

A MINI-REVIEW ON LARGE LOCAL REACTIONS TO MOSQUITO BITES OR SKEETER SYNDROME TO SALIVA AND OTHERS' SALIVA

By

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Abstract

No doubt, blood-sucking insect- vectors are rapidly increasing worldwide with climatic changes. Mosquitoes spread infective stages through bites, such as viruses, bacteria, and parasites, which cause serious zoonotic diseases. Meanwhile, some people especially children and pregnant women are mosquito magnets to be bitten. But, babies are new to the world, without any protection yet, and their reactions to bites can be stronger. Some things include blood type, body temperature, and ammonia in sweat. Bites may be simple or complicated, as swelling, fluid-filled blisters, welts, impetigo, or lymphangitis. Cellulitis is a common complication of insect bites.

Key words: Mosquitoes, Pathogenesis, Diagnosis, Differential diagnosis, Treatment, Prevention

Introduction

Mosquitoes are about 3,600 species of family Culicidae. They are ubiquitous and responsible for majority of insect bites worldwide (Seda and Horrall, 2021). Mosquitoes in Egypt stand out among all numerous blood-sucking species that annoy man, but its more risky, is their role in transmission of many serious diseases (Mikhail *et al*, 2009). Mosquito's saliva is transferred to host while bite to take a blood meal, and can cause an itchy rash, as many species can ingest pathogens with blood, and transmit them to new hosts (Brown, 1993). Reactions to mosquito bites are caused by an immunologic response to proteins in saliva. Many people who are bitten by mosquitoes develop an immune response to these proteins (Vogt *et al*, 2018). Nevertheless, only a small proportion of these people develop clinically relevant allergic reactions, but most commonly large local reactions (Hemmer and Wantke, 2020)

Review and Discussion

Normal mosquito bites: Local cutaneous reactions to mosquito bites typically consist of immediate wheals (swelling) with surrounding flares (redness) that peak at 20 minutes and delayed, itchy indurated (firm) papules peak at 24 to 36 hours and resolve over next 7 to 10 days (Manuyakorn *et al*, 2017).

Typical clinical sensitization course and natural desensitization to mosquito-salivary allergens was known initially in 1940s (Mellanby, 1946), evolved over months or years in an individual (Tab.1). People who have never been exposed to a mosquito don't develop reactions to initial bites from this mosquito (Ellwanger *et al*, 2021). Therefore, bites cause the appearance of delayed local skin reactions. After repeated bites, immediate wheals develop. With more exposure, delayed local reactions wane and eventually disappear, but immediate reactions persist (Kulthanan *et al*, 2010). People repeatedly exposed to bites by same species lose their immediate reactions. Duration of each of the five different stages differs, depends on intensity and timing of mosquito exposure. Typical reactions are annoying but, somewhat not dangerous. Immunologic basis of sensitization and natural desensitization to bites was known in 1990s (Reunala *et al*, 1994). IgE & IgG, as well as lymphocytes were involved in development of local reactions. Serum mosquito salivary gland-specific IgE and IgG levels correlated significantly with the immediate size of skin reaction to bites, but lymphocyte proliferation to antigens correlated with the delayed reaction (Peng *et al*, 1996). IgE-mediated allergic reactions to sa-

liva components range from immediate or delayed large local reactions (wheals & flares) to rare life-threatening anaphylaxis; presyncope, hypotension, and syncope (Peng *et al*, 2004). Histamine is a key player by mosquito saliva itself or by activating the mast cells by IgE or an IgE-independent pathway (Kanagaratham *et al*, 2020). Others as tryptase and leukotrienes may cause non-histaminic itch (Hemmer and Wantke, 2020). Direct saliva histamine reaction is an IgE-mediated (type I) hypersensitivity reaction and an IgE-independent inflammatory response (Fostini *et al*, 2019).

Large local reactions to bites: These reactions are by far the commonest type of allergic reactions to mosquito bites. Large local reactions or Skeeter syndrome consist of an itchy or even painful redness area, warmth, swelling, and/or induration ranges from 2 < 10cm in diameter. Large local reactions may develop within hours of bite, progress over 8 to 12 hours or more, and resolve within 3 to 10 days (Abdel-Motagaly *et al*, 2017). They can involve the entire periorbital region and much of the face or an entire extremity, especially in an infant or child. They can interfere with seeing, eating, drinking, or normal use of an extremity and can be accompanied by low-grade fever and malaise (Simons and Peng, 1999). By inspection and palpation, it may be difficult to differentiate between allergic inflammation by mosquito bites and inflammation caused by secondary bacterial infection or cellulitis after bites scratching (Raff and Kroshinsky, 2016). So, onset time of red, warm swollen area at site of a witnessed or likely mosquito bite in relationship to bite time is indicated, as large local reactions begin within hours; secondary bacterial infections begin within days (Engler, 2001).

