

Venom Immunotherapy

Reimbursement: A Time for Change

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EXECUTIVE SUMMARY

Allergy to insect venom is relatively rare yet can be fatal. All major guidelines recommend venom immunotherapy (VIT) for the safe and effective prevention of insect sting anaphylaxis. VIT is life-saving. It has been shown to be disease-modifying and is a proven treatment: it has been provided to sensitive patients for more than 40 years (Hunt 1978). To maintain a high safety threshold, doses of VIT are matched to each individual patient's sensitivity. This approach provides safe and effective therapy but is labor-intensive. Studies have shown that most patients prefer VIT to the administration of epinephrine after a reaction starts and that they do not find the treatment regimen of regular injections burdensome.

Unfortunately, the current reimbursement schedule is so outdated that many providers have found that VIT is no longer financially feasible for their practices and have stopped offering it. While a 2016 reevaluation of immunotherapy to aeroallergens (such as ragweed, grass, and others) resulted in an increase in the labor input into the CMS fee schedule, reimbursement for VIT has seen no adjustment in recent years. This, coupled with the rising cost of venom antigen manufacturing, has left providers to bear the brunt of higher costs, both for venom extracts and other supplies, and for the labor costs of preparing the personalized treatment and monitoring patient status. To ensure that this life-saving, disease-modifying treatment remains available to patients and is financially feasible for allergists, relevant stakeholders must initiate steps toward requesting reimbursement that fairly reflects current costs.

VENOM ALLERGY – PREVALENCE

Allergy to insect venom includes allergies to honey bee, yellow jacket, yellow hornet, white-faced hornet, and wasp. Published data on the epidemiology of insect venom allergy is relatively scarce. The self-reported prevalence of insect venom allergy has been variously reported as between 0.5% and 3.3% or between 5% and 7.5% of the population (Gelniczek 2015, Ludman 2015). Additionally, in a nationwide, random digit dial telephone survey designed to estimate the prevalence of anaphylaxis in the US, 19% (between 500,000 and 600,000 patients) of self-reported anaphylaxis in adults was attributed to insect stings (Wood 2014). However, apparently most patients don't receive

disease-modifying treatment for their life-threatening allergy. Internal estimates developed at Jubilant HollisterStier suggest that approximately 50,000 – 75,000 patients are treated with VIT (Constable, personal communication).

ANAPHYLAXIS CAUSED BY INSECT VENOM ALLERGY

The rate of death from an anaphylactic reaction to an insect sting is estimated to be approximately 0.1/ million people in the US population or between 3 and 6 deaths/million-person years in individuals allergic to insect venom (Turner 2017).

On July 14, 2018, 34 year-old Brian Baker was stung by yellow jackets when finishing electrical work on his screened-in porch at his home in Winchester, New Hampshire. He had been diagnosed with insect sting allergy in 2017 and given an epinephrine auto-injector but never told about venom immunotherapy. After the sting, his wife, Mandi, administered the epinephrine and called 911. Paramedics took Brian to a local hospital which then transferred him to a major medical center where he was put on life support. Four days after the sting, when it was clear that Brian had suffered major brain damage, the family had to make the decision to end life support. It was only after Brian died that Mandi learned about venom immunotherapy (VIT). She told ‘Allergic Living’ “I want people to know just how dangerous [sting allergy] really is. Immunotherapy can help. Research and go to an allergist and get answers.” (Allergic Living 2018)

The number of emergency department (ED) visits resulting from insect sting anaphylaxis grew 59% over 10 years to a 2014 estimate of at least 1.3/100,000 population. This conclusion was based upon a US retrospective claims analysis (Motosue 2017).

The costs of caring for these anaphylaxis patients includes not only paramedic services and the emergency department but also inpatient care. In one multi-center study, 87% of insect sting anaphylaxis patients were admitted. This compared with admission rates of 53% in patients who developed anaphylaxis due to food allergy (Pawankar 2011). Like Brian Baker (inset), many are admitted because they were unresponsive to epinephrine or because they had lost consciousness (Golden 2005, Mikals 2016).

In a study of disability related to insect sting allergy, 17% of patients reported work disability and 16% reported economic loss (Paolucci 2014).

