

Anaphylaxis to Stinging Insect Venom



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KEYWORDS

• Stinging • Insect • Allergy • Anaphylaxis • Hymenoptera • Venom • Immunotherapy

KEY POINTS

- The clinical history of an insect reaction is key to determining the diagnostic evaluation and therapeutic options that are needed.
- Patients with Hymenoptera venom allergy should be assessed for factors that may place them at risk during the diagnostic evaluation and treatment of venom allergy.
- Venom immunotherapy is the treatment of choice to decrease future risk in Hymenoptera venom allergy and should be considered for all patients with insect-triggered anaphylaxis. Patients deemed to be at high risk for relapse should be candidates for lifelong immunotherapy.

INTRODUCTION

Stings from insects are a common nuisance throughout the world. For some, insect stings carry significant morbidity due to the development of severe allergic reactions. Stinging insects from the order Hymenoptera are common triggers for allergic reactions. **Fig. 1** shows the important taxonomic relationships within the Hymenoptera order, with 3 distinct families of importance: Apidae (bees), Vespidae (yellow jackets [YJ], hornets, wasps), and Formicidae (stinging ants of several genera).

PREVALENCE

The prevalence of Hymenoptera venom allergy (HVA) in adults is 0.3% to 3.3% in the United States and 0.3% to 7.5% in Europe.^{1,2} In children, prevalence of insect sting allergy is estimated to be 0.8%.³ Based on survey data, anaphylaxis to the imported fire ant (IFA) is seen in 2% of the population in endemic areas of the United States.⁴

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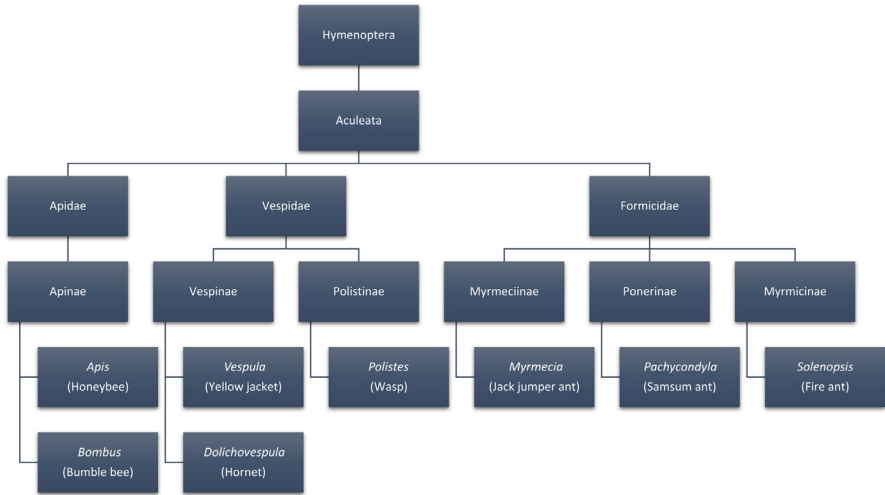


Fig. 1. Hymenoptera taxonomy.

Fatal reactions occur at an annual rate of 0.1 cases per million.⁵ Although the incidence of all-cause anaphylaxis and HVA has increased over decades, the fatality case rate has remained stable. In the United States, male sex, older age, and white race were noted as risk factors for fatal insect reactions.⁶

CLINICAL PRESENTATION

Important historical information needs to be gathered from patients to determine the culprit stinging insect and the clinical pattern of reaction. Some Hymenoptera species will only sting if feeling threatened (eg, *Polistes* spp), so occupations that are more likely to disturb nests in trees or in the ground may experience increased stings from these insects. Other species (eg, *Vespula* spp) are commonly found in areas where humans are eating and can sting with little provocation.

Reactions to stinging insects range from painful, localized cutaneous symptoms to anaphylaxis. For IFA stings, normal local reactions also include the development of a sterile pseudopustule at the site of the sting. Large local reactions (LLRs) are typically defined as erythema and induration of 10 cm or larger starting 12 to 24 hours after a sting and lasting 3 to 10 days. Generalized reactions range from single organ system involvement (eg, systemic cutaneous reactions characterized by generalized urticaria with or without angioedema) to anaphylaxis, which has multiorgan involvement. Biphasic reactions are uncommon with insect stings, although the reason for this may be that they are underreported. In a prospective study, Hymenoptera stings were the cause of 25% of biphasic reactions.⁷

NATURAL HISTORY OF STINGING INSECT REACTIONS

The natural history of stinging insect reactions will determine what, if any, additional evaluation or treatment is needed. For example, asymptomatic venom sensitization or evidence of specific IgE (sIgE) without a correlating reaction history has been noted in up to 15% of adults.² The risk of future sting anaphylaxis in individuals with asymptomatic sensitization is relatively small, and thus no testing or venom immunotherapy

(VIT) is required. The natural history in other (symptomatic) sensitized individuals is reviewed later in the article.

