



Review: allergic contact stomatitis

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Allergic contact stomatitis (ACS) is an oral mucosal immunoinflammatory disorder variably characterized clinically by erythematous plaques, vesiculation, ulceration, and/or hyperkeratosis and by pain, burning sensation, or itchiness. ACS is brought about by a T cell–mediated, delayed hypersensitivity immune reaction generated by a second or subsequent contact exposure of an allergen with the oral mucosa, in a genetically susceptible, sensitized subject. Lichenoid contact reaction is a variant of ACS brought about by direct contact with the oral mucosa of certain metals in dental restorations. The features of ACS are neither clinically nor histopathologically specific, so the diagnosis is usually presumptive and can only be confirmed by resolution of the inflammation after withdrawal or removal of the suspected causative allergen. When ACS is suspected but an allergen cannot be identified, patch testing is necessary. In persistent cases, topical corticosteroids are the treatment of choice, but for severe and extensive lesions, systemic corticosteroid and systemic antihistamines may be indicated. In this short review, we highlight the clinical, immunologic, and histopathological features of ACS, and provide some guidelines for diagnosis and management. (*Oral Surg Oral Med Oral Pathol Oral Radiol* 2017;123:559-565)

Allergic contact stomatitis (ACS) is an immunoinflammatory disorder caused by an antigen-specific T cell–mediated hypersensitivity immune reaction to an exogenous allergen or allergens that are in direct contact with the oral mucosa. Many agents have been reported to induce ACS^{1–14} (Table I), and patch testing is often necessary to identify the allergen.¹⁵ However, a positive reaction to a patch test may be merely an indication of immunologic sensitization, and therefore a diagnosis of ACS must be supported by a relevant history and clinical findings.¹⁶ Treatment includes the avoidance or removal of the allergen, and in persistent cases, the use of topical, sublesional, or systemic glucocorticosteroids.^{17,18}

ACS occurs in patients who are genetically susceptible to it, but prior exposure to a particular sensitizer is necessary to generate an antigen-specific, T lymphocyte–mediated, delayed hypersensitivity immune response after primary exposure. It takes 12 to 72 hours for ACS to develop after second or subsequent contact exposure.^{1,17–19} The mechanisms by which the allergens induce T-cell activation are uncertain. However, it has been suggested that molecules of the exogenous allergens bond covalently to endogenous proteins to form a hapten-peptide complex, which is presented in the regional lymph nodes to naïve T lymphocytes by dedicated antigen-presenting cells, in association with the human leukocyte antigen (HLA)

system that encodes the major histocompatibility complex (MHC) proteins. The recognition of these hapten-peptide complexes by T cell receptors (TCRs) is MHC restricted.^{17,19–21}

It has been documented that in drug-specific T cell–mediated hypersensitivity immune responses, binding of the particular allergen to a specific HLA molecule brings about molecular alterations to the MHC peptide-binding groove, which in turn induces the activation of T cells.^{17,19,21} However, exogenous allergens also directly interact with TCRs or equivalent “immune receptors” on other cells in the microenvironment, contributing to the development of ACS.^{17,21}

Once the exogenous allergen has induced the T-cell immune response, a clinical phenotypical reaction, to a major extent, is determined by the particular effector cells, which may be CD4+ T cells, cytotoxic T cells, monocytes/macrophages, eosinophils, or plasma cells, by the collaboration between the activated cells and by the types of chemokines and cytokines secreted into the microenvironment (Figure 1).^{17,21}

After a primary episode of allergic contact dermatitis (ACD), recurrent episodes can be induced by systemic exposure to the same or to a chemically closely-related allergenic substance. Such a systemically induced

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Statement of Clinical Relevance

The clinical appearance of allergic contact stomatitis (ACS) depends on the nature, potency, and concentration of the allergen, and on the period of exposure. It is accompanied by pain, burning sensation, or itchiness. Resolution occurs after removal or withdrawal of the allergen.

Table I. Some agents that may induce allergic contact stomatitis

- Medications
 - Mouthwashes: chlorhexidine, Listerine⁴
 - Topical anesthetics,⁵ topical glucocorticoids⁶
 - Inhaled budesonide²
- Food, spices (particularly cinnamon), candies, chewing gum⁷
- Gloves, rubber dams⁸
- Dental impression material, gingival retraction cords⁹
- Dental restorative metals¹⁰
- Acrylic denture materials¹¹
- Dental implants^{12,13}
- Metal orthodontic devices¹⁴

recurrence may occur not only at the site of the initial contact eruption.¹⁵ However, it is unknown whether systemic exposure to an allergen can play any role in sensitizing the oral mucosa to recurrent allergic contact stomatitis.