VENOM IMMUNOTHERAPY – HOW IT’S DONE

Diagnosis

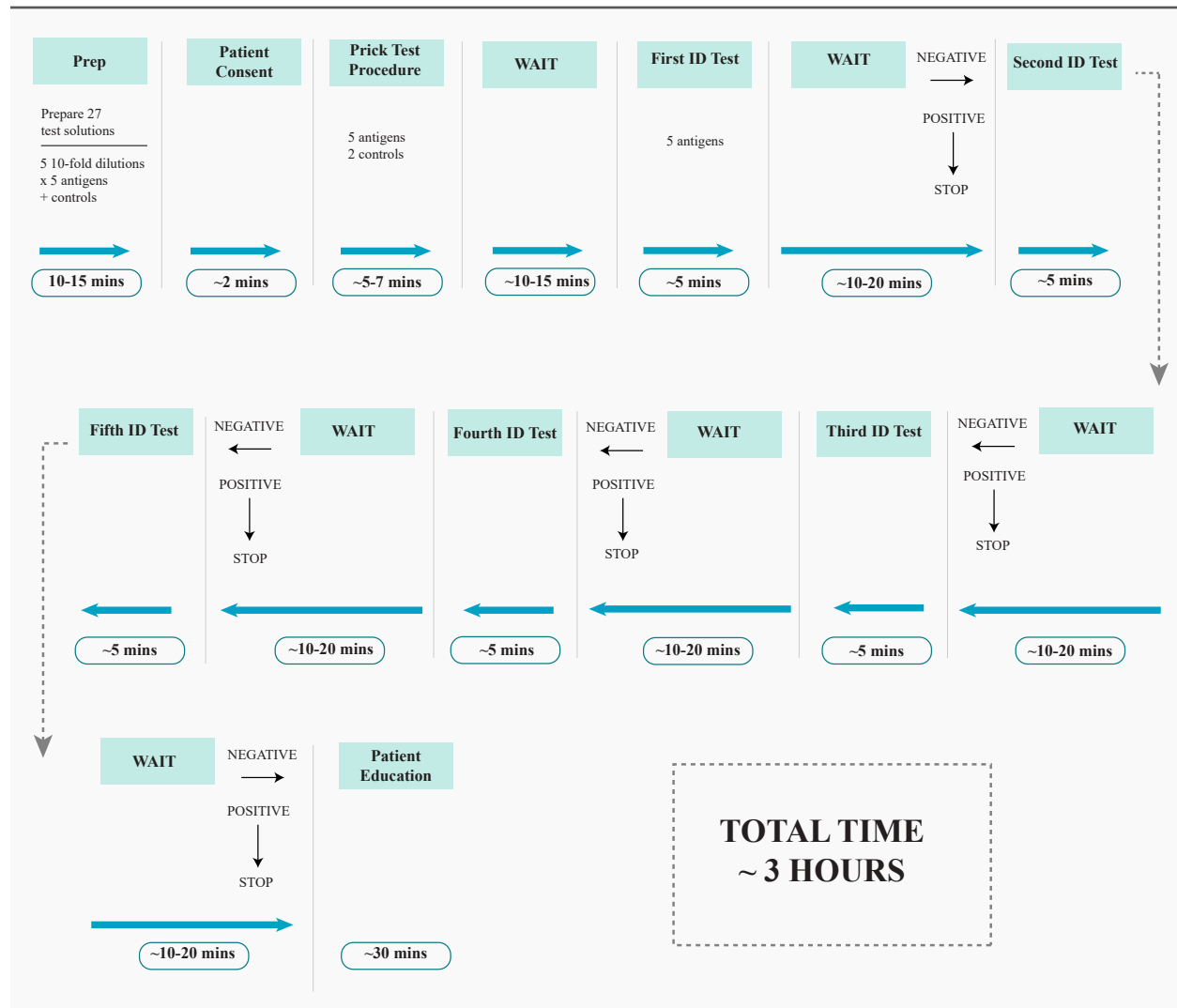
Guidelines generally recommend skin tests for allergy over blood tests because of their greater sensitivity and specificity. Blood test results are considered supportive of skin tests. Skin test results are also used to guide dosing for the safe administration of disease-modifying immunotherapy (Golden 2017).

