Itch
International Forum for the Study of Itch

OPEN

Beat the bite: pathophysiology and management of itch in mosquito bites

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Abstract

Mosquito bites are the most common cause of acute itch in humans. The pathophysiology of itch in mosquito bites is not well understood, but 3 mechanisms have been hypothesized. These mechanisms are based on the assumption that mosquito salivary components are somehow implicated in the pruritus that results after a bite. In the first mechanism, salivary components such as histamine are said to directly induce itch via classic pruritic pathways. The second mechanism involves an IgE-dependent hypersensitivity response to salivary components. Finally, in the third mechanism, salivary components modulate an IgE-independent inflammatory response. Individuals' susceptibility to being bitten relies on factors that may be altered by genetics, as certain immune-related loci have been associated with mosquito bite trait characteristics. Furthermore, certain disease states such as hematologic cancers and HIV may exaggerate the response to mosquito bites. Several preventative measures such as mosquito repellants should be used to prevent the bite of a mosquito, and in cases where bites cannot be avoided, most treatment options serve to relieve symptoms.

Key Words: Itch, Pruritus, Mosquito bite, Pathophysiology, Treatment, Scratching

Mosquitoes are a ubiquitous group of biting insects that commonly cause acute itch in humans[1]. Pruritic manifestations can be debilitating, especially in individuals that are susceptible to an increased biting frequency. Despite the high frequency of the symptom, the pathogenesis of itch associated with mosquito bites is poorly understood. Although self-limited in the majority of cases, mosquito bites may impact the quality of life of certain populations that exhibit exaggerated cutaneous reactions. Moreover, the consequences of scratching can lead to superinfection, hyperpigmentation, and scarring.

Epidemiology

Mosquitoes are classified within the order Diptera, family Culicidae, and there are over 3500 species of mosquitoes[2]. The most common genus of mosquitos in the United States is the *Aedes* genus[3]. *Aedes aegypti* (Linn.) and *Aedes albopictus* (Skuse) in particular are vectors of many life-threatening viruses, such as Zika, Dengue, and Chikungunya. While *Aedes aegypti* originated in Africa and *Aedes albopictus* originated in Asia, today, both species are widespread throughout Asia and the Americas. According to records from national entomological surveys, the geographic distribution of this genus is the widest ever recorded, and *Aedes* is now widespread across all continents. Both species had the highest occurrence in Taiwan and Brazil, as well as particularly high occurrences in the United States (*Aedes albopictus* occurrence specifically was exceptionally high in the United States)[4].

Other mosquito genera that are common in the United States include *Culex*, *Anopheles*, *Culiseta*, and *Coquillettidia*[5]. The *Anopheles* genus is known most commonly for its transmission of malaria worldwide[6]. The *Culex*, *Culiseta*, and *Coquillettidia* genus are responsible for the transmission of many diseases, such as Eastern Equine Encephalitis, St. Louis Encephalitis, and West Nile virus[7–9].

Unlike male mosquitoes, female mosquitoes are known to bite humans and animals in order to complete their life cycle, and are therefore the main perpetrators of pruritic manifestations. Female *Aedes albopictus* mosquitoes tend to bite humans around the ankles and knees[10]. Mosquitoes are more likely to bite on humid summer nights, are attracted to specific properties of skin and sweat, bright colors, and carbon dioxide[1,3,11,12]. High temperatures associated with global warming contribute to an increased biting frequency and the likelihood of disease transmission because of its effects on mosquitoes' extrinsic incubation period[13].

Clinical manifestations and immunologic response to mosquito bites

Mosquito bites may cause a local cutaneous manifestation consisting of an immediate wheal and flare reaction that peaks after

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Itch (2019) 4:e19

Received 8 June 2018; Accepted 17 October 2018

Published online 4 January 2019

http://dx.doi.org/10.1097/itx.0000000000000019

20 minutes. Delayed pruritic indurated papules may arise within 24–36 hours and then diminish over several days or weeks. Larger local manifestations vary from pruritic, warm tumefaction to bullous reactions. The spectrum of manifestations may differ depending on subject susceptibility. Noteworthy there is no cross-reactivity between species of mosquitos. Therefore when a human is beaten by one species, there will be no sensitization to other species. Desensitization may occur during childhood or with continuous mosquito antigen exposure[14,15].