This short review focuses on the pathogenesis and clinical aspects of ACS, and provides some practical guidelines for diagnosis and management, with consideration of whether there are significant differences between cases of ACS induced by different allergens, and whether lichenoid tissue reactions should fall within the spectrum of ACS.

ORAL MUCOSAL IMMUNITY

The oral mucosa is constantly exposed to a wide range of foreign agents, some of which might be allergens with the capacity to generate antigen-specific, T cell-mediated, delayed hypersensitivity immune reactions.

The epithelium of the oral mucosa provides the outermost barrier, protecting deeper tissues from physical damage, invasion by microorganisms with their associated antigens and toxins, and penetration of water and water-soluble molecules, including habit-related agents like alcohol and tobacco products.²² The keratinized epithelium of the masticatory mucosa of the hard palate and gingiva are less permeable and physically tougher than the non-keratinized epithelium of the buccal mucosa, ventrum of tongue, and floor of the mouth.²²

The epithelium and the underlying lamina propria are endowed with innately immune cells, including antigen-presenting dendritic cells, natural killer cells, and polymorphonuclear leukocytes with their associated cytokines and chemokines. These, together with keratinocyte-derived biological mediators, salivary flow, salivary secretory immunoglobulin A, and gingival crevicular fluid, all contribute biological and physical elements to oral mucosal immunity.²³

Bearing in mind that so many immune cells and biological mediators that can initiate hypersensitivity

immune responses are an integral part of the oral mucosa, and that oral epithelium is a thin, semipermeable structure constantly exposed to exogenous allergens, episodes of ACS are less common than might be expected. The relatively low incidence of ACS^{16,24} is probably explained by the constant flow of the saliva in the mouth, which flushes away potential allergens from the epithelium by the physical coating of the oral mucosa by the saliva, which excludes some potentially allergenic exogenous agents from direct contact with the epithelium, and by the abundant blood supply of the oral mucosa that clears the allergens relatively quickly.^{24–26}

It is possible that either dysregulation of oral mucosal immunity or some dysfunction in the mechanisms that exclude or limit contact of allergens with the oral mucosa may have the consequence of developing oral mucosal hypersensitivity immune reactions.

MECHANISMS OF IMMUNE RESPONSES IN THE CONTEXT OF ACS

Allergens which can induce T cell-mediated hypersensitivity immune reactions are usually low-molecular-weight substances, and an overt ACS will develop only after repeated exposure to subthreshold concentration of the allergen, because each exposure is insufficient to generate allergic signs and symptoms. It may therefore require weeks or months of repeated exposures before the allergic reaction will occur.²⁰

The induction of ACS requires sensitization of a genetically predisposed subject to a specific allergen. The exogenous allergen must gain access both to viable keratinocytes that have the capacity to act as immunocytes and to innate immune cells within the epithelium that can detect those molecular structures of allergens or endogenous molecules termed *danger-associated molecular patterns*. This occurs through their germline-encoded pattern recognition receptors, including Toll-like receptors and the nucleotide-binding oligomerization domain-like receptor family.^{20,23,25,27,28} The endogenous danger-associated molecular patterns, including reactive oxygen species, heat-shock proteins, ATP, uric acid, and low-molecular-weight hyaluronic acid, are generated by tissue-damaging factors such as hypoxia, trauma, or toxins, which elicit danger signals.^{20,23,27,29}

In a susceptible subject, stimulation of these receptors, singularly or in combination by allergens or by allergen-induced danger signals, may trigger the production of pro-inflammatory cytokines and chemokines including tumor necrosis factor- α (TNF- α) and interleukin 1 β (IL-1 β), which play essential roles in the mobilization of dedicated antigen-presenting cells to the area of the mucosa in contact with the allergen.^{27,30} The non-specific inflammatory signals induced by the

