



Allergic reactions to hymenopteran stings: a literature review

Reações alérgicas a ferroadas de insetos da classe Hymenoptera: uma revisão de literatura

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ABSTRACT

Insects of the order *Hymenoptera* such as bees, wasps, and ants can cause severe and even fatal allergic reactions. These insects have venom with allergenic components that they inject through their stingers, which can cause local and systemic reactions. This study aims to carry out a systematic literature review on allergic reactions to *Hymenopteran* stings, analyzing the immune mechanisms involved, clinical manifestations, risk factors, diagnostic methods, prevention strategies, and available therapeutic options. The literature review was conducted in August 2023, in a six-stage process. Articles were obtained by searching databases using Medical Subject Headings descriptors related to the topic. Initially, 50 articles were identified; however, only 10 of these met the inclusion criteria. We found that methods for detecting reactions include skin tests with *Hymenopteran* venoms and serum analysis for IgE specific to such venom. Risk factors that influence the outcome of anaphylactic reactions include the time interval between stings, the number of stings, the severity of the previous reaction, and the type of insect. This review provides a comprehensive overview of allergic reactions to *Hymenopteran* stings, contributing significantly to the understanding, diagnosis, and management of these conditions.

Keywords: Anaphylaxis, insecta, bee venoms, ant venoms, wasp venoms.

Introduction

The phenomenology of the reactions caused by stings from *Hymenoptera* order of insects, which includes bees, wasps, and ants, is remarkably complex,

RESUMO

Insetos como abelhas, vespas e formigas da ordem *Hymenoptera* podem causar reações alérgicas graves e até fatais. Esses insetos possuem venenos com componentes alergênicos e os injetam por meio de suas ferroadas, que podem causar reações locais e sistêmicas. O objetivo deste artigo é realizar uma revisão sistemática de literatura sobre as reações alérgicas às ferroadas de insetos da ordem *Hymenoptera*, com o intuito de analisar os mecanismos imunológicos envolvidos, as manifestações clínicas, os fatores de risco, os métodos de diagnóstico, as estratégias de prevenção e as opções terapêuticas disponíveis. Trata-se então de revisão sistemática de literatura realizada em agosto de 2023. O processo envolveu seis etapas. Os artigos foram obtidos pela busca em bases de dados, utilizando descritores em Ciências da Saúde relacionados ao tema. Foram identificados inicialmente 50 artigos, no entanto, apenas 10 deles atenderam aos critérios de inclusão. Para detecção das reações incluem-se testes cutâneos com venenos de *Hymenoptera* e análise do soro para IgE específica do veneno de *Hymenoptera*. Os fatores de risco que influenciam o resultado de uma reação anafilática incluem o intervalo de tempo entre as ferroadas, o número de ferroadas, a gravidade da reação anterior e o tipo de inseto. Esta revisão oferece uma visão abrangente das reações alérgicas às picadas de insetos *Hymenoptera*, contribuindo significativamente para o entendimento, diagnóstico e manejo dessas condições.

Descritores: Anafilaxia, insetos, venenos de abelha, venenos de formiga, venenos de vespas.

with four distinct categories: local reactions, extensive local reactions, systemic reactions, or anaphylactic reactions based on immunological mechanisms,

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and toxic or nonimmunological reactions.¹ Systemic reactions are predominantly the result of an acute response mediated by immunoglobulin E (IgE), within the context of type I hypersensitivity. Systemic reactions predominantly result from an acute response mediated by immunoglobulin E (IgE), within the context of type I hypersensitivity. A previous exposure to the allergenic components of insect venom is essential for triggering this allergic response, either through previous stings or indirect antigenic exposure through inhalation or digestion.¹⁻³

Many species of insect have the ability to cause allergic reactions, usually local reactions that momentarily interfere with normal activities, causing itching, pain, or erythema at the site of the lesion. However, more serious reactions have been observed among insects of the *Hymenoptera* order, such as bees, wasps, and ants, and in severe cases they have been fatal for some individuals.³ The *Hymenoptera* order includes a diversity of insect species that have the remarkable ability to produce venoms with different allergenic components and, in addition, are able to inoculate this venom into an individual through a sting.^{3,4}