The natural history of mosquito bite reactions among an individual has been described in 5 stages. Stage 1 is a period of nonreactivity that occurs in individuals that have been bitten for their first time. As individuals are exposed to additional bites, they exhibit only delayed reactions (stage 2). In stage 3, individuals develop immediate reactions followed by a delayed reaction. In stage 4, only delayed reactions occur, and in stage 5, individuals are desensitized and therefore exhibit no reaction at all[1,16].

Pathophysiology

Although the pathophysiology of itch in mosquito bite reactions is not well understood, it has been noted that when the salivary duct of a female mosquito has been cut, her bite does not produce itching or whealing[17]. Thus one can assume that itch associated with mosquito bites may be related to the components found in mosquito saliva. Mosquito saliva contains a large number of biological substances, including lysozymes, antibacterial glucosidases, anticoagulants, antiplatelet aggregating factors, vasodilators, immunomodulators, and possibly other compounds that have not yet been determined[1,14]. On the basis of the limited data reported in literature, the authors have hypothesized that these components may elicit itch via 3 different mechanisms, which are not mutually exclusive (**Fig. 1**). The first mechanism involves direct induction of itch utilizing classic pruritic pathways, the second is an IgE-mediated hypersensitivity reaction, and in the third, salivary antigens modulate the hosts immune response.

First, it is possible that some of these components induce an itch response by directly activating well-recognized pruritic pathways. Histamine, one of the most historically acknowledged direct mediators of itch, has been found in the saliva of *Culex pipiens* (Linn.), and it also has anticoagulant property[18,19]. Histamine elicits itch by binding to histamine-specific receptors located on sensitive nerve endings in the skin. It is implicated in a number of itchy dermatological conditions such as urticaria and mastocytoses[20]. The amount of histamine contained in the saliva of mosquitoes seems to be enough to induce itch, depending on individual tolerance. Other mosquito saliva components including other anticoagulant factors, vasodilators, and enzymes may be involved in the direct elicitation of bite-induced itch, but data are currently lacking[1].

A second mechanism may involve the onset of an IgE-mediated hypersensitivity reaction in response to salivary components. IgE-mediated activation of mast cells at the site of the bite causes the release of a number of mediators, including histamine, tryptase, cytokines, and eicosanoids (such as leukotrienes), all of which may play a central role in the development of itch. Histamine

