

Mosquito bite pathogenesis in necrotic skin reactors

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Mosquito bite exposure results in a variety of reactions and secondary complications. Clinical hypersensitivity manifests primarily as local reactions with anaphylaxis being a very rare event. Risk factors for more severe local reactions include immunodeficiency, young children and visitors to an area with new exposure to indigenous mosquitoes. Necrotic skin reactions to mosquito bites have been associated with a newly recognized hemophagocytic syndrome in predominantly oriental populations. Diagnostic and therapeutic agents in the clinical management of mosquito hypersensitivity remain limited, but recent discovery of 3 recombinant proteins (rAed a 1, rAed a 2, rAed a 3) shared by several mosquito species promise to be more specific skin test antigens for the future. *Curr Opin Allergy Clin Immunol* 1:349–352. © 2001 Lippincott Williams & Wilkins.

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Abbreviations

DTH delayed-type hypersensitivity
NK natural killer (cell)

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Introduction

Mosquito bite hypersensitivity is a common affliction for children and adults, typically manifesting as immediate or delayed local reactions [1–6]. Large local reactions may be severe and mistaken for a skin infection [7]. Young children, immune-deficient persons, and immigrants or visitors to an area with 'new' exposure to indigenous mosquitoes may be at increased risk for more severe reactions [7,8]. Increased severity of local reactions to mosquito bites has been associated with HIV infection [9,10].

Clinical manifestations of mosquito bite reactions

Immediate-onset large local reactions (wheal and flare) following mosquito bites appear to be IgE mediated. Reunala *et al.* [11] demonstrated heat-sensitive passive transfer of this type of cutaneous hypersensitivity, as well as in-vitro basophil histamine release with mosquito salivary proteins (from *Aedes communis*) using passively sensitized basophils from otherwise nonreactive subjects. Mosquito saliva-specific IgE was also demonstrated on immunoblotting to multiple components. Peng *et al.* [12] studied 30 individuals with local reactions to mosquito bites (23 with immediate and delayed, six with immediate, and one with delayed only) and 11 persons with no bite reactions. The mean mosquito-specific IgE and IgG concentrations were highest in those persons with immediate local reactions. There was a direct correlation between the size of the local reaction and the levels of IgE and IgG, suggesting that both IgE and IgG immune complex-mediated hypersensitivity mechanisms may be involved in cutaneous hypersensitivity reactions. In-vitro mosquito antigen-specific lymphocyte proliferative responses were highest in those persons with delayed local reactions, and the degree of response correlated with the size of the delayed local reaction. Severe delayed onset cutaneous reactions at the point of scar formation have been described as a purely cell-mediated immune response [delayed-type hypersensitivity (DTH)] in a child with congenital agammaglobulinemia and absent IgE (<0.2 IU/ml) [8]. Seasonal bullous eruptions have been linked to mosquito bites in one case report from England [13]

Delayed-onset cutaneous hypersensitivity reactions may result in prolonged papule formation, and it is noteworthy that mosquito whole-body extract has been described as a potentially useful DTH skin test antigen. One study of 321 normal volunteers [14] demonstrated 19% with a classic DTH skin test response to mosquito extract.

Large local reactions to mosquito bites can be successfully prevented or decreased in severity by pretreatment with antihistamines such as loratidine, cetirizine, and ebastine [2,3,15–18]. Topical corticosteroids may alleviate the severity of the prolonged and delayed-onset local reactions. It is noteworthy that some studies [17,18] demonstrated efficacy of antihistamines for prevention of delayed symptoms as well as immediate local responses.

Recurrent serum sickness-like reactions to mosquito bites have been described. A 62-year-old man with a 20-year history of recurrent delayed-onset illness starting approximately 6 h after a mosquito bite was identified [19], with a symptom complex that included malaise, chills, fever, headache, cervical lymph node enlargement, arthromyalgia, generalized purpura, and leukopenia. The presence of both mosquito salivary protein-specific IgE and IgG are postulated to be the co-operative immune responses that lead to the clinical manifestations.

Pathogenesis of response to mosquito bite

A small series of patients has been described with necrotic skin reactions at mosquito bite sites and associated systemic symptoms such as fever, lymphadenopathy, and hepatosplenomegaly. Reported in predominantly oriental populations (particularly of Japanese heritage), this clinical presentation of hemophagocytic syndrome is associated with natural killer (NK) cell leukemia, where the malignant cells are infected with monoclonal or oligoclonal Epstein–Barr virus [20]. The NK cells were characterized as NK1 type, expressing interferon- γ and interleukin-10 on stimulation with interleukin-2 or interleukin-12. These cells are in a highly activated state and express functional CD94 inhibitory receptors maximally, as well as the NKG2A and NKG2C molecules, but no p70 or NKAT2 killer cell inhibitory receptors (a pattern that is not seen in normal resting or activated NK cells). However, there is no altered expression of HLA-E. It is postulated that the CD94⁺ NK leukemic cells (with normal cytolytic activity, an NK1 cytokine profile, and susceptibility to interleukin-2 or interleukin-12, but lacking the killer cell inhibitory receptors p70 and NKAT2) have disordered regulation, which results in exaggerated local and systemic reactions to mosquito bites. Biopsy specimens from skin lesions demonstrated infiltration of lymphocytes bearing the phenotype of NK cells. In addition, these locally infiltrating NK cells were shown by in-situ hybridization to express EBER-1, supporting the hypothesis that the local skin reaction is mediated by Epstein–Barr virus DNA-positive NK cells [20]. Other types of malignant histiocytosis and related disorders (including mantle cell lymphoma) have been described in the context of severe hypersensitivity to mosquito bites [20,21].