The goal of testing is to confirm a clinical history of sensitivity by demonstrating that the patient’s dermal

immune system reacts to the problematic allergens. The nurse prepares for the diagnostic visit by making dilutions of the stock allergen before the patient arrives for testing. (Figure 1). Generally, 4 or 5 ten-fold dilutions of each allergen are prepared, each in a sterile vial and each labeled with the correct strength of the allergen. Because the very dilute concentrations are not stable, they must be prepared within 24 hours of the patient’s test or treatment.

Due to the risk of adverse reactions, testing is conducted in a stepwise manner. The patient is first tested by the prick method using a 1 microgram/mL solution of each venom extract. If the reaction is positive at the end of the 20 minute wait time, the patient is considered sensitive. If the reaction is negative, testing continues using the intradermal method. Intradermal test results are also used to guide the choice of dose for immunotherapy, thus prick-positive patients also receive an intradermal test. During the intradermal test, the lowest dilution is tested first. If the result is negative after the 20 minute period allowed for the reaction to develop, the nurse will then test the next higher dilution. The process continues until a positive reaction is achieved and can take a total time of up to 3 hours. If a 1 microgram/mL intradermal dose results in a negative result, the patient is diagnosed as not allergic to that insect. The time taken for the diagnostic process allows the nurse to carefully monitor the patient for signs of an adverse systemic reaction after each injection, thus maintaining the safety of the process. This time is also used to also inform and educate the patient about their life-threatening allergy.

Figure 1: VIT Diagnostic Process



This personalized approach to testing results in more sensitive patients receiving fewer intradermal injections than less sensitive patients. Any prepared dilutions not needed for a specific patient are discarded. Because the allergist can only bill for extract that has been administered, practices regularly are required to discard extract for which they will never be reimbursed.

The results of the intradermal tests also inform the clinician about how sensitive the patient may be and are thus used as a guide to determine the initial dose of venom for the build-up phase of immunotherapy.

Treatment

The doses used in allergen immunotherapy are

personalized to each patient. To ensure safety, immunotherapy patients are started with a low dose of venom, based upon the results of their intradermal test, and ‘built up’, with successively higher doses over the course of approximately 26 weeks, to the maintenance dose. To achieve a durable tolerance to the allergen, guidelines recommend that treatment at the maintenance dose is continued for 5 years or indefinitely if high risk factors are involved (Golden 2017).

After the patient is treated, the nurse spends at least 20 minutes with the patient, monitoring their clinical status for signs of post-injection reactions. This close observation facilitates rapid intervention and administration of the appropriate treatment if a reaction does occur. Nurses generally take the opportunity

to continue the patient education begun during the diagnostic procedure during this time of observation.

This personalized approach to diagnosis and dosing is labor-intensive but has proven to be critical to patient safety. Additionally, it allows the clinical staff to help the patient understand the importance of adherence over the 5 years of treatment required for the patient to develop tolerance.

VENOM IMMUNOTHERAPY – EFFECTIVE PREVENTION OF VENOM-INDUCED ANAPHYLAXIS

The most common approach to managing insect venom anaphylaxis is the prophylactic prescription of epinephrine auto-injectors however, like Brian Baker's, the more severe reactions can be refractory to single or even multiple doses of epinephrine (Graft 2018). All major allergy guidelines recommend venom immunotherapy (VIT) for the safe and effective prevention of insect sting anaphylaxis (Golden 2017, Sturm 2018, Pfaar 2014, Cox 2011). VIT is disease modifying and has been shown to induce a shift from the pro-allergic Th2 immunologic profile to the tolerant Th1 / Treg profile and to induce IL10 (Scheiner 2017). The regimen of desensitizing shots given approximately every 4 weeks for 3 to 5 years is life-saving (Golden 2005). An early clinical trial showed that VIT prevented systemic reactions to stings in 98% of patients (Golden 2005). A more recent Cochrane review evaluated the results of 7 trials and a total of 392 trial participants. The reviewers found that VIT was effective in preventing symptoms and allergic reactions to insect stings, whether the stings were accidental or administered in a clinical study. In these trials, 2.7% of VIT-treated participants had subsequent systemic reactions to stings compared with 39.6% of participants who received placebo. The risk ratio favoring VIT was 0.10 with a 95% confidence interval of 0.03 to 0.28. Additionally, VIT was found to be effective in preventing large local reactions which are rarely fatal but often require treatment. The study also found that the risk of systemic reactions to VIT is real. Systemic reactions after VIT administration were experienced by 9.3% of VIT participants but, in clinical practice, are generally well-managed by the allergist and staff and are not costly to payers (Tracey

2018, Boyle 2012).