Sometimes large local reactions develop an ecchymosis appearance or form blisters, vesicles, or bullae in association with 1- Epstein-Barr virus (EBV), although Wells Disease etiology is unknown, studies suggested that mosquito bites may cause or propagate disease course as patients develop extreme

reactions to bites (Koga *et al*, 2010). 2- Wells syndrome (eosinophilic panniculitis), or patients diagnosed with hematologic cancers such as chronic lymphocytic leukemia and mantle cell lymphoma have an aggressive response to bites (Tatsuno *et al*, 2016). 3- HIV patients are more susceptible to intense mosquito bite reactions. One skin disorder that HIV patients may experience is pruritic papular eruption, but without known etiology (Jiamton *et al*, 2014).

Systemic allergic reactions to bites include papular or acute generalized urticaria and rarely, anaphylaxis, serum sickness, or combination of lymphadenopathy, hepatosplenomegaly, fever, and necrotic skin reactions at bite sites (McCormack *et al*, 1995). Bitten patient showed systemic mastocytosis and recurrent anaphylaxis (Reiter *et al*, 2013). Besides, the Zika, West Nile, Chikungunya and dengue viruses infections cause a generalized itchy maculopapular rash (Huang *et al*, 2016), and anti-malarial drug chloroquine caused pruritus (Aghahowa *et al*, 2010).

Epidemiology: People at risk of allergic reactions to mosquito bites include: 1-Those with a high level of exposure (i.e., frequently outdoors), 2- Infants and young children, once bitten and sensitized, but prior to the natural immunity development, 3- Newcomers or visitors to indigenous mosquitoes areas who had not encountered, once bitten and sensitized, but prior to the natural immunity development, & 4- Patients with primary or secondary immunodeficiency diseases that may paradoxically have elevated antibody titers to mosquito salivary gland antigen, associations between immunity-related genes and bite size, itch, and self-perceived attractiveness to mosquitoes (Jones *et al*, 2017). Dobson (2000) added that pregnant women were twice as attractive to infective *Anopheles* as non-pregnant ones. Peng *et al*. (2004) reported that infants and children were at increased risk of bites allergic reactions. They added that antibody levels declined via childhood and adolescence with the occurrence of natural desensitization.

Clinical features and pathogenesis of large local reactions: *Aedes aegypti* saliva contains >30 potentially allergenic proteins, more than 11 of them were identified in the saliva. Four such proteins, termed *Aed* 1 (an apyrase), *Aed* 2 (Female-specific protein, D7), *Aed* 3 (an as yet undefined protein), and *Aed* 4 (an α -glucosidase) were purified as recombinant proteins (Juckett, 2013). Pathogenesis of large local reactions to the bites was reported in a study of five otherwise healthy young children aged two to four years who developed large local reactions within hours of witnessed bites and five age-matched control children who developed smaller typical reactions within hours of bites. All children with large local reactions were diagnosed initially with bacterial cellulitis and received systemic antibiotic. In two of them, radiographs were obtained to rule out osteomyelitis underlying the extensive soft tissue swelling. (McKnight *et al*, 2011).

An ELISA is used to measure IgE and IgG 1-4 subclasses (IgG1-4), recognizing salivary gland allergens of the indigenous mosquito, *Aedes vexans* (Fontaine *et al*, 2011). In children with large local reactions, serum levels of IgE, IgG1, IgG3, & IgG4 to its salivary gland allergens were significantly elevated, as compared to levels in control children (Garib *et al*, 2022). Specific IgE and IgG concentrations were significantly higher at the end of summer, as compared with levels at the next winter end after no mosquitoes exposure had occurred for six months. Thus, the large local reactions involved the same mechanisms (IgE & IgG antibody production) and as smaller, typical reactions. Those with large local reactions mount a more robust immune response, yet still underwent the same natural desensitization.

History of large local reactions: Large local reactions prognosis to bites were favorable. Children often continue to develop recurrent large local reactions to bites for several summers, after which reactions cease to occur (Peng and Simons, 1998). However, the resolution time varied, depended on the fre-

quency and intensity of the patient's exposure to mosquitoes, which was reduced by efforts to avoid mosquitoes and prevent bites (Palosuo *et al*, 1997). Children were at high risk of developing allergy, as urticaria (irregular pruritic papules groups) and Skeeter syndrome (Simons and Peng, 1999). Among 402 children lived in Canada where large local reactions to mosquito bites occurred, levels of mosquito saliva-specific IgE & IgG correlated inversely with age, peaked at one to six months of age, and decreased after five years of age and 18% of 1059 adult blood donors had antibodies to mosquito salivary allergens due to natural desensitization (Peng *et al*, 2002). In children with bite reactions, 32% had an accompanied atopic disease such as asthma, allergic rhinitis, or atopic dermatitis (Yavuz *et al*, 2021).

