

What's Eating You? Mosquitoes (Culicidae)

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PRACTICE POINTS

- Common local reactions to mosquito bites include immediate and delayed hypersensitivity reactions. With repeated exposure, reactions can increase in severity.
- Hypersensitivity to mosquito bites is a severe systemic reaction to mosquito salivary gland components characterized by bullous necrotic skin lesions associated with systemic manifestations such as high fever, malaise, liver dysfunction, proteinuria, hematuria, hepatosplenomegaly, and lymph node enlargement.
- Hypersensitivity to mosquito bites is closely associated with chronic Epstein-Barr virus infection and lymphoproliferative disorders.

Mosquito bites cause a variety of reactions ranging from pruritic papules to severe systemic hypersensitivity reactions. The salivary glands of mosquitoes have been found to contain more than 70 different allergens. Herein, we describe the pathophysiology and clinical appearance of mosquito bite reactions as well as proper management of this condition.
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Incidence and Characteristics

Mosquitoes are insects categorized into the order of Diptera and family of Culicidae, and more than 3500 different species have been identified.¹ In the United States, the most common genus of mosquitoes is *Aedes*, with other common genera including *Culex*, *Anopheles*, *Culiseta*, and *Coquillettidia*. Most bites are performed by female rather than male mosquitoes, as it serves to complete their life cycle (Figure 1).¹

There are a variety of possible reactions to mosquito bites. Severe local reactions that are large (papules >30 mm in diameter) or are accompanied by systemic manifestations are referred to as hypersensitivity to mosquito bites (HMB).² These hypersensitivity reactions vary according to multiple factors, including comorbid

conditions, genetic predisposition, and geographic location. The majority of the world's population will exhibit local reactions to mosquito bites at some point during life, with the median age of onset of the first bite at 2 years of age.³ In a study by Arias-Cruz et al,⁴ the incidence of patient-reported large local reactions was 2.5%. Hypersensitivity to mosquito bites, perhaps the most rare reaction, is more common among Asian and Central American children.⁵ The median age of diagnosis for HMB is 7 years, and most reactions occur during the first 2 decades of life.^{6,7}

Clinical Presentation

Mosquitoes bite vertebrates in an attempt to feed and thus must locate the host's blood vessels through a process known as probing, which often necessitates changing the bite site several times. Once the vessel is located and lacerated, the mosquito feeds either from the vessel directly or the hematoma around it. Not only does the bite cause trauma to the skin, but a cutaneous reaction also may occur in response to salivary gland secretions that concurrently are deposited in the host tissue.⁸ Mosquitoes' salivary gland components are the primary cause of cutaneous reactions, as one study showed that bites from



FIGURE 1. Female mosquito.

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mosquitoes lacking salivary gland ducts were not associated with these reactions.⁹ Mosquito saliva contains a large number of compounds with biologic activities, including lysozymes, antibacterial glucosidases, anticoagulants, antiplatelet aggregating factors, and vasodilators, as well as a potentially large number of unknown allergenic proteins. As of 2016, 70 mosquito-derived allergens have been identified, but this number continues to grow.² After a bite from a mosquito, these compounds may result in host sensitization over time, though interestingly, sensitization to mosquito bites from a species different from the original offender does not occur due to lack of cross-reactivity between species.¹

Because mosquitoes reproduce by laying their eggs directly on or near water, people who live near bodies of water or wetlands are at the highest risk for mosquito bites. Patient factors that have been found to lead to increased rates of mosquito bites include lower microbial diversity on the skin, the presence of sweat or body odor, pregnancy, increased body temperature, type O blood, dark clothing, and perfumes.² Exaggerated bite reactions are associated with Epstein-Barr virus (EBV) infection and hematologic malignancies.¹⁰

Immediate hypersensitivity is mediated by a specific IgE antibody and is characterized by erythema and a wheal at the bite site that peaks within minutes of the bite. In contrast, delayed hypersensitivity is lymphocyte mediated; occurs 24 hours after the bite; and causes an indurated, pruritic, and erythematous 2- to 10-mm papule that may blister.¹¹ Although the evidence of immediate hypersensitivity disappears within hours, symptoms of delayed hypersensitivity may last days to weeks. Accompanying symptoms may include local swelling, pain, and warmth. The itch that often is experienced in conjunction with erythema and papule formation is elicited in 3 main ways: direct induction utilizing classic pruritic pathways, IgE-mediated hypersensitivity reaction to salivary components, and IgE-independent host immune response to salivary antigens. Papular urticaria is a common additional finding in children with mosquito bites.¹ As an individual is repeatedly bitten, they may undergo 5 stages of sensitization: stage I (neither immediate nor delayed reaction), stage II (delayed reaction), stage III (immediate and delayed reaction), stage IV (immediate reaction), and stage V (neither immediate or delayed reaction).¹¹

Although most mosquito bites cause common local reactions, patients rarely demonstrate systemic reactions that can be much more severe. Skeeter syndrome is a milder systemic response characterized by large local reactions (papules >30 mm in diameter) developing hours after a bite with accompanying fever.¹² The reaction typically peaks over days to weeks.² Although the reaction may resemble cellulitis clinically, a history of a preceding mosquito bite can help make the distinction.¹³

A more severe systemic reaction is HMB, which is characterized by intense local skin findings as well as generalized systemic symptoms. Initially, indurated, clear, or hemorrhagic bullae appear at the bite site (Figure 2). Later, there is progression to swelling, necrosis, and ulceration.¹⁰ Biopsies from the skin lesions associated with HMB reveal necrosis, interstitial and perivascular eosinophilic and lymphocytic infiltrates, and small vessels with fibrinoid necrosis.⁷ Systemically, high fever, general malaise, liver dysfunction, proteinuria, hematuria, hepatosplenomegaly, and lymph node enlargement may occur. Patients typically experience these severe symptoms each time they are bitten.¹⁰