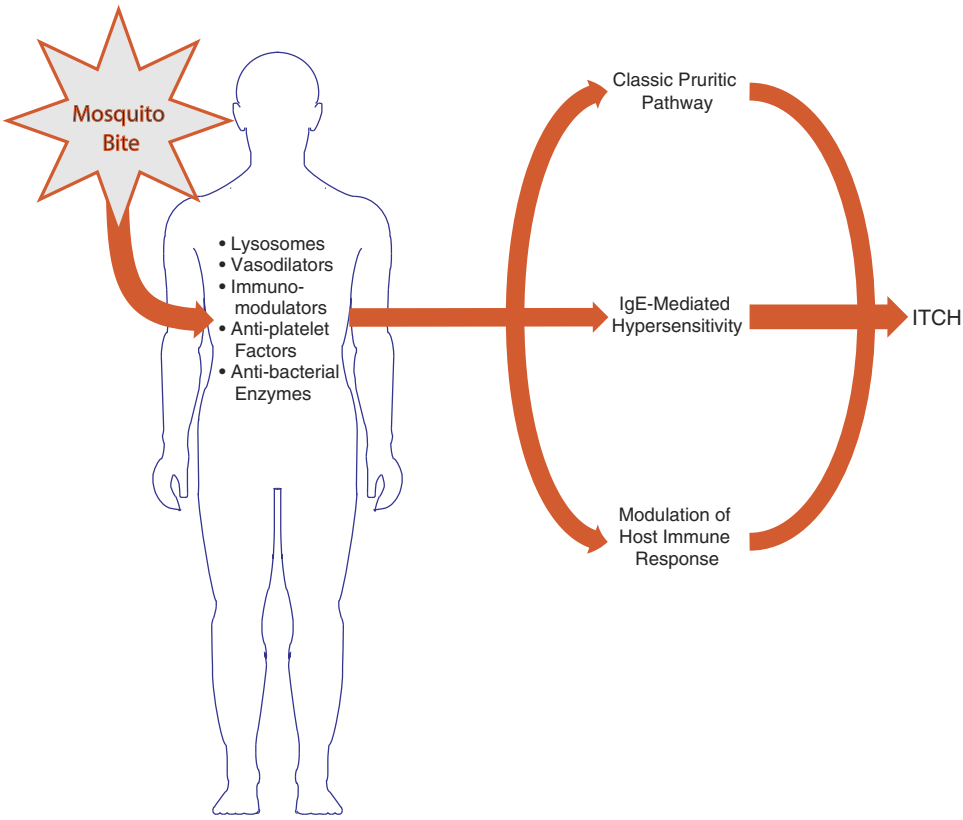

Figure 1. Proposed pathophysiology of mosquito bite itch.

causes itch via mechanisms stated previously. Kuraishi and colleagues suggested that 5-lipoxygenase metabolites other than leukotriene (LT) B4 and cysteinyl leukotrienes (LTC4, LTD4, and LTE4) may be involved in mosquito bite-induced itch. This conclusion was made due to the observation that the 5-lipoxygenase inhibitor zileuton suppressed scratching in a murine model after an intradermal injection of mosquito salivary gland extract. In contrast, a leukotriene B4 antagonist, the cysteinyl LT antagonist pranlukast, and the LTD4 antagonist MK-571 did not suppress scratching[21].

Finally, in the third mechanism, salivary components may modulate an IgE-independent inflammatory response. This modulation may involve direct mast cell degranulation and/or stimulated skewing to a Th2 delayed hypersensitivity response. *Anopheles stephensi* (Lis.) degranulation in vitro led to the release of different mediators including histamine and tryptase, both of which are involved in the itch pathway[22]. Salivary components may also modulate the immune system by shifting host immune responses to a Th2 phenotype. It has been demonstrated that certain mosquito saliva components, in particular sialokinin and SAAG-4, tend to alter host immune responses away from a Th1 phenotype and towards a Th2 phenotype in mice. This is reflected by the decrement of expression of IFN-γ and the rise of interleukin (IL)-4 in murine models[23–25]. The Th2 switch determines the release of cytokines such as IL-4, IL-5 and IL-13 and IL-31, which have been previously implicated in the pruritic pathway of Th2 delayed hypersensitivity response pathway[26,27]. IL-5 has been identified as a player in the development of atopic dermatitis, a condition associated with severe pruritus[28,29]. Furthermore, its intracellular percentage correlates with the severity of disease in atopic children[30].

It is worth noting that in addition to the ways in which mosquito salivary gland components may act to induce itch, it is possible that some of these components may actually be antipruritic. Specific saliva proteins have been identified that bind biogenic amines (particularly serotonin, histamine, and norepinephrine), thereby inhibiting host responses that may disturb feeding. These host responses include itching, platelet activation, inflammation, and vasoconstriction. These proteins have been identified in the small D7 family of proteins contained in the saliva of *Anopheles gambiae* (Giles), and in a D7 long form from *Aedes aegypti*[31]. Moreover, mosquito saliva may contain protease inhibitors that can act as elastase inhibitors, and may play a role in the suppression of the PAR2 itch-mediated pathway[32]. These agents, in particular chemotrypsin inhibitors, have been detected in the saliva of *Anopheles stephensi*[33]. These mechanisms may explain why itch does not occur as a mosquito is in the active process of biting, but only shortly thereafter.

Genetic susceptibility for mosquito bites and itching intensity

Recent genome-wide association studies have provided interesting information regarding the interaction between humans and mosquito bites[25]. Three phenotypes have been analyzed: bite size, itch intensity, and self-reported attractiveness to mosquitoes. The 3 traits were found highly correlated, at the phenotypic and genotypic level. Furthermore, a causal relationship between bite size and the perception of both itch intensity and attractiveness to mosquitoes was suggested[25]. Moreover, females were more likely to report a severe itch response after a mosquito-bite, rather than a mild or non-noticeable itch response, in comparison to males. The authors of the study suggested that a specific locus in the human leukocyte antigen (HLA) region confers a 3-fold effect on itch intensity in females compared with males[25].