Diagnosis of large local reactions to mosquito bites is based on history and physical examination, as laboratory specific testing is not commercially available (Crisp and Johnson, 2013).

History and physical examinations: Diagnosis is based on the time of onset (hours) of the reaction in relationship to a witnessed or likely mosquito bite and on the physical finding of an itchy, red, warm swollen area at the site of the bite.

Laboratory testing: Skin testing or serum-specific IgE antibody testing for the antibodies in mosquito saliva is not practical, as the only commercially available mosquito reagents are unstandardized whole body extracts that contain minimal salivary allergens, yet may contain irritant proteins (Peng and Simons, 1996). Obtaining pure blood sucking salivary allergen for use in skin tests and in vitro tests by dissecting out salivary glands or by direct collection from living ones is labor intensive and time-consuming (Abou-Gamra *et al*, 1992). Mosquito bite challenge tests are contraindicated because of the risk of disease transmission through a wild mosquito bite with risk of causing another severe large local reaction in a susceptible patient (Wang *et al*, 2007). Recombinant sali-

vary allergens were developed only as a research tool (Peng *et al*, 2016)

Differential diagnosis: Of a large local reaction to a mosquito bite includes bacterial cellulitis and large local reactions to other insects bites and stings (Golden, 2015).

Bacterial cellulitis: The key information needed to distinguish a large local reaction to a mosquito bite from cellulitis is the time elapsed between a witnessed mosquito bite (or exposure to mosquitoes and a likely mosquito bite) and the appearance of an itchy, red, swollen area at the bite site. This time is typically hours with large local reactions and days with cellulitis. Cellulitis, abscess, or both are among the commonest skin and soft tissue are one of the risk infections in both the community and hospital settings, up to 4.8 million emergency department visits annually (Martinez, 2020). Patient's skin must be thoroughly evaluated to find the cellulitis potential source by looking for micro-abrasions of the skin secondary to injuries, insect bites, pressure ulcers, or injection sites, if it affected his lower extremities, careful evaluation must be made to look between toes for fissuring or *tinea pedis* (Kaye *et al*, 2019). Cellulitis affects lymphatic system causing underlying lymphadenopathy, and with edema it can lead to formation of vesicles, bullae, and edema surrounding hair follicles leading to peau d'orange (Swartz, 2004). Some risk factors can increase cellulitis, including: skin injury, skin conditions, such as athlete's foot or eczema, chronic swelling of the legs or arms, obesity, or diabetes (CDC, 2020)

Large local reactions to other insect bites and stings: Mosquito bites are painless, in contrast to painful bites from other blood sucking ones (Morsy, 2012), and bees, wasps, yellow jackets, yellow & white-faced hornets stings (Abdel-Rahman *et al*, 2015), or the fire ants that cause large local reactions (Sanad *et al*, 2002), or HDM allergic response (Morsy *et al*, 1994) or atopic lice dermatitis or vagabond disease (Morsy *et al*, 2001).

Bedbugs (*Cimex lectularis*) infestation produce a pungent odor and bite at night face,

neck, hands, and arms, noted upon awakening or one to several days later, especially among children. Bite can be presented as a 2 to 5mm erythematous maculo-papular lesion or wheal with a central hemorrhagic punctum and can be secondarily infected with the impetigo or cellulitis (El-Bahnasawy *et al*, 2018). Bedbug bites must be differentiated from scabiasis, fleas, ticks HDM and parasitic mites and other blood sucking insects producing similar allergy (Saleh *et al*, 2013).

Fleas are a significant cause of papular urticaria, mainly in tropics and subtropics; commonly in pediatric patients (2.4 to 16.3%). rash improved at the age of 7, but can last into adulthood (Halpert *et al*, 2017). Youssefi and Rahim (2014) reported that papular urticarial is a dual Type I & Type IV hypersensitivity reaction, involving both IgE and cell-mediated responses. The rash appears as small, raised, erythematous, pruritic lesions affecting exposed skin, feet and ankles in clusters and linear patterns known as a breakfast, lunch and dinner pattern. Another species *Tunga penetrans* in tropical and subtropical climates causes skin irritation as female flea embeds itself into the skin epithelium of medial foot, under nails and between toes (Sanusi *et al*, 1989). In Egypt, up to 47 Genera and Species of fleas were reported (Lewis, 1967). Bakr *et al*. (1996) found that in some Egyptian Governorates, particularly in the Nile Delta, the increase in rodent population is followed by an increase in many zoonotic fleas with overall index of 0.59. Ticks are second only to mosquitoes for vector-borne disease worldwide (Takayama and Takagaki, 2020) Ticks are important arthropod-vectors that transmit pathogens to man and animals all over Africa, about 52 tick species were identified in Egypt (Hoogstraal, 1956). Ticks have been reported in ancient Egypt; an archaeological study of a mummified dog dating back to the Roman time showed evidence of brown dog tick *Rhipicephalus sanguineus* infestations (Huchet *et al*, 2013). Its saliva is a toxic secretion contains hundreds of functionally versatile proteins, secreted in