Incidence of anaphylaxis in response to mosquito bite

Considering the population exposure rates in billions of people over the past century, the scarcity of clinical cases of anaphylaxis due to mosquito bites is remarkable. Since the early 1900s, well-described clinical reports of systemic immediate hypersensitivity reactions following mosquito bites number well below 100 [22–24]. Evidence of specific sensitization by skin test reactivity or in-vitro evidence of specific IgE is variably documented. The actual incidence, prevalence, and natural history of anaphylaxis secondary to mosquito bites remain undefined. A 1996 American Academy of Allergy, Asthma and Immunology Insect Committee survey of practicing allergists specifically interested in insect allergy ($n=337$) [25] found that 15% (18 out of 119) of those who responded had seen patients with mosquito anaphylaxis. Although this indicates that mosquito anaphylaxis may occur more frequently than is suggested by the published literature, well-defined incidence and prevalence studies in the literature are lacking. In addition, the possible role of mosquito bite-related anaphylaxis as a cause of sudden deaths or idiopathic anaphylaxis episodes remains unstudied. Because the presence of IgE is not specific to anaphylaxis, there is no screening test except direct bite challenge to determine the presence of anaphylactic sensitivity.

Whole-body immunotherapy

More than 100 individuals have been described in the literature who were tested and treated with whole-body extract for mosquito bite hypersensitivity, mostly for nonanaphylactic reactions [22–24,26]. Skin test-related anaphylaxis (requiring emergency treatment) can occur with whole-body extract even at low concentrations such as 1:1000 to 1:10 000 weight per volume, or with prick concentrations of 1:10 or 1:20 weight per volume dilutions. Although most reports of immunotherapy outcome were subjective, the majority of reports were favorable, with exceptions being rare. Serious complications with whole-body immunotherapy have rarely been reported, although one patient with immunotherapy-related recurrent serum sickness (preventing further attempts at desensitization) required prolonged corticosteroid therapy [22]. There are no prospective studies with bite challenge testing that have defined the duration of immunotherapy needed for efficacy. Because the natural history of mosquito hypersensitivity is associated with decreasing reactivity over time, it is difficult to differentiate true efficacy from the natural history of disease. The US Food and Drug Administration no longer approve commercially available mosquito extracts for treatment, although practitioners continue to use extracts off label if the patient's specific benefit–risk ratio favors a therapeutic trial beyond medication alone.

Clinically relevant antigens

Developments in the characterization of mosquito saliva-sensitizing antigens, particularly for local reactions, have resulted in an improved understanding of the diagnostically and potentially therapeutically relevant components. Currently, whole-body extracts for only *Aedes aegypti*, *Aedes* spp., *A. taeniorhynchus* and *Culex pipiens* are the only available commercially mosquito extracts, with no source available for *Anopheles* spp. [27]. Seven different commercial products were evaluated for protein content and immunoreactive proteins that bind IgE and IgG from persons with clinical hypersensitivity. The products were highly variable, with protein concentrations ranging from 0.1–4.9 mg/ml. Two out of three aqueous extracts elicited neither immediate nor delayed skin test reactivity in persons with clinical sensitivity on bite challenge. All four extracts that were preserved by 50% glycerin exhibited skin reactivity and visible protein bands, suggesting that 50% glycerin optimally stabilizes the antigenic potency.

Seasonal increases in mosquito saliva-specific IgE and IgG have been documented [28], similar to the seasonal rise in pollen-specific IgE. Strong cross-reactive skin and IgE responses, as well as species-shared antigens, exist among the three most important mosquito species distributed globally: *Aedes aegypti*, *Culex quinquefasciatus* and *Aedes vexans* [29]. Recent reports suggest that some mosquito bite sensitive patients are reactive to a hyaluronidase with cross-allergenicity to wasp (*Vespa* 3) [30] and a component of horsefly [31].

The single most important contribution to our understanding of mosquito allergy in the 21st century must be the report by Simons and Peng [32] of three recombinant proteins, shared by *Aedes vexans* and other mosquito species: rAed a 1, rAed a 2 and rAed a 3. In twenty-eight mosquito bite test-positive persons, 43% had a positive skin test in response to rAed a 1, with a wheal and flare reaction comparable to the bite challenge reaction. Another 11% reacted to rAed a 2 and 32% reacted to rAed a 3. None of 15 subjects who were nonreactive to *A. aegypti* bite tests had a positive skin test to any of the recombinant antigens. The utility of these antigens in anaphylactic patients remains to be determined.

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