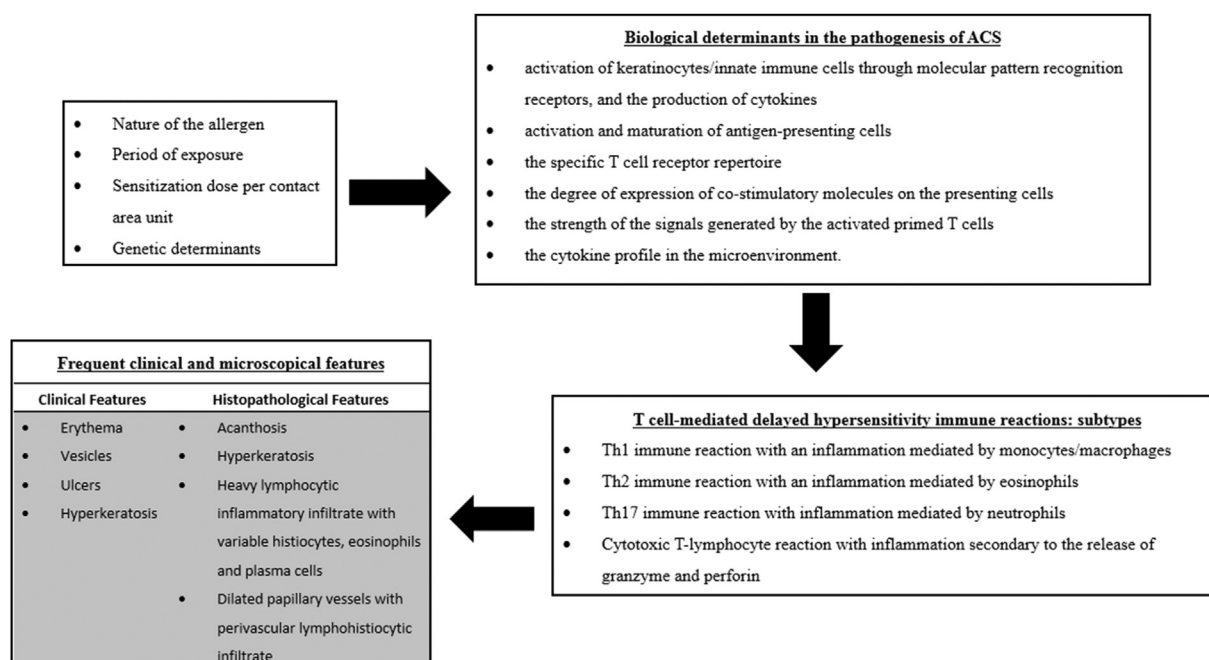


Fig. 1. Allergic contact stomatitis: factors implicated in the pathogenesis that determine its clinical phenotype and microscopic features.

allergen penetrating the oral mucosa are essential for initiating the delayed T cell–mediated hypersensitivity immune reaction.²⁹ In addition, it appears that mast cells, in a histamine-dependent manner, have the capacity to mediate early innate immunoinflammatory responses to haptens and to promote T cell differentiation, thus possibly playing a role in the pathogenesis of contact hypersensitivity.³¹

The magnitude and the duration of the allergen-induced T cell-mediated immune response is dictated to a large extent by the interactions between the intracellular signaling pathways of specific combinations of activated pattern-recognition receptors, which determine the characteristics of the cytokine profile in the local microenvironment.²³ In this regard, it is possible that the nature of the activation of the pattern recognition receptors depends on the burden of the allergen in contact with the immunocytes, and a critical minimal threshold of allergen is required for immunocytes to produce a full set of inflammatory mediators that will ultimately result in clinically detectable ACS.

Allergens are haptens that, after penetrating the integument, combine with tissue proteins to form immunogenic conjugates. The hapten-protein complex functioning as an antigen is processed by immature dedicated antigen-presenting cells of the monocyte lineage (epithelial Langerhans cells and/or lamina propria dendritic cells) that subsequently express the antigen on their surfaces in association with HLA

molecules. The immature antigen-presenting cells undergo a process of maturation with upregulation of expression of MHC surface molecules and of co-stimulatory surface molecules as they migrate to the regional lymph nodes via the lymphatics. This process is mediated by specific pattern recognition receptors on dendritic cells in response to signals received from the local microenvironment.^{17,20,23,25}