The amount of venom released during a sting varies significantly among species and even within species. For example, bees, on average, release between 50 µg and 140 µg of venom per sting, although the total content of the venom sac can reach 300 µg or more. The subfamily *Vespinæ*, which includes wasps, injects smaller amounts of venom per sting, which vary among genera. This variety in venom inoculation demonstrates the complexity of these insects in terms of allergic reactions.⁴⁻⁷

Although there have been advances in the use of purified venoms, diagnosis, and treatment, allergy to the venom of *Hymenoptera* insects is still epidemiologically relevant. Between 0.15% and 8% of the general population has a personal history of systemic reactions.¹⁻³

The complexity of allergic responses stands out when we consider systemic reactions, which can be varied, ranging from cutaneous manifestations to severe anaphylactic reactions. The severity of these systemic reactions, in many cases, cannot be underestimated, and *Hymenoptera* stings are responsible for a considerable number of deaths every year.⁶

Furthermore, a thorough analysis of generalized skin reactions, vasculitis, polyradiculitis, and

glomerulonephritis provides a comprehensive view of the possible systemic complications resulting from these stings.¹⁻³

Accurate diagnosis of these reactions is fundamental and relies on a detailed clinical assessment, including investigation of the history of the patient and specific tests, such as skin and serological tests. It is of the utmost importance that the species responsible for the sting is known, guiding appropriate treatment and prevention.⁵

In terms of treatment, this study will cover everything from local measures for simple reactions to more complex interventions for severe systemic reactions. Specific immunotherapy has emerged as an effective strategy to prevent recurrent anaphylactic reactions, thus presenting a significant advance in the therapeutic approach to these conditions.⁴⁻⁶

In summary, this systematic review of the literature aimed to provide a comprehensive overview of allergic reactions to *Hymenoptera* insect stings, underscoring the complexity of these phenomena and outlining comprehensive diagnostic, treatment, and prevention strategies. This study aims not only to contribute to the advancement of scientific knowledge in the field of insect allergy, but also to provide crucial information for clinical practice, allowing health professionals to offer more accurate and effective care to patients affected by these specific allergic reactions.¹⁻⁶

Objective

To conduct a literature review on allergic reactions to stings from *Hymenoptera* insects, aiming to analyze the immunological mechanisms involved, clinical manifestations, risk factors, diagnostic methods, prevention strategies, and therapeutic options offered.

Methods

This is a systematic literature review conducted in August 2023. The literature review consisted of six stages: (1) identifying the topic; selecting the guiding research question and the databases; (2) establishing criteria for including and excluding studies and searching the literature; (3) defining the information to be extracted from the selected studies; (4) categorizing the studies; (5) evaluating the studies included in the review and interpreting them; and (6) presenting the review.

The articles were retrieved from the Scientific Electronic Library Online (SciELO), Medical Literature Analysis and Retrieval System Online (MEDLINE), Virtual Health Library (VHL), and Google Scholar databases. Descritores em Ciências da Saúde (DeCS)/Medical Subject Headings (MeSH) were used, such as “reações alérgicas,” “allergic reactions,” “ferroadas de insetos,” “insect bites,” “Hymenoptera,” “imunoterapia,” “immunotherapy” combined with the commands “AND” or “OR” to search for relevant results in the titles of articles. The search included articles in Portuguese, English, and Spanish published in the last fifty years, starting on January 1, 1973.

The articles were then critically analyzed, the data were collected, the results were discussed, and the systematic literature review was presented.

The exclusion criteria included open studies, studies in which the outcome did not assess systemic reactions after the provocation test, double-blind trials randomized to receive pretreatment with antihistamines or not, or outcomes assessing changes in cytokine patterns after immunotherapy. Other exclusion criteria included the following: a history of systemic arterial hypertension, heart disease, poorly controlled lung disease, and a negative skin test.