Large Local Reactions

LLRs are late-phase IgE-mediated reactions that are typically self-limited but can cause significant morbidity. Historical data have shown that patients with LLRs are likely to have recurrent LLRs with repeat stings and only a 1.4% to 7% risk for systemic symptoms.^{8,9} However, in a recent European study of patients with LLRs to Hymenoptera, repeat stings led to systemic reactions (SRs) in 24% of patients.¹⁰ Additional testing or VIT is generally not recommended in patients with LLRs; however, it may be considered in cases in which unavoidable stings cause recurrent LLRs that affect quality of life (QOL).

Systemic Cutaneous Reactions and Anaphylaxis

The single best predictor for recurrent reactions is the severity of a previous insect-related reaction. For example, most individuals with a history of a cutaneous SR to a stinging insect go on to have the same or less severe symptoms on a subsequent sting. The risk of a more severe reaction is best estimated up to 3%, although some studies with limited data suggest risk up to 15%.^{9,11–13} Although adults with previous cutaneous SRs to stings have been historically advised to receive VIT, in the most recent stinging insect allergy practice parameter, both children and adults with cutaneous SRs are advised that routine testing or VIT are not needed because the risk with future stings is relatively low.¹⁴ As with LLR, VIT may be considered for those with cutaneous SRs due to other risk factors or impaired QOL. By comparison, patients with anaphylaxis to Hymenoptera have a 30% to 67% risk for recurrent anaphylaxis on a subsequent sting and thus require evaluation and VIT.^{9,11,12}

EVALUATION

The decision to test for HVA is based on the detailed history of a stinging insect reaction, an assessment of current and future risks, and a consideration for medical and lifestyle factors that may place someone at increased risk with future stings. As patients may not be proficient at correctly identifying flying insects, it is recommended that testing for all available flying Hymenoptera (FH) species is done.

Skin Testing and Serologic Testing

Standard testing options include an assessment for venom sIgE through skin test (SKT) or serologic testing. Given the significant morbidity associated with HVA, the variability of venom SKT responses and limited concordance between testing modalities, patients with negative results on one type of test should have repeat testing via the other modality because they may still be at risk for subsequent Hymenoptera reactions.¹⁵ Similarly, if all initial testing results are negative, then repeat testing after 1 to 2 months should be done. Neither the SKT sensitivity nor the absolute serum sIgE level is predictive of the severity of a Hymenoptera sting reaction.

Although SKT is generally considered safe, testing protocols can be time consuming and may be limited in certain populations due to discomfort. A single-step intradermal (ID) test at a concentration of 1 µg/mL was noted to be safe in a retrospective study.¹⁶ Simultaneous ID testing (ie, placement of multiple ID concentrations) has also been deemed safe.¹⁷ Concurrent or single-step testing protocols seem to be safe, faster, and more cost-effective methods in assessing for HVA compared with the standard sequential approach of testing.

Imported Fire Ant Hypersensitivity Testing

IFA testing follows the same protocol as for FH. Testing for IFA alone is reasonable in patients who live in an endemic area and can clearly identify IFA as the culprit insect. IFA whole-body extracts (WBE) that include *Solenopsis invicta*, *Solenopsis richteri*, or a mixture are commercially available for SKT. Similar to FH, in vitro testing for IFA IgE is also available and should be considered for patients who are not SKT candidates or in patients who have a negative SKT despite a convincing history of IFA-triggered systemic symptoms.