In the lymph nodes, the mature dendritic cells, through their MHC molecules, present the allergenic agent to naïve T cells, which become primed, and then differentiate and proliferate into clones of antigen-specific memory effector CD8+ and CD4+ T cells and into regulatory T lymphocytes (Tregs). Treg cells regulate the magnitude of the immune reaction, or induce immune tolerance depending on the antigen and other determinants in the local microenvironment.^{15,17,19,20,23,25,28,30,32,33} Treg cells exert their regulatory effects both in the lymph nodes during the induction of the T cell-mediated immune response, and in the peripheral tissue, suppressing immunoinflammatory reactions through the cytokines IL-10 and TGF- β that they secrete.³²

Once primed, some of the activated effector T cells remain in the lymph nodes, others migrate via efferent lymphatic vessels and enter the circulation, and some reach the oral mucosa. Upon subsequent allergenic challenge to the oral mucosa, allergen-specific memory T cells both in the circulation and in the oral mucosa will be recruited to the area of exposure to the allergen,

precipitating an immunoinflammatory reaction.^{19,32} It is possible that designated tissue-specific memory T cells act as immune surveillance cells initiating allergen-specific T cell-mediated immune responses when they encounter the same allergen.³²

It has been reported that in lymphoid foci in the lamina propria in some regions of the oral mucosa there are memory B and T cells that have been primed in regional lymph nodes. Although these oral lymphoid foci do not function as proliferative germinal centers where *de novo* induction of immune responses can be generated, allergen-specific memory T cells may interact with any allergen-presenting myeloid cells to augment local effector immune responses.^{23,32}

There are several subtypes of T cell responses that probably are determined by the nature of the interaction between the T cells, the antigen-presenting cells, and the biological mediators secreted in the microenvironment. Interferon- γ , IL-2, and TNF- α direct a Th1 immune response through an inflammatory process mediated by monocytes/macrophages; IL-4, IL-5, and IL-13 direct a Th2 immune response with an inflammatory process mediated by eosinophils; and IL-17, IL-21, and IL-22 direct a Th17 immune reaction through an inflammatory response mediated by neutrophils.^{15,17,19,21,25,34}

During the process of T cell polarization, IL-12 and IL-18 secreted by mature dendritic cells will generate a Th1 immune response, and TNF- β , IL-1 β and IL-23 will generate a Th17 immune response.^{25,29} However, polarized T cells retain functional versatility with the capacity to produce cytokines that are not considered lineage-specific in response to microenvironmental stimuli.^{15,34}

It appears that both Th1, cytotoxic T cells (Tc1), and their associated cytokines predominate in the immune reaction that brings about ACS, with Th2 and Th17 cells playing only a minor role.^{19,30} Contact allergy can be induced by either Th1, Tc1, or both, depending on the nature of the antigen, and via the intracellular pathway by which it was processed. Both Th1 and Tc1 produce cytokines and chemokines that recruit monocytes and other effector cells to the area of mucosa in contact with the allergen, eliciting an immunoinflammatory reaction manifesting as ACS.^{15,35}

The TCR repertoire, the degree of expression of co-stimulatory molecules by the antigen-presenting dendritic cells, the strength of signals generated by the activated T cells consequent to the antigen-TCR interaction, and the interaction between the different innate immune cells in the microenvironment, all contribute to the development of the immunoinflammatory reaction.²³ Thus, the diversity of the cytokine profiles and effector cells that have the capacity to generate different subtypes of

Table II. Some oral mucosal conditions to be considered in the differential diagnosis of allergic contact stomatitis^{3,16,26}

• Irritant contact stomatitis
• Erythroplakia
• Erythroleukoplakia
• Lichen planus
• Plasma cell gingivitis
• Mucosal changes secondary to anemia
• Burning mouth
• Non-specific inflammatory mucositis
• Immunoinflammatory conditions such as pemphigus vulgaris and mucosal pemphigoid

antigen-specific T cell-mediated delayed hypersensitivity immune reactions, and the diversity in genetic factors, may explain the multiple clinical phenotypes and the clinical courses of ACS.^{17,18,21}

