of a rush venom immunotherapy. *Ann Allergy Asthma Immunol* 2016;116:360-5.
- Tunon-de-Lara JM, Villanueva P, Marcos M, Taytard A. ACE inhibitors and anaphylactoid reactions during venom immunotherapy. *Lancet* 1992;340:908.

42. Ober AI, MacLean JA, Hannaway PJ. Life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor. *J Allergy Clin Immunol* 2003;112:1008.
43. Hepner MJ, Ownby DR, Anderson JA, Rowe SC, Sears-Ewald D, Brown EB. Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990;86(Pt 1):407-11.
44. White KM, England RW. Safety of angiotensin-converting enzyme inhibitors while receiving venom immunotherapy. *Ann Allergy Asthma Immunol* 2008;101:426-30.
45. Rank MA, Oslie CL, Krogman JL, Park MA, Li JT. Allergen immunotherapy safety: characterizing systemic reactions and identifying risk factors. *Allergy Asthma Proc* 2008;29:400-5.
46. Ruëff F, Przybilla B, Bilo M, Müller U, Scheipl F, Aberer W, et al. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. *J Allergy Clin Immunol* 2010;126:105-11.
47. Stoevesandt J, Hain J, Stolze I. Angiotensin-converting enzyme inhibitors do not impair the safety of Hymenoptera venom immunotherapy build-up phase. *Clin Exp Allergy* 2014;44:747-55.
48. Stoevesandt J, Hosp C, Kerstan A, Trautmann A. Hymenoptera venom immunotherapy while maintaining cardiovascular medication: safe and effective. *Ann Allergy Asthma Immunol* 2015;114:411-6.
49. Müller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol* 2005;115:606-10.
50. Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol* 2017;118:28-54.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.