Serum Basal Trypsase

Obtaining a serum basal tryptase (sBT) level should be considered in all patients with HVA because an elevated sBT level is a marker for mast cell burden and mast cell disease (MCD). Elevated sBT levels are associated with increased risk for HVA, sting reaction severity, side effects during VIT in both children and adults, and relapse after VIT.^{18–20} Moreover, although the accepted upper limit for a normal sBT level is 11.4 ng/mL, this cutoff may be inadequate because levels greater than 5 ng/mL may be predictive of sting reaction severity.¹⁸ In fact, sBT levels can be used to risk stratify patients with HVA.²¹

A recent study noted that elevated sBT levels may be due to hereditary α -tryptase-mia (H α T). H α T, a genetic condition with multiple copies of the α -tryptase gene, is seen in 5.6% of healthy individuals. H α T is more frequent in patients with Hymenoptera reaction (with increased severity of reaction), in those with mastocytosis, and in idiopathic anaphylaxis.²² For patients with HVA, even those with normal sBT levels, an additional biomarker identified is the detection of the *KIT* p.D816V mutation in peripheral blood, which correlated with a higher frequency of severe symptoms.²³ Additional data regarding the limitations and advantages of these tests is needed before recommending their routine use in HVA evaluations.

Component Resolved Diagnostics

Evidence of IgE to multiple venoms may be due to clinically relevant cosensitization, cross-reactive carbohydrate determinants (CCDs), or homologous venom protein epitopes leading to cross-reactivity. The use of CCD-free, species-specific recombinant allergens has been described as a way to increase the accuracy and sensitivity of venom testing. In vitro testing with YJ venom spiked with recombinant Ves v 5 (rVes v 5) increases the sensitivity of the test from 83.4% to 96.8%.²⁴ However, testing with single recombinant allergens may not suffice. In a cohort of honeybee (HB) allergic patients, evidence of IgE to single recombinant allergens (rApi 1–3, rApi m 5, and rApi m 10) ranged from 47.9% to 72.2%. However, when taken together, positive tests to at least 1 recombinant HB allergen was noted in 94.4% of patients.²⁵ Recently, component resolved diagnostics (CRD) for Hymenoptera venoms has been approved by the US Food and Drug Administration and has become more available, although limitations still exist, which prevent its use routinely. For example, the clinical availability of full panels of recombinant allergens is needed to ensure that diagnostic sensitivity is improved with the use of CRD. In addition, component testing needs to take into account the geographic distribution of Hymenoptera whereby component panels for all relevant species in a location need to be commercially available to be clinically useful. If available, the main clinical application of venom CRD is in elucidating dual sensitization patterns in patients with HB and YJ sensitivity.^{26,27} CRD can distinguish those who need both HB and YJ for VIT and those who need only the one that is their primary allergen. This approach will be more useful in the United

States when it can be applied to *Polistes*/YJ dual sensitivity. **Table 1** has a listing of recombinant allergens and their corresponding native allergens. Finally, as there remains a single commercial supplier of venom for testing and treating there may be a cost savings opportunity by treating with a single venom versus multiple venoms.

Basophil Activation Test

The basophil activation test (BAT) is a functional test of basophil reactivity that measures upregulation of CD63 or CD203c on basophils after allergen exposure. The BAT is a sensitive test that can detect sensitization in patients with HVA with inconclusive serologic and SKT results and in those with double sensitization.²⁸ Decreased BAT sensitivity (ie, percent CD63 basophil response) is associated with successful VIT induction of tolerance and thus serves as an in vitro marker for VIT effectiveness and for treatment failure.^{29,30} Finally, high BAT sensitivity as measured by concentration-dependent activation ratios was noted to be predictive for reactions during VIT in children and adults.^{31,32} Although the characteristics of the BAT make it a potentially useful test, current limitations include a lack of commercial availability and inconsistent methodology, analysis, and reporting of results. However, at this time BAT has begun to evolve as a more available diagnostic tool.

RISK FACTORS

In addition to the clinical history of a stinging insect reaction, there are several factors that may predispose individuals to increased risks for HVA. Some risk factors may be modifiable (eg, underlying asthma control), whereas other nonmodifiable risk factors (eg, age) still need to be accounted for and used to determine an individual's risk profile.