DIAGNOSIS, CLINICAL AND HISTOPATHOLOGICAL FEATURES AND MANAGEMENT OF ACS

Few patients with ACS, when informed of the suspected diagnosis, are aware of having been exposed to any of the common contact allergens (Table I). The features of ACS are neither clinically nor histopathologically specific, so the diagnosis is usually presumptive and can only be confirmed by resolution of the inflammation after withdrawal or removal of the suspected causative allergen.^{7,16,26} Circumscribed stomatitis is usually suggestive of a localized allergenic trigger, and allergenic agents in mouthwashes, food flavorings, or the like cause widespread stomatitis (Table I).²⁴ Table II lists several oral mucosal conditions that should be considered in the differential diagnosis of ACS.^{16,26}

Clinically, ACS may manifest as intense erythema, vesicles, erosions, ulcers, shaggy hyperkeratosis, or a combination that may extend beyond the presumed zone of contact with the allergen, and it is commonly accompanied by pain, burning sensation, or itchiness. The clinical signs and symptoms usually resolve gradually after withdrawal of the causative allergen, if this can be identified.^{7,15,19,24,26} The clinical appearance depends on the nature and potency of the allergen, period of the exposure, concentration of the allergen, specific variant of the T cell-mediated response generated, and indeterminable degree of dysregulation of the genetically programmed immunoinflammatory response.^{17,19,30} ACS does not have a distinct age predilection but is more common in women than in men.²⁴

Microscopically, the epithelium of the affected oral mucosa may appear acanthotic and hyperkeratotic with

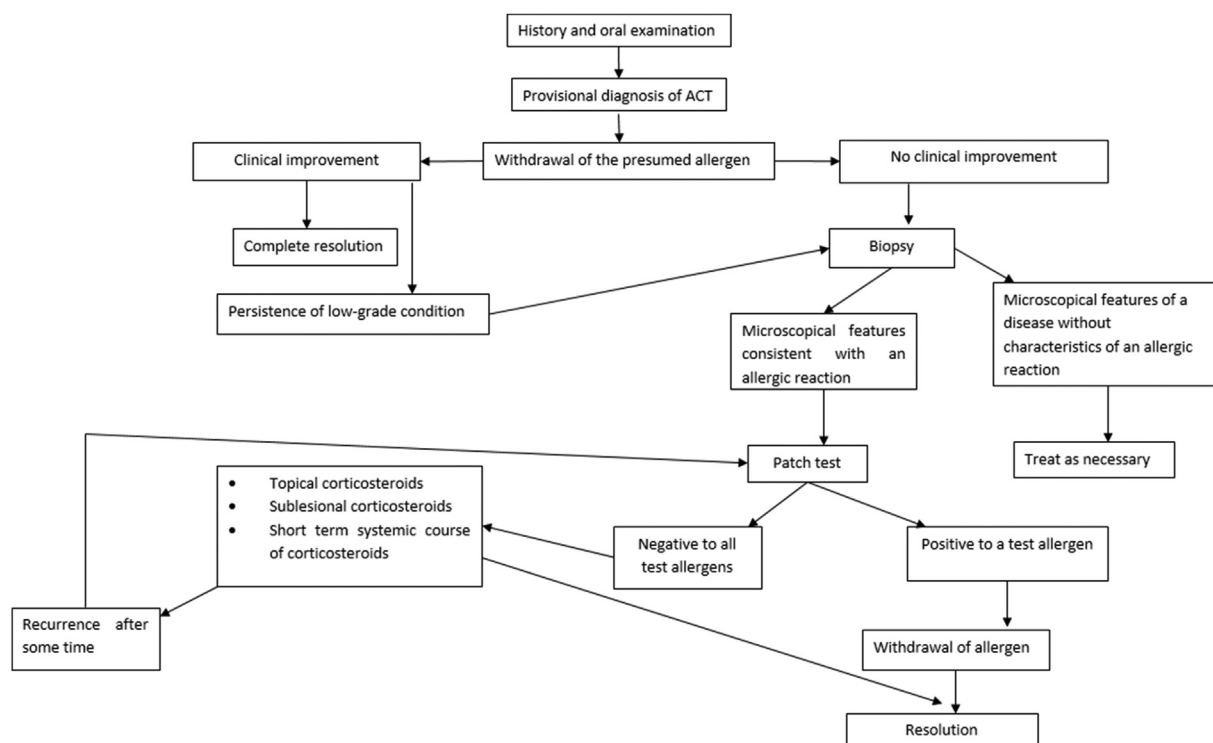


Fig. 2. Algorithm for diagnosis and management of allergic contact stomatitis (ACT). Adapted from Calapai et al.²⁶

elongated rete ridges; the superficial lamina propria is heavily infiltrated predominantly by lymphocytes, but also by plasma cells, histiocytes, or by eosinophils; and the papillary vessels are dilated, with a perivascular lymphohistiocytic infiltrate (Figure 1).^{19,24}