Pathophysiology

In individuals who have previously been sensitized, a new contact with the allergen will result in the

activation of mast cells and basophils, triggering the degranulation of these cells and the subsequent release of preformed mediators such as histamine, serotonin, and chemotactic factors, not to mention neoformed mediators such as prostaglandins and leukotrienes. This degranulation occurs through the interaction between IgE antibodies present on the surface of mast cells and basophils and the allergen, in this case, venoms.^{4,5}

Minor local reactions are intrinsically linked to the pharmacological properties of the venom, illustrated, for example, with the formation of pustules resulting from ant stings, attributed to the toxicity of the alkaloid components present in the venom of these insects.

Several risk factors have been identified for the appearance of serious systemic reactions in response to the venom of *Hymenoptera* insects. These include age, the length of time between two stings, the species of insect, high baseline serum tryptase levels, the presence of cardiovascular disease, systemic mastocytosis, and use of beta-adrenergic blockers (which can reduce the effectiveness of adrenaline in treating anaphylaxis) and angiotensin-converting enzyme inhibitors (which can aggravate hypotension during anaphylaxis).^{6,7}

A detailed comprehension of the pathophysiology of these allergic reactions resulting from *Hymenoptera* insect stings is imperative to effectively diagnose, manage, and prevent these potentially lethal conditions. Accurate clinical management and patient

Table 1

Descriptors used in database searches

Database	Descriptors	Articles found
PubMed - Search 1	<i>“Insects bites or Hymenoptera and allergic reactions”</i>	26 articles
PubMed - Search 2	<i>“Anaphylaxis and immunotherapy and poison”</i>	19 articles
SciELO - Search 1	<i>“Insects bites or Hymenoptera and allergic reactions”</i>	3 articles
SciELO - Search 2	<i>“Anaphylaxis and immunotherapy and poison”</i>	2 articles
Google Scholar	<i>“Insects bites or Hymenoptera and allergic reactions”</i>	0 articles
Biblioteca Virtual em Saúde (BVS)	<i>“Insects bites or Hymenoptera and allergic reactions”</i>	0 articles

education about risk factors play a central role in mitigating the risks associated with such allergic reactions.⁸

Types of reactions

Reactions to *Hymenoptera* stings can be divided into local and systemic reactions, which can be further divided into allergic and nonallergic. Local reactions are defined as any reaction in which the signs and symptoms are limited to the tissues adjacent to the sting site. Most people develop this type of reaction, which is not considered a form of allergic reaction as it is produced by the action of the venom at the site of the sting. The symptoms are pain, edema, and erythema, which usually disappear after a few hours.^{4,9} Less commonly, patients can develop an extensive local reaction, with painful edema and erythema limited to the skin and subcutaneous tissues adjacent to the site of inoculation of the venom. The affected area is usually more than 10 cm in diameter on average. These reactions gradually worsen, peaking between 24 and 48 hours and lasting between 3 and 10 days.⁹ In this case, an inflammatory reaction occurs, which can be followed by nausea, vomiting, a significant drop in general condition and secondary infection. The extensive local reaction can be considered an allergic reaction.⁴ Patients with a history of an extensive local reaction most often have the same type of reaction in subsequent stings.⁹

It is not yet known whether the risk of developing these reactions changes over time or whether it is influenced as a result of the frequency of stings. The risk of a systemic allergic reaction after an extensive reaction has been estimated at approximately 7%, based on observational studies. The risk of anaphylaxis, on the other hand, is lower and is estimated to occur in less than 3% of cases. Even when more severe, these reactions are still limited to the skin (generalized urticaria and angioedema) and are therefore called systemic skin reactions.^{10,11}

Systemic reactions can cause signs and symptoms far from the sting site and include a spectrum of manifestations, which range from mild to potentially fatal. Systemic reactions can be divided into reactions involving several systems and reactions limited to the skin, as already mentioned.¹²