Medications

Medications such as β -blockers (BB) or angiotensin-converting enzyme (ACE) inhibitors (ACE-I) may be associated with an increased risk for severe anaphylaxis due to interference of the endogenous compensatory mechanisms or exogenous therapeutic interventions (eg, epinephrine) use to treat anaphylaxis. Data from Europe showed that both ACE-I and BB were associated with increased severity of anaphylaxis in patients with HVA and non-HVA patients, although the medication effect may have been related to underlying cardiovascular disease.³³ On the other hand, there was no

Table 1
Hymenoptera venom allergens and recombinant component allergens

Genus and Species	Allergen	Name/Function	Recombinant Allergen
<i>Apis mellifera</i>	Api m 1	Phospholipase 2	rApi m 1
	Api m 2	Hyaluronidase	rApi m 2
	Api m 3	Acid phosphatase	rApi m 3
	Api m 5	Dipeptidyl peptidase	rApi m 5
	Api m 10	Carbohydrate-rich protein	rApi m 10
<i>Vespula vulgaris</i>	Ves v 1	Phospholipase 1	rVes v 1
	Ves v 3	Dipeptidyl peptidase	rVes v 3
	Ves v 5	Antigen 5	rVes v 5
<i>Polistes dominulus</i>	Pol d 1	Phospholipase 1	rPol d 1
	Pol d 5	Antigen 5	rPol d 5

correlation between HVA reaction severity and the use of BB, ACE-I, or both in a retrospective review of 657 patients with HVA.²⁰ There is now increasing evidence that points to the safety of these medications in patients on VIT.^{34,35} In the largest prospective study to date, neither BB nor ACE-I use were associated with increased risk for SRs or severity of SRs on VIT.³⁶ Furthermore, efficacy of VIT was not affected for patients on these medications, which adds supporting data to the notion that BB and ACE-I can be safely continued during VIT.

Mast Cell Disease

The close relationship between MCD and HVA has been elucidated over the last 3 decades. Insect stings are a leading cause for anaphylaxis in patients with underlying MCD. The prevalence of clonal MCD in patients with SRs to Hymenoptera is 1% to 7.9%.³⁷ Conversely, 88.2% of patients with HVA with an elevated sBT level were subsequently diagnosed with MCD.³⁸ Although an elevated sBT level may indicate the possibility of MCD, cases of MCD in patients with HVA with normal sBT levels have also been described.³⁹ In patients with normal sBT levels, insect-triggered hypotension without cutaneous symptoms may be the most critical historical factor to identify concurrent MCD.³⁹ Because SKT and serologic testing may be negative in patients with MCD, use of CRD or a decrease in the threshold sIgE cutoff may help to establish a diagnosis of HVA.^{40,41}

MCD also predisposes patients to increased severity of sting-related reactions with rare fatal stings described.⁴¹ VIT is the treatment of choice for HVA in patients with MCD. Systemic side effects with VIT are seen in up to 13.9% of patients with MCD.³⁷ Successful conventional and rush immunotherapy using IFA WBE in patients with MCD has also been described.⁴² Finally, MCD is also a risk factor for relapse in patients who have completed a course of VIT.⁴³ For this reason, patients with MCD and HVA should be considered candidates for prolonged VIT courses.

Trigger Insect

The particular insect that triggered the allergic reaction may also impact risk. For example, vespid stings were associated with increased risk for field sting reaction severity before VIT, whereas HB allergy was an independent predictor of side effects during VIT.^{18,19} HB allergy has historically been considered higher risk, although the exact reasons are unclear. One reason may be related to the increased venom content released by HBs compared with vespids (50–140 µg vs 2–17 µg, respectively). It is also theorized that venom composition in extracts used to diagnose HB allergy (eg, lack of Api m 10) as well as differences in individual sensitization profiles may play a role.^{25,44} Predominant Api m 10 sensitization was the best predictor for treatment failure in patients on HB VIT confirmed via a sting challenge.⁴⁵

THERAPEUTICS

Acute treatment of anaphylaxis follows the same algorithm as other triggers of anaphylaxis. Once acute symptoms are resolved, patients require a referral to an allergy specialist for further evaluation of HVA. Patients also need to be educated on avoidance measures, wearing of medical alert jewelry, and carrying self-injectable epinephrine in case of future stings. **Fig. 2** is a flow diagram for the evaluation and management of insect-triggered reactions that takes into account clinical history and risk factors.