Lichenoid contact reaction induced by a T cell–mediated delayed hypersensitivity immune reaction is a variant of ACS occasionally brought about by direct contact of certain metallic dental restorations with the oral mucosa (mercury, silver, tin, copper, zinc, palladium, nickel, gold, cobalt, zirconium).^{1,3,36} Oral lichenoid reactions are also clinical manifestations of lupus erythematosus, graft-versus-host disease, and fixed drug eruptions, clinically and histologically mimicking lichen planus,^{37,38} but in a lichenoid tissue reaction, there is a focal perivascular infiltrate with a mixed inflammatory infiltrate containing plasma cells deep in the lamina propria, in addition to the more superficial lymphocytic infiltrate at the basement membrane zone.^{37,39}

Clinically, oral lichenoid eruptions, including ACS, are erythematous, erosive lesions but usually with a lichen-like hyperkeratosis. Although oral lichenoid contact reactions erupt in response to topical allergens and are localized to the mucosal site of the contact, oral lichenoid reactions are a response to systemic factors and are haphazardly more widespread. In contrast, oral lichen planus is idiopathic and is almost invariably widespread, symmetric, and bilateral.³⁹

Oral lichenoid contact eruptions most commonly affect the posterior buccal mucosa and ventral or lateral borders of the tongue, confined to the mucosa in close proximity to dental restoration. As in any other case of ACS, they resolve some time after the removal of the offending agent.^{24,38}

Labeling this variant of ACS as an oral lichenoid reaction does differentiate it from classical lichen planus⁴⁰ but is confusing in this context because “lichenoid reaction” may be precipitated by certain systemic drugs or contact allergens, or it may be an oral manifestation of several systemic diseases.³⁸

In the context of the clinical phenotype and course of ACS, the condition may be aggravated by concurrent exposure to an allergenic agent, generating additive or synergistic immune reactions in addition to the contact allergen. Local mechanical irritation will reduce the critical threshold of the allergen necessary for the generation of an overt T cell-mediated, delayed hypersensitivity immune response. If the epithelium is disrupted by mechanical irritation, it becomes more permeable, and the contact allergen can more readily reach the deep keratinocytes and innate immune cells. The mechanical irritation also upregulates the expression of proinflammatory cytokines and inflammatory mediators potentiating the immune reaction brought about by the contact allergen.¹⁶

In patients with ACS, patch testing is useful in identifying the causative contact allergens, but only if

allergenic agents putatively relevant to the condition are tested. Test patches are usually applied to the upper back for 48 hours. A second reading should be taken 96 hours after removing the patch so that allergens that provoke a more delayed immune reaction are not missed. Erythema, edema, or small vesicles are considered to be positive results indicative of allergic contact sensitivity.^{19,39,41}

Once a positively-testing allergenic agent has been identified, the patient should be instructed to avoid or remove the allergen. Topical corticosteroid is the treatment of choice in most cases, but for severe and extensive lesions, systemic corticosteroids and systemic antihistamines may be indicated.^{16,19,24} Figure 2 shows an algorithm for the diagnosis and management of ACS.

Interestingly, patients with oral mucosal conditions, including recurrent aphthous stomatitis, oral lichen planus, angioedema, erythema multiforme, orofacial granulomatosis, and burning mouth syndrome, more frequently test positively on patch tests for allergens such as metals, flavoring, and preservatives than do controls.^{16,42,43} It is possible that some allergens may provoke a superimposed delayed hypersensitivity immune reaction that aggravates the clinical phenotype and clinical course of these mucosal conditions.⁴²

CONCLUSION

Allergic contact stomatitis is an immunoinflammatory disorder caused by an antigen-specific T cell-mediated hypersensitivity immune response to exogenous allergen or allergens that are in direct contact with the oral mucosa. Identification and subsequent avoidance or removal of allergen is essential for definitive diagnosis and management, and when the allergen cannot be identified, patch testing is necessary.

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