Anaphylactic reactions are those involving signs and symptoms secondary to the release of mediators present in the mast cell, such as histamine, and which affect more than one organ system. The skin

is commonly involved, but respiratory or circulatory symptoms are also prevalent, and to a lesser extent, the gastrointestinal tract can be affected. Some of the most serious reactions (for example, sudden hypotension) occur in the absence of any skin findings and can be refractory to single or multiple doses of adrenaline (the main treatment).^{13,14} *Hymenoptera* stings cause at least 40 identified deaths annually in the United States, and the rates reported are similar in other parts of the world.¹⁵⁻¹⁷

A toxic (nonallergic) systemic reaction can occur when the individual is stung multiple times, causing toxic pharmacological effects to the components of the venom: phospholipase A2, melittin, apamin, hyaluronidases, vasoactive amines, etc. The clinical manifestations are similar to allergic reactions, and it is difficult to differentiate them; these reactions can even lead to death.^{4,18}

Late systemic reactions can also occur. They manifest as vasculitis, polyradiculitis, and glomerulonephritis. These reactions are rare and of unknown pathogenesis.⁴

Generalized skin reactions consist of signs and symptoms limited to the skin (such as pruritus, erythema, urticaria, and angioedema), which generally involve the skin that is not close to the sting site. Reactions involving angioedema of the tongue or larynx, which can compromise the airway, are generally excluded from this category and are considered anaphylactic reactions.⁹

Diagnosis

The diagnosis of a reaction to *Hymenoptera* venom will be essentially determined according to the clinical history and the investigation of venom-specific IgE antibodies. This investigation can be either through a skin test (prick test and/or intradermal test) or an *in vitro* test. These tests can determine the previous sensitization of the patient to the venom. This sensitization occurs in more than 30% of adults within weeks of being stung. Sensitization can be self-limiting, disappearing in 30% to 50% of cases after 5 to 10 years, while it can also persist for decades, even if there is no re-exposure.¹⁹

Importantly, these tests should be performed at least 3 to 4 weeks after the acute event to reduce the likelihood of false-positive results within the refractory period.³ These tests not only confirm the diagnosis, but also identify the appropriate venom to be used in

immunotherapy.²⁰ All patients with systemic reactions should undergo this subsequent evaluation, while patients with local reactions generally do not require these tests.

Skin tests (prick test and/or intradermal test) or *in vitro* tests ought to be performed at least 3 to 4 weeks after the acute event, to reduce the likelihood of false-positive results within the refractory period.³

Table 2 shows the key steps for diagnosing sensitization to *Hymenoptera* venom.

Clinical history

These stings are extremely painful, and patients easily realize that they have been stung, although often they may not have seen the insect clearly. In cases of anaphylaxis, people close to the patient may notice changes in the voice (laryngeal angioedema), mental confusion or reduced level of consciousness, skin changes, or angioedema.

A comprehensive history should review whether the patient has had similar episodes before and the risk of future stings (i.e., occupation and hobbies) and determine whether their reaction was local or

systemic. Some questions should be asked during patient assessment, including the following.

- How long has the accident occurred?
- How many times have you been stung and where on your body? For example, a sting to the face can cause extensive facial angioedema as part of a local reaction, whereas the same symptom following a sting to the leg or back would indicate a systemic response.
- How long has it been between the sting and the onset of symptoms? You should actively ask what symptoms the patient has experienced.
- Which insect has stung you? (This information is often unreliable).
- Have you taken any medication that could interfere with the onset of symptoms or the response to treatment, such as angiotensin-converting enzyme (ACE) inhibitors or beta-blockers? This information is relevant for assessing the risk of more serious reactions and treatment refractoriness.
- How has the reaction been treated and have there been any late symptoms?