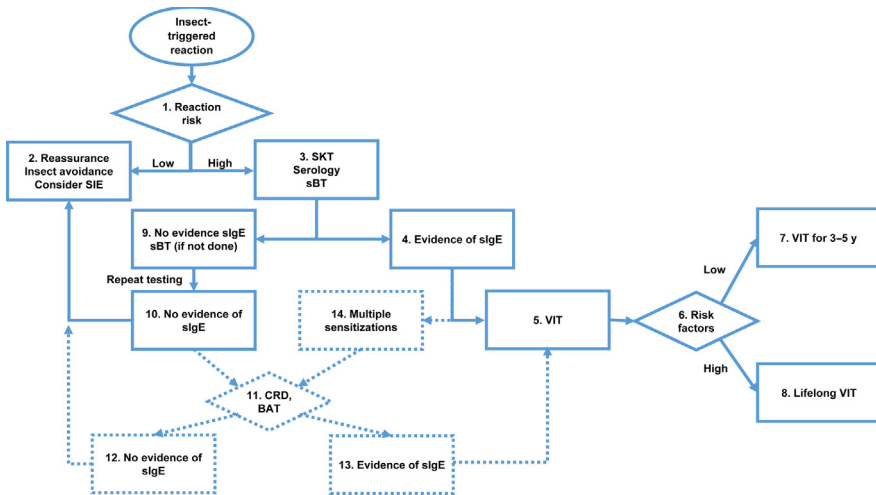


Fig. 2. Flow diagram for the evaluation and management of insect-triggered reactions. BAT, basophil activation test; CRD, component resolved diagnostics; SIE, self-injectable epinephrine. Solid lines describe current clinical practice; dashed lines indicate the potential workflow with the availability of adjunct tests. (1) The first decision point is an assessment of a patient's future risk with a subsequent insect sting. (2) Low-risk reactions (eg, large local reactions) require reassurance and education on insect avoidance. In select cases, SIE may be prescribed. (3) For high-risk reactions (eg, anaphylaxis), SKT and/or serology is recommended. An sBT is recommended because it will help with risk stratification. (4 and 5) Evidence of sIgE that is consistent with the clinical history requires VIT. (6–8) Risk stratification that takes into account the reaction history and the patient's medical history is needed to determine duration of treatment. (9) If no evidence of sIgE is discovered, the tests should be repeated in 1 to 2 months. An sBT can be considered at this stage if not already done. (10) If repeat testing still fails to show evidence of sIgE, then it is recommended that patients be counseled on insect avoidance and have SIE prescribed. (11) If available, CRD or BAT testing should be considered. (12) If additional tests fail to show evidence of sIgE, then it is recommended that patients be counseled on insect avoidance and have SIE prescribed. (13) Evidence of sIgE after CRD or BAT testing that is consistent with the clinical history requires VIT. (14) If multiple sensitizations are noted without a correlating history, then CRD and BAT testing should be considered to further delineate true sensitization versus cross-reacting carbohydrate determinants.

Venom Immunotherapy

VIT is the single best therapy to decrease the risk of anaphylaxis with future stings in HVA. VIT reduces the risk of subsequent sting-related reactions to 3% to 5%, although the efficacy may be lower for high-risk groups (eg, 75% to 85% efficacy for VIT for HB allergy or in MCD).^{9,37,46,47}

Dosing and Schedules

For FH, the maintenance dose (MD) is 100 µg, although a higher MD of 200 µg may be considered in refractory cases (eg, field sting triggered symptoms while on MD VIT). Once MD is reached, the schedule can be spaced to every 4 weeks. Extended maintenance intervals (EMI) of 6 to 8 weeks can be considered after 12 to 18 months of monthly MDs. EMI of up to 12 weeks have been shown to be safe and effective after 3 to 4 years on MD treatment.⁴⁸

Duration

Current recommendations for length of VIT treatment is 3 to 5 years in both children and adults, although longer treatment courses may be superior. Higher risk for recurrence was noted in patients experiencing more severe initial sting reactions, those with SRs to VIT injection, in HB allergic individuals, and in those with MCD.⁴⁹ Longer VIT treatment duration should be considered for patients deemed to be at high risk for relapse. Lifetime treatment is recommended to patients with mastocytosis because of the reported risk of fatal reaction. There are no long-term data to determine how long to extend VIT in high-risk patients. The risk of sting reaction remains even when the SKT becomes negative.⁵⁰

Safety

Adverse reactions to VIT include minor local reactions, LLRs, and SRs that occur mostly during the build-up phase. Compared with accelerated schedules for aeroallergen immunotherapy, accelerated VIT protocols have not been associated with a similarly increased risk of side effects.⁵¹ Risk factors for reactions include treatment with HB venom, an elevated sBT level, and use of an ultrarush build-up protocol.¹⁹ The use of H1 and H2 antagonists for premedication can decrease the risk of local and systemic side effects during VIT.⁵² Finally, omalizumab has been used as a pretreatment and concurrent treatment strategy for patients with and without MCD who experience recurrent reactions to VIT.⁵³