This study relates mosquito bite trait characteristics to certain immune-related loci. Many of these loci play a role in the acquired immune response to antigenic stimulation. These loci have also been found to overlap with loci that have previously been identified in certain immune-mediated diseases, such as atopic dermatitis[34]. A number of cytokine/receptor pairs, such as IL-21, IL-4, IL-13, and STAT3 (transcriptional regulator signal transducer and activator of transcription 3), were found to be involved in the itch response. Most of them are already known to have a role in the onset of itch in other conditions. The roles of IL-4 and IL-13 in the development of itch have been discussed previously. STAT3 is a transcription factor that resides in the cytoplasm in an inactivated form; STAT3 transmits signals to the nucleus when activated by cytokines and growth factors such as IL-6, IL-10, IL-22, granulocyte colony stimulating factor and oncostatin M[35]. IL-31, a cytokine whose role in itch has been identified in several dermatologic conditions, also stimulates STAT3, a transcription factor which has a role in itch induction[36–39].

It has previously been shown that body odor contributes to the difference in attractiveness of humans to mosquitoes[40]. Interestingly, body odors from identical twins showed a high correlation in attractiveness to mosquitoes, while body odors from nonidentical twins showed a lower correlation. These results revealed that human body odor has heritable factors, and genetic differences among individuals is detectable by mosquitoes through olfaction[41].

Exaggerated reactions to mosquitoes in specific populations

Certain susceptible populations have been known to exhibit exaggerated cutaneous reactions to mosquito bites. These reactions are associated with itch and can be debilitating. Children bitten by mosquitoes may exhibit papular urticaria. This is a recurrent allergic eruption of pruritic papules that are often found in irregular clusters[3]. Epstein-Bar virus (EBV) infection and natural killer (NK) cell proliferative disorder have been known to occur in association with EBV-associated hypersensitivity to mosquito bites (HMB), and together, the triad is known as HMB-EBV-NK (or HEN) disease. When these individuals are bitten by mosquitoes, the resulting lesion is an indurated, clear, or hemorrhagic bulla that often results in necrosis or ulceration. In HEN patients, $CD4^+$ T cells producing IL-4 and IFN-γ proliferate in response to mosquito salivary gland extracts, and NK cells enhance this response[42,43]. Patients with hematologic cancers such as chronic lymphocytic leukemia may also exhibit an exaggerated immune response characterized by red itchy papules or plaques[44]. This mechanism is related to a mosquito-bite induced Th2-skewed immune response and to a consequent increase in the number of $CD4^+$ T cells that produce IL-4[42]. Wells syndrome (eosinophilic cellulitis) is a condition of unknown etiology characterized by pruritic, scattered erythematous plaques and blisters. It has been hypothesized that the disease may be evoked or worsened by the bite of a mosquito. $CD4^+$ T cells seem to be the primary responders to mosquito antigen in this disease as well, which may contribute to the characteristic increase

in number of eosinophils[42,45]. Finally, patients infected with HIV sometimes exhibit a skin disorder called pruritic papular eruption, a disease of unknown etiology characterized by pruritic papules. It has been suggested that the lesions occur due to the bite of a mosquito. Positive responses to insect body antigens in hypersensitivity skin tests, elevated IgE levels, decreased $CD4^+$ levels, and eosinophilia have been found in these patients. Interestingly, studies have shown that HIV patients also have an increased incidence in Th2-mediated diseases such as asthma and atopic dermatitis[46,47].

Prevention of mosquito bites

Factors that may predispose an individual to a higher frequency of biting include: lower microbial diversity on the skin, sweat, body odor, pregnancy, higher body temperature, blood O type, alcohol, applied scents, and dark clothing[1,48]. Preventative measures can be taken in order to avoid the bite of a mosquito, which are summarized in **Figure 2**[49]. It is recommended to wear protective clothing and gear treated with permethrin, a pyrethoid agent. However some mosquitoes have been shown to develop pyrethoid resistance[50,51].

Several mosquito repellants have proven to be effective in preventing bites. However, some of them, such as Diethyltoluamide (DEET) and IR3535 must be used with caution due to their potential toxicity[1,52]. The United States Environmental Protection Agency has created a search tool that can assist individuals in helping choose the right insect repellant based on several different factors (www.epa.gov/insect-repellents/find-repellent-right-you)[53]. Naturally derived repellants, such as Para-methane-diol (PMD) and citronella have also been used as means of preventing mosquito bites[54,55].

Daily dosing of prophylactic oral antihistamines can be used to reduce reactivity to mosquito bites when bites cannot be avoided. Prophylactic administration of cetirizine has been shown to decrease immediate whealing and pruritus as well as delayed papules following a mosquito bite[56,57]. Loratidine has been proven to reduce skin reactions in children specifically[57–60].