Table 2

Patients with a convincing history of systemic sting reaction but negative venom-specific IgE tests may be at risk of a future systemic reaction due to unclear mechanisms

Sting reaction	Skin test result or venom-specific IgE test	Is venom immunotherapy indicated?
Generalized, nonlife-threatening skin reaction: generalized urticaria, angioedema, erythema, pruritus	Positive	It may be recommended in specific cases: frequent exposure to insects and impact on quality of life
Life-threatening systemic reaction: skin symptoms associated with respiratory symptoms (laryngeal edema or bronchospasm) or cardiovascular symptoms (hypotension, shock)	Positive	Yes
Systemic reaction	Negative	No
Significant local reaction (> 4 inches or 10 cm in diameter, lasting > 24 hours)	Positive or negative	It can be considered if the test is positive
Regular reaction (≤ 4 inches or 10 cm in diameter, lasting < 24 hours)	Positive or negative	No

- Have you been stung before and, if so, has this resulted in any local, extensive local, or systemic symptoms?
- Have you been stung subsequently and, if so, what symptoms have you developed?
- Are you regularly exposed to insects of the *Hymenoptera* class? (as a result of occupational or recreational activities).²¹

Identifying the culprit species

Identifying the insect responsible for the allergic reaction and its habitat is of paramount importance for the diagnosis, prevention, and treatment of patients.²² The two families of winged *Hymenoptera* responsible for most stings are the *Apidae* family (honey bees and drones) and the *Vespidae* family (wasps).

The family of wingless *Hymenoptera* also involved in accidents is the *Formicidae* family (fire ants).^{3,23}

Hymenoptera generally sting people in self-defense or to protect their nests or hives. Their stings are extremely painful, and the patient can tell that they have been stung even though they may not have seen the insect. Identifying the species of winged *Hymenoptera* responsible can be somewhat difficult, as the resulting lesions are similar in appearance. A culprit species can sometimes be identified from the location and appearance of the nest or hive, geographical location, or body site where the sting occurred.²⁴

Persons stung by bees are normally able to visualize the stinger. In wasp stings, on the other hand, it is generally not possible to identify the stinger, as most of these insects do not leave the stinger in place; however, some members of the *Vespidae* family may leave a stinger.²⁵ Fire ant (*Solenopsis sp.*) usually sting the lower limbs, are less painful, can be multiple, and tend to occur in the warmer months of the year.²⁶⁻²⁸

It is worth noting that bees generally leave their sting at the site of the lesion, as do some species of wasp. Ants, on the other hand, do not leave a stinger.²⁹⁻³⁰

Treatment

The type of treatment to be administered will depend on the type of reaction the person has had.

Local reactions can be treated with cold compresses to reduce local pain and swelling. Oral antihistamines

and analgesics are also used to reduce local pain or itching associated with skin reactions. Oral corticosteroids are also effective in these cases. Secondary infections in immunocompetent people are rare complications, so antibiotics are not indicated in the absence of signs of acute infection.³¹⁻³⁷ If an ant has stung a person, the pustule that may form should be kept intact.³⁸

Extensive local reactions are usually treated in the same way as local reactions, however, on some occasions they can be severe and manifest as extensive edema and erythema. Topical or oral corticosteroids and anti-inflammatories should be used to control the pain, which can be intense.³⁹⁻⁴²

The treatment of systemic reactions depends on the severity of the reaction. Mild generalized reactions can only be treated with antihistamines.¹⁴ In severe cases, injectable antihistamines and parenteral corticosteroids should be administered, in addition to maintaining a clear airway and controlling blood pressure. If an anaphylactic reaction is identified, which by definition is a severe allergic reaction with a rapid onset and which can cause death, the treatment should be similar to that for anaphylaxis due to other causes, with intramuscular injection of adrenaline into the anterolateral region of the thigh being the first-line drug of choice.³¹ The concentration is 1:1000 in aqueous solution, at a dose of 0.3 mL to 0.5 mL (adult dose) and 0.01 mL/kg up to a maximum of 0.3 mL (infant dose), at intervals of 5 to 15 minutes.⁴³