Whole-Body Extract Immunotherapy

Immunotherapy using crushed FH was not shown to be better than placebo, whereas IFA WBE has been shown to reduce the risk of subsequent sting reactions to 2.1%.^{46,54} The MD for IFA WBE is 0.5 mL of a 1:100 weight/volume extract concentration.^{54,55} The build-up schedule for IFA WBE is less well defined compared with that for FH VIT. In general, build-up occurs with once to twice per week doses until MD is reached at which point the interval can be extended to monthly doses.¹⁴ The suggested duration of IFA WBE treatment is 3 to 5 years. In one small retrospective study, patients receiving less than 3 years of IFA WBE noted a similar level of protection as patients who received 3 or more years.⁵⁶ Larger controlled studies are needed to delineate the optimal duration of IFA WBE treatment. Because frequency of exposure is considered a risk factor, and the attack rate for IFA is much higher than for FH, extended treatment may be considered.

Venom Extracts and Availability

Venom extracts are the cornerstone for the evaluation and treatment of HVA. Knowledge of location and relevant species is key because this will determine whether commercial extracts will be diagnostically and therapeutically useful (eg, because *Polistes dominulus* has incomplete cross-reactivity with other *Polistes* spp; availability of a *P dominulus* extract is desirable in locations where this species is present).⁵⁷

Concern about the availability of venom extracts was highlighted by the shortage of extracts in 2016 after the loss of an extract supplier in North America.⁵⁸ Mitigation strategies such as the use of EMI or the switch to a different manufacturer's extracts are both feasible plans. Safety and efficacy of lowered MDs (eg, 50 µg) has been studied and shown to provide good efficacy in children, although the data in adults are conflicting.^{59–61} Other long-term strategies include improvement in diagnostics such as CRD to ensure that patients are only treated with extracts that are clinically relevant. Other venom extract preparations such as depot and dialyzed venoms are currently

not available in North America. Access to VIT is also an issue. For instance, insurance reimbursement has not kept pace with the cost of venom extracts, contributing to a decrease in the number of allergy clinics that offer venom testing and treatment. Finally, delays in provision of VIT can also arise from a lack of demand as seen during the coronavirus 2019 pandemic, which necessitated the need to space out or even stop VIT in some locations to slow the spread of the virus.

SUMMARY

Allergic reactions to members of the Hymenoptera order of insects are associated with significant morbidity for the world's population. Knowledge of taxonomic relationships is key to understanding and interpreting diagnostic tests and management of HVA. The clinical history of an insect-triggered reaction is the most important aspect to the diagnosis of HVA because it impacts what evaluation and treatments are required. A risk assessment for all patients needs to occur because it will guide recommendations for evaluation and treatment duration. Finally, although much is known about HVA, questions still remain that need further research to move the field to one of precise and individualized medical care.

CLINICS CARE POINTS

- The details of the clinical history of an insect-triggered reaction are the most important factors that will determine if evaluation and treatment of HVA is indicated.
- Patients with insect reactions should be referred to an allergist/immunologist for education and to conduct an assessment of risk factors to determine the risk of anaphylaxis, the need for evaluation and VIT, and the duration of VIT treatment.
- For patients with a convincing history of HVA, an sBT level should be ordered to rule out MCD. When initial skin or serologic test results are negative, testing should be repeated. Additional testing modalities (eg, CRD, BAT, peripheral *KIT* p.D816V mutation) should be considered if available.
- VIT is the treatment of choice to decrease future risk for cases of HVA. Although it is important to identify risk factors, in general the risk of untreated HVA outweighs the risks associated with chronic medical conditions, antihypertensive medication use, or MCD.

DISCLOSURE

K.E. Adams has nothing to disclose. J.M. Tracy serves on the advisory boards for Pharming, Biocris, and Thermo-Fischer; Honoraria: UpToDate. D.B.K. Golden serves on the speaker bureau for Genentech; as a consultant to ALK, Stallergenes, Allergy Therapeutics, Kaleo, and Aquestive; as a section editor for UpToDate and receives clinical trials support from Genentech, Novartis, and Allergy Therapeutics.

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