Lack of patient compliance has a significant impact on the translation of clinical trial results to real world effectiveness and patients' preference for or concerns about a treatment can impact compliance. To investigate this question of patient perceptions about treatments for venom allergy, a one-year, prospective trial of 193 adults who had previously experienced one or more anaphylactic reactions to yellow jacket stings randomized participants to VIT or to receiving an epinephrine auto-injector. Of the patients enrolled, about 50% refused randomization but were allowed to continue in the trial with the treatment of their choice. Nearly 75% of those who refused randomization chose VIT over the epinephrine auto-injector. The remainder were randomized to VIT or an epinephrine auto-injector. The authors do not report any drop-outs during the one year period of the study. After the treatment period, 91.5% of patients who received VIT were positive or extremely positive about their treatment and 85% stated their intent to choose it again. Of the patients who received the epinephrine auto-injector, 48% were positive about their treatment however 68% of those positive about epinephrine stated a preference for treatment with VIT. Patients who had carried the epinephrine auto-injector indicated that it made them feel safe but was inconvenient and troublesome. They expressed fears of side effects, of the process of using the auto-injector, and anxiety about whether a single injection would be sufficient to control symptoms. Conversely, none of the patients who received VIT were negative about that treatment (Oude Elberink 2006).

After the patients had experienced both treatments, none of those randomized to VIT stated a preference for the epinephrine auto-injector as their only treatment. Of note, this study found significant evidence that patients perceived carrying an epinephrine auto-injector to be burdensome, perhaps contributing to poor compliance, however, in spite of the regular office visits required, there was no evidence that patients found VIT burdensome.

In this study, one patient in each treatment group was accidentally stung during the trial. The epinephrine auto-injector was used to treat the one patient in the

Table 1 - Direct Medical Costs of Anaphylaxis due to Food Allergy (USD 2007)

Type of Cost	Mean Costs per Patient (SD)	Total Annual Costs (In Millions)
Inpatient Care	\$4,719 (\$9,136)	\$26.6
ED visits	\$553 (\$462)	\$44.8
Office-based physician visits	\$193 (\$119)	\$118.2
OPD visits	\$280 (\$89)	\$8.7
Ambulance runs	\$469.5	\$6.9
Epinephrine devices	\$50.7	\$19.7
Total	NA	\$224.9

Abbreviations: SD – standard deviation; ED – emergency department; OPD – outpatient department

Notes: *Unit costs per ambulance run or epinephrine device, hence no SDs are available.

Source: Patel, 2011

epinephrine arm and the patient in the VIT group experienced no symptoms from the sting. In contrast with the results reported in the Cochrane review, there were no systemic side effects associated with VIT in any of the patients (Oude Elberink 2006).

ECONOMIC CONSEQUENCES OF VENOM ALLERGY

The health economics of venom allergy and resulting anaphylactic episodes have not been well studied but, given the costs of the emergency and inpatient care required for treating anaphylaxis, experts believe that honeybee venom allergy continues to exert substantial adverse financial impact on healthcare costs (Pawankar 2011).

In the absence of research documenting the costs of venom-induced anaphylaxis, data from food allergy-induced anaphylaxis can be used to estimate the budget impact of insect venom-induced anaphylaxis. Patel et al. studied the direct medical costs of food-induced allergic reactions and anaphylaxis in the US in 2007 (Table 1, Patel 2011). They estimated that direct medical costs were \$225 million. Emergency department visits accounted for 20%, inpatient hospitalization for 11.8%, and epinephrine devices for 8.7% of the direct costs. Because patients presenting

with insect venom-induced anaphylaxis require post-ED hospitalization more frequently than food allergy patients, the costs of caring for a patient presenting with venom-induced anaphylaxis are likely to be higher (Patel 2011).