Bees have a barbed stinger that lodges in the skin and detaches from the body of the insect with the venom sac once it has stung. The venom is released in the first few seconds following the sting,⁴⁴ so if the insect or stinger can be pulled out of the skin immediately, this can help limit the amount of venom injected. If the patient comes to the clinic a long time after being stung, it will not be necessary to remove the stinger immediately, as the venom will already have been completely expelled. However, the remaining stings should be removed because they can occasionally cause foreign body reactions. Some patients may present with ants attached to their skin,^{45,46} as they can firmly grasp the patients' skin with their mandibles and inflict multiple bites and stings, so they should also be removed immediately.²⁷

Prophylaxis of allergic reactions

Patients who have developed some kind of systemic reaction after a sting, essentially anaphylaxis,

should be given some extremely important information before they are discharged from hospital. They should be informed that venom allergy is a potentially fatal disorder, that further evaluation is needed, and that venom immunotherapy is available to prevent anaphylaxis from future stings. In addition, they should be instructed to purchase an adrenaline auto-injector pen, which they should carry with them at all times, as well as instructions on how and when to use this device.²⁸

Patients should also be informed of certain precautions, such as avoiding the use of sweet or strong perfumes, to prevent attracting insects; not walking barefoot in gardens or near swimming pools; and wearing boots in rural areas.⁴

Patients with a suspected systemic allergic reaction following a *Hymenoptera* sting (of any severity) should be referred to an allergist and immunologist to determine whether they are candidates for venom immunotherapy.⁹

Specific immunotherapy

Immunotherapy is considered a safe and effective treatment to prevent *Hymenoptera* sting-induced anaphylactic reactions in persons with a history of systemic reactions. Immunotherapy targets T cells, modifying the TH2 response in favor of the TH1 response, and this has been the only way to change the natural course of the disease in patients who have had systemic reactions.^{4,37}

Protection against recurrent anaphylactic reactions seems to be effective in most patients within a week of receiving maintenance doses.³⁸ Immunotherapy not only reduces the risk of recurrent systemic reactions, but also improves quality of life by reducing anxiety and allowing patients to participate in outdoor activities as they please.^{39,40} The risk of the patient having a new systemic reaction is reduced to less than 5%, and even those few patients who have anaphylactic reactions after immunotherapy tend to have much milder symptoms compared to the first reaction.⁴¹⁻⁴³

Table 1 summarizes the indications for immunotherapy, which is mostly administered through a series of subcutaneous injections.⁴³⁻⁴⁷

Practical implications

Initiating the correct management at Basic Health Units (BHU) for children or adults following an insect sting is fundamental to ensuring the health and well-

being of patients. Correctly identifying the species that caused the sting is crucial for effective treatment, avoiding complications and ensuring an adequate response.

For this reason, innovative applications and ready-made forms for detecting the species of insect have become a valuable tool. These technological solutions enable rapid identification, allowing health care professionals to act with accuracy and efficiency in patient care. In addition, applications can provide useful information to parents, advising on immediate care to be taken at home before seeking professional help.

By integrating technology with health care services, not only are we speeding up the diagnostic process, but also empowering the community to deal proactively with insect stings. This innovative approach promotes prevention and education, helping to build a healthier and more informed society and reducing the progression to more serious or fatal conditions.

Conclusions

This literature review on allergic reactions to stings from insects of the *Hymenoptera* order provides a thorough overview of these complex phenomena. The comprehensive approach included the categories of reactions, immunological mechanisms, diversity in venom inoculation, and epidemiological relevance.

The importance of accurate diagnosis, supported by clinical history and specific tests, is emphasized. An analysis of the pathophysiology, types of reactions, and risk factors reveals the complexity of these allergic responses.

As for treatment, which includes local measures and interventions for anaphylaxis, the study emphasizes the importance of taking the right approach. Prophylaxis, patient education, and specific immunotherapy are prioritized as crucial strategies in preventing future reactions.

In summary, this review provides a comprehensive overview of allergic reactions to *Hymenoptera* insect stings, contributing significantly to further understanding, diagnosis, and management of these conditions. Specific immunotherapy has emerged as an effective tool for reducing the risk of recurrent anaphylactic reactions, underlining the continued importance of research and education in the field of insect allergy.

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