The mechanism of the HMB reaction is complex but has a close association with natural killer (NK) cell lymphoproliferative disorder and EBV infection (Figure 3). In fact, it is not uncommon for HMB patients to develop malignant lymphomas during their clinical course, even those unrelated to EBV.¹⁴ Epstein-Barr virus, one of the human herpesviruses, produces latent infection in NK cells. It is hypothesized that after a mosquito bite, EBV may be reactivated within these cells by induced expression of the viral lytic-cycle transactivator gene BamHI Z fragment leftward open reading frame 1, *BZLF1*.⁶ In response to mosquito salivary gland components, CD4⁺ T cells proliferate and induce expression of the EBV oncogene latent membrane protein 1, *LMP1*, on NK cells, which then infiltrate the bite site.¹⁵ These EBV-infected NK cells also overexpress the Fas ligand, thus contributing to organ and tissue damage.⁶ In addition to activating oncogene expression on NK cells, T cells also activate the basophils and mast cells carrying mosquito-specific IgE, both of which also add to the severe skin reaction of HMB.¹⁵ The particular triad of HMB, chronic active EBV infection, and NK cell lymphoproliferative disorder commonly is known as HMB-EBV-NK or HEN disease.¹ Patients with HMB should be monitored for malignancy. The mortality of

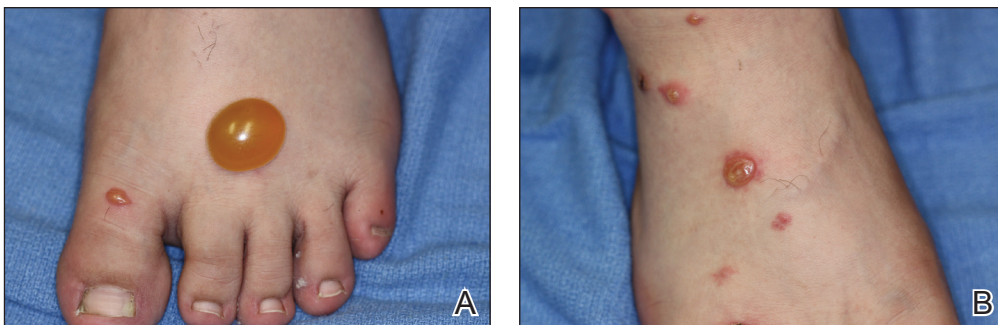


FIGURE 2. A and B, Hypersensitivity reaction to mosquito bites characterized by bullous lesions at the bite sites.

HMB is increased in patients in whom onset occurs when they are older than 9 years and with *BZLF1* messenger RNA in skin lesions.⁶

Other rare reactions to mosquito bites include Wells syndrome, anaphylaxis, and superficial lymphangitis. Wells syndrome (also known as eosinophilic cellulitis) is characterized by erythematous or violaceous plaques and pruritic blisters. Although its etiology has not been defined, it is thought to be evoked or exacerbated by insect bites, with CD4⁺ T cells playing a primary role.¹ Anaphylaxis (angioedema, urticaria, and wheezing) rarely may occur due to mosquito salivary gland components but typically is caused by other stinging insects. Superficial lymphangitis, often misdiagnosed as an infection of the lymphatic system, presents within minutes as nontender pink streaks originating from the bite site. A biopsy with eosinophil and mast cell infiltrates consistent with an allergic-type reaction confirms the absence of infection. Patients respond well to glucocorticoid treatment.

Mosquitoes are vectors for many blood-borne diseases, including dengue hemorrhagic fever, malaria, Chikungunya virus, La Crosse encephalitis, St. Louis encephalitis, West Nile virus, and yellow fever.¹⁶ Additionally, scratching the bites may lead to superinfection and scarring.¹

Prevention and Treatment

Patients with known mosquito sensitivity should avoid areas of stagnant water and utilize preventative measures such as wearing protective clothing and using mosquito repellent containing DEET (N,N-diethyl-meta-toluamide), IR3535 (ethyl butylacetylaminopropionate), picaridin, or 2-undecanone (methyl nonyl ketone or IBI-246) when outdoors. Essential oils such as lemon, eucalyptus, citronella, and garlic are somewhat effective.¹ Additionally, prophylactic dosing of antihistamines may prevent milder reactions.

Although often supportive, treatment and management of mosquito bites depends on the extent of the reaction. For common local reactions, symptomatic management with topical anesthetics, calamine lotion, or corticosteroid creams is appropriate. If superinfection from scratching is a concern, antibiotics may be appropriate.

Management of more severe and systemic reactions such as HMB also is supportive, and the addition of oral corticosteroids to decrease inflammation is required.⁷ Severe HMB also has been treated with immunosuppressive and anticancer drugs, though the efficacy is limited. Venom immunotherapy is a preventative option for patients with mosquito-specific IgE antibodies, and hematopoietic stem cell transplant may be required in patients with HMB.^{14,16}

Conclusion

Mosquito allergens can cause a variety of reactions, ranging from those limited to the skin to those characterized by severe systemic effects. Although common local reactions can be symptomatically treated with topical medication, more severe reactions such as HMB require more involved clinical management. Hypersensitivity to mosquito bites



FIGURE 3. Hypersensitivity reaction to a mosquito bite in a patient with chronic lymphocytic leukemia.

is an important condition to recognize, as it is related to multiple organ impairment as well as later development of malignancy. Patients should be closely monitored during the entire clinical course and in the years following.

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