In a separate study, the costs of VIT for reducing the risk of anaphylaxis and for cure of insect sting allergy have been estimated at \$7,876 and \$2,278 per life year saved or \$81,747 and \$29,756 per death prevented, respectively (Pawankar 2011). This compares with the incremental costs of the current approach to care, prophylactic epinephrine auto-injectors, in mild childhood venom anaphylaxis which were estimated at \$469,459 per year of life saved and \$6,882,470 per death prevented (Shaker 2007).

THE IMPACT OF REIMBURSEMENT ON VIT PROVIDERS

Allergy shots (immunotherapy) – whether given for allergy to aeroallergens or to venom – are reimbursed via CPT codes. The codes used for reimbursement of venom diagnostics and 2018 national reimbursement rates are provided in Table 2 and the codes that guide reimbursement of VIT are in Table 3. Specific rates can vary by Medicare Administrative Contractor

Table 2 CPT Codes associated with allergy diagnosis

CPT Code	Description	2018 CMS Rate
9501	Allergy testing, any combination of percutaneous (scratch, puncture, prick) and intracutaneous (intradermal), sequential and incremental, with venoms, immediate type reaction, including test interpretation and report, specify number of tests	\$7.92
99203	Office / Outpatient Visit (general office visit code, not specific to VIT)	\$109.70

Source: <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PFSlookup/>

Table 3 CPT Codes associated with allergy diagnosis

CPT Code	Description	2018 CMS Rate
95115	Immunotherapy one injection	\$9.00
95117	Immunotherapy injections	\$10.44
95245	Antigen therapy services (single venom)	\$26.28
95146	Antigen therapy services (2 venoms)	\$48.24
95147	Antigen therapy services (3 venoms)	\$51.48
95148	Antigen therapy services (4 venoms)	\$73.44
95149	Antigen therapy services (5 venoms)	\$96.48

Source: <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PFSlookup/>

Table 4 CMS inputs for the 2019 Fall Schedule

CPT CODE	Description	Labor			Supply	
		Nurse Rate (\$/min)	Duration of Process (minutes)	Total Labor Input	Antigen Supply	Total Supply Input
95017	Diagnostic	\$0.37	4.2	\$1.554	\$1.374273	\$2.596
95115	Single injection	\$0.37	15	\$5.55	N/A	\$0.859
95117	Multiple injections	\$0.37	17	\$6.29	N/A	\$1.482
95145	Professional services for the supervision of preparation and provision of antigens for allergen immunotherapy (specific number of doses); single stinging insect venom (mixing)	\$0.37	2.3	\$0.851	\$21.945	\$22.4306
95146	Two single stinging insect venoms (serum)	\$0.37	3.3	\$1.221	\$43.89	\$44.5852
95147	Three single stinging insect venoms (mixed vespids)	\$0.37	2.3	\$0.851	\$45.8675	\$46.3531
95148	Four single stinging insect venoms (mixed vespids + one additional bee)	\$0.37	3.3	\$1.221	\$67.8125	\$68.4681
95149	Five single stinging insect venoms (mixed vespids +2 additional bees)	\$0.37	4.3	\$1.591	\$89.7575	\$90.5831

Note: Total supply input includes cost of non-antigen supplies (e.g. gloves, vials etc.).

Source: Revisions to Payment Policies under the Medicare Physician Fee Schedule, Quality Payment Program and Other Revisions to Part B for CY 2019 <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/PFS-Federal-Regulation-Notices-Items/CMS-1693-P.html>

locality.

The formula for calculating the payment schedule amounts entails adjusting relative value units (RVUs), which correspond to services, by the Geographic Practice Cost Index (GPCIs), which correspond to payment localities. Components in the payment schedule include 3 RVUs: physician work, practice expense (PE) and professional liability insurance (PLI). PE captures the resources used in providing care and includes Supplies, Equipment, Labor and Indirect Costs.

Across all CPT codes, the PE component accounts for an average of 45% of the total RVUs for a service. However, in the case of VIT, supply costs are much more than the 45% average.