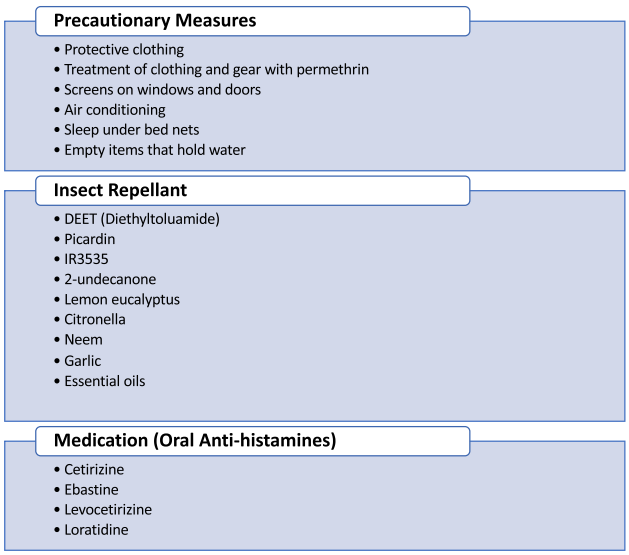

Figure 2. Prevention of mosquito bites.

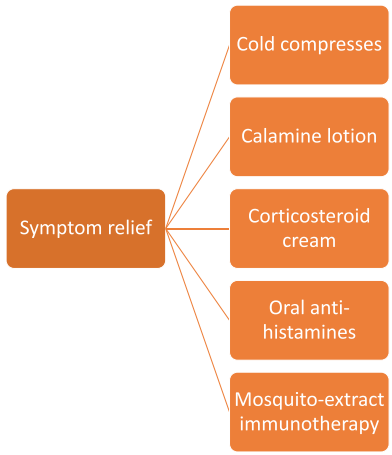

Figure 3. Treatment of mosquito bites.

Treatment

Options to relief symptoms after the mosquito bite are shown in **Figure 3**. Topical agents to help reduce inflammation and itching include calamine lotion and corticosteroid creams. In contrast, although topical antihistamines are widely available over-the-counter, they may put individuals at risk for allergic contact dermatitis[1,61], especially diphenhydramine, mepyrapine, promethazine, and antazoline[62,63]. Sensitization by topical diphenhydramine has resulted not only in cases of contact dermatitis[64], but also in photoallergic dermatitis and connubial dermatitis as well. Connubial dermatitis refers to dermatitis resulting from close contacts, in which the dermatitis-inducing agent has not been used by the patient but by his or her partner[65–67].

Antihistamines are not typically mentioned as effective treatment in delayed mosquito bite reactions, as studies have not yielded consistent results in proving their benefit once a cutaneous reaction has ensued[16]. The efficacy of rupatidine (a long-acting histamine receptor blocker) against histamine and platelet-activating factor-induced flare responses has been shown to reduce dermal flares, however this drug is not available in the United States[1,3,68].

For many individuals who may be extremely sensitive to mosquito bites, mosquito-extract immunotherapy may serve as a treatment option. Only one randomized study was conducted, one group of children was treated with extract of *Aedes aegypti*, and another was treated with antihistamines. The immunotherapy group showed a decrease in their wheal and flare reactions, in the duration of the reaction, and in the need for additional medication[69]. However, additional studies are needed to establish the efficacy of this treatment[16,69].

Conclusions

Pruritus associated with the bite of a mosquito can be bothersome, and in prolonged cases of hypersensitization may also impair quality of life and sleep. Despite its ubiquitous nature, itch transmission in mosquito bites is elusive and conclusive information is lacking. Available data suggest that mosquito salivary antigens play a central role in mechanisms of itch. Preventative measures can be taken to avoid the bite of a mosquito, but in

unavoidable cases, treatment options are mostly supportive unless reactions are severe.

Conflicts of interest

G.Y. is member of scientific advisory board and consultant of Trevi, Menlo, Opko, Sienna, Sanofi, Regeneron, Eli Lilly, Galderma, Novartis, Pfizer, Bayer. He is a PI and funded by Sun Pharma, Pfizer, Kinska, Vanda. The remaining authors declare that they have no financial conflict of interest with regard to the content of this report.

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