CMS made a major effort to better align supply costs and reimbursement for the 2019 fee schedule. Adjustments based upon the results of independent primary and secondary market research are now planned to be phased in over the 4 years between 2019 and 2022. While these supply cost adjustments better align reimbursement with practice supply expense,

they do not fully account for current costs, as well as anticipated cost increases over the 4 years required to reach the adjusted levels. There is concern that many allergy offices will conclude that VIT is not a financially feasible part of their practice. Table 4 summarizes the 2019 CMS Labor and Supply inputs for VIT CPT Codes.

Labor Costs

In 2016 CMS re-ran its screen for high expenditure services across specialties to identify procedures with aggregate Medicare-allowed charges of \$10 million or more. CMS identified the top 20 codes by specialty based upon allowed charges. CPT code 95165 (preparation of antigens for allergy shots [used for aeroallergens but not for venom]) was identified by this screen and code 95144 (antigens other than stinging insect) was included as part of the family. These services were presented for review of physician work and practice expense at the January 2016 RVS Update Committee (RUC) meeting. Because VIT is reimbursed by separate codes and because fewer patients receive VIT than immunotherapy for aeroallergens, the VIT codes were not included in this review.

At this meeting, leading specialty societies presented compelling evidence that the direct practice expense inputs had substantively changed since the previous valuation of these services. The original inputs were based on calculated clinical staff time collected via surveys. At that time, the most recent survey had been conducted in 2002 and the most recent review had been in 2006.

In 2007, United States Pharmacopeia (USP) revised standards for chapter 797 on sterile compounding. For the first time, this revision specifically addressed standards for preparation of allergen extracts. These standards became mandatory in 2013, with the passage of the Drug Quality and Security Act (DQSA).

The 2007 revision to USP Ch. 797 sterile compounding standards for allergen extracts require a number of staff activities which were not the standard in 2006 when the 95165 code had been last reviewed. With the passage of the Drug Quality and Security Act (DQSA) in

2013, clinicians treating patients with immunotherapy had to change the way they prepare allergen extracts to meet the more stringent USP requirements. These changes included specific cleaning standards for the antigen preparation area and requirements that staff be gowned and masked, adding both supply costs and additional labor time to the allergists' costs (AMA/Specialty Society 2016).

To further understand the impact of USP 797 on practices, a mini survey was conducted prior to the 2016 meeting. Based on responses from 27 small to large practices (1 to 121 physicians), it was found the median time to prepare 10 doses of allergen immunotherapy was 30 minutes (mean of 37 minutes). These results confirmed the expert panel's belief that the new standards required more time (AMA/Specialty Society 2016).

Because of USP 797 as well as the labor-intensive nature of preparing allergen immunotherapy injections (see VIT – How it's done, above), in 2016 it was recommended that code 95165 allow for a total of 30 minutes for 10 doses or 3 minutes per dose. This was an increase from 2.3 min per dose in the previous fee schedule. The RUC agreed that there was compelling evidence to increase the clinical labor time associated with these procedures and the 3 minutes/dose was instituted for aeroallergens. The labor time for mixing a single vial of venom antigen (95145, 95147) remained at 2.3 minutes.

Similarly, reimbursement for diagnosis of venom allergy remains out of step with other diagnostic procedures. The process for diagnosing penicillin allergy is generally similar to that used for venom allergy but experts agree that testing for the 5 species of insects causing venom allergy is more complicated than the single drug required for accurate diagnosis of penicillin allergy. Yet penicillin allergy testing is reimbursed under CPT code 95018 at 5.3 minutes / percutaneous test while venom allergy testing is reimbursed at 4.2 minutes / percutaneous test (CPT code 95017).

The codes reviewed in 2016 omitted the codes used to reimburse VIT because, in aggregate, VIT is not a high-cost item and did not appear in the

screen for procedures costing more than \$10 million annually. Thus, the reimbursement of diagnosis and immunotherapy for aeroallergen sensitivity was increased while reimbursement of the analogous tasks for VIT, despite the life threatening nature of venom therapy, remained at the lower levels.

Supply Costs

All allergen extracts are natural products and are manufactured from pollens, molds, and other allergenic species. Because they are natural, they may be more variable than drugs synthesized chemically and this variability must be controlled for in manufacturing and quality control procedures, which are time-consuming and labor-intensive.

Of all allergen extracts, insect venoms are among the most demanding to manufacture. Insects must be captured and, in the case of honey bees, induced to release their venom by stinging through a fine mesh. Vespid venom is stored in the insects' venom sacs. These pin head-sized sacs must be individually dissected out of each insect. Between 40 and 50 venom sacs are required for each single dose of extract. After dissection, they are pooled and processed - a manufacturing operation that requires highly trained staff and that is time-consuming and fully manual.

Insect collection for allergenic extract manufacturers was formerly a task undertaken by farmers and other people looking to supplement their income. As collectors retire and few young farmers enter the collection business, insects have become more and more difficult and expensive for manufacturers to obtain.

All of these issues exert cost and supply pressures on manufacturers and have resulted in modest price increases over the last decade. In February, 2018, ALK, long a supplier of insect venom extracts to US allergists, announced that they were discontinuing production of the Pharmedgen® line of insect venom extracts because of increasing production costs and declining sales (Figure 2, ALK 2018). As a result of ALK's departure from supplying venom extracts, Jubilant HollisterStier was required to purchase, install, and validate a significant expansion of their

Figure 2: ALK announcing the discontinuation of Pharmedgen® venom products.

Fighting the Cause of Allergy

February 23, 2018

Subject: Announcing the discontinuation of Pharmedgen® Venom Products

Dear Health Care Provider,

After thorough consideration, ALK has made the decision to discontinue our Pharmedgen® venom product line (lyophilized venom allergenic extracts). Our decision to eliminate the Pharmedgen® product line was very difficult since this was ALK's first product in the North American market and instrumental in establishing our scientific leadership in allergy immunotherapy. Pharmedgen® is no longer a viable product due to production capacity constraints in Horsholm, coupled with the increasing overall costs of production and declining sales of Pharmedgen®.



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Source: ALK 2018

venom manufacturing facilities and also to ask more of their insect collectors.

Supply inputs into the VIT CPT codes are reviewed annually however changes in supply reimbursement rates have been minor. As discussed above, there was a re-review for the 2019 fee schedule that get closer to current costs, however they are being phased in over the next four years. The supply reimbursement rates do not align with increased list prices of venom extracts or with these recent pressures on manufacturers or providers which have resulted in increased costs.

Reimbursement of VIT: Summary

In summary, neither labor nor supply inputs into the current VIT reimbursement rates accurately reflect the actual costs paid by providers. Even though VIT is a treatment proven to be a safe and effective approach to saving lives, many providers have stopped offering it solely because it is not financially feasible for their practices.

The reimbursement of life-saving VIT stands in stark contrast to examples of relatively newer biologics which also save lives. The 5 year treatment regimen (including drug costs, all supplies, and physician and nurse labor but excluding the diagnostic testing and treatment "build-up" period) of VIT is reimbursed at between about \$2,000 and \$6,400, depending upon the number of allergens required for treatment.

Imatinib (Gleevec) is a tyrosine kinase inhibitor that

revolutionized outcomes for patients with Philadelphia chromosome-positive chronic myelogenous leukemia or acute lymphocytic leukemia. Gleevec was launched in 2001 at a drug cost of \$30,000 per year; this cost excludes the cost of administering the drug and patient monitoring. In 2014, the annual drug cost of Gleevec was \$132,000, an approximately 26% annual increase (Nelson 2016). Similarly, checkpoint inhibitor drugs save lives in patients with melanoma, lung, and other cancers. Nivolumab (Opdivo), approved by the FDA in 2014, costs \$150,000 for the initial treatment sequence (Beasley 2017).

A TIME FOR CHANGE

Venom immunotherapy is a life-saving treatment for the small population of individuals highly sensitive to insect venom. Because VIT is cost-saving, it benefits payers as well as patients however reimbursement has lagged so far behind the costs paid by providers that some have stopped offering VIT to patients. Appropriate reimbursement is required to support physician efforts to save lives. Allergy societies, patients, and other stakeholders must work together to make the case for a realistic reimbursement rate that makes VIT a financially feasible treatment option for appropriate patients.

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Disclosure

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