varying amounts throughout the feeding process (CDC, 2018). Allergic reactions ranged from mild (with large local swelling and inflammation at bite site) to severe (anaphylaxis), its disturbance while feeding may lead it to inject more allergen-containing saliva causing tick paralysis (Gothe *et al.*, 1979). Tick paralysis pictures in Egyptian children were confused with rabies; myasthenia gravis; botulism; diphtheritic polyneuropathy encountered in rural area (Mosabah and Morsy, 2012). Islam *et al.* (2021) reported that based on the reviewed articles, median flea, louse, mite, and tick indices were highest in Israel (4.15), Egypt (1.39), Egypt (1.27), & Saudi Arabia (1.17), respectively.

Prevention of large local reactions consists of mosquito avoidance and prophylaxis with an oral non-sedating H1 antihistamine. Treatment of large local reactions involves antihistamines and for severe reactions, glucocorticoids (Simons and Simons, 2008).

Mosquito avoidance: Written information about insect repellents and environmental control measures to reduce mosquito populations near the home should be provided for patients who have experienced large local reactions and for parents and caregivers of children who have experienced such reactions (Fradin and Day, 2002): 1- Activities should be modified to avoid mosquito bites. Measures might include staying indoors at dawn and dusk and avoidance of wetlands. 2- Standing water must be eliminated around the home or other immediate environment in order to reduce breeding areas for mosquitoes. Screens on windows and doors must be well-maintained. 3- Permethrin insecticide is suitable applied to fabrics (as camp tents, sleeping bags, or clothing) but not for direct application to human skin. Permethrin-impregnated clothes were available commercially. But, permethrin has some toxicities, such as a reduction in male fertility parameters and reduced testosterone in rodents (Zhang *et al.*, 2021), and hepatotoxicity (Hołyńska-Iwan and Szewczyk-Golec, 2020). 4- Different insect repellents are available in

various formulations & concentrations. The most effective ones are DEET (N, N-diethyl-3-methylbenzamide) and picaridin (Katz *et al.*, 2008). Syed and Leal (2008) in USA reported that the insect repellent DEET is effective against a variety of medically important pests, but its mode of action still draws considerable debate. The widely accepted hypothesis that DEET interferes with lactic acid detection was challenged by demonstrated DEET-induced repellency in absence of lactic acid. The higher DEET concentration, longer protection lasts. DEET (10%) can be applied safely to a child skin over two months of age. It may be neurotoxic if applied in high concentrations to abraded or sunburned skin or if by mistake ingested or inhaled. DEET is a plasticizer, and as such, and dissolves mosquito nets, spandex, rayon, leather, as well as plastic eyeglass frames and watches (Cohen and Hebert, 2011). Swale *et al.* (2014) reported that DEET is likely targeting octopaminergic synapses to induce neuroexcitation and toxicity in insects, while acetylcholinesterase in both insects and mammals has low (mM) sensitivity to DEET. Its ion channel blocking action in neurons may contribute to numbness experienced after inadvertent application to human lips or mouth. Haris *et al.* (2022) reported that *Carpesium abrotanoides* essential oils, trans-nerolidol, have potential to formulate as repellent comparable of DEET.

Unfortunately, man attracts mosquitoes by his body odor, skin temperature, and exhaled CO₂ (Verhulst *et al.*, 2013). Also, there is relation between the skin bacteria and mosquito attractiveness, including direct attraction of mosquitoes to odors produced by these bacteria (Michalet *et al.*, 2019). CO₂, heat and black color, mosquitoes had a significantly stronger response to moist and the heated objects (van Breugel *et al.*, 2015). Zhou *et al.* (2018) reported that CO₂ and other chemicals affect mosquito blood meal seeking behavior, but relative to CO₂, heat, odorants, black color and humidity showed lesser effects on its landing.

Picaridin blocks insects' ability to find human skin by forming a barrier on skin was odorless, leaves no residue, with long-lasting effect between 8 to 10 hours (Van Roey *et al*, 2014). Compared with DEET, Picaridin can be more effective against mosquitoes and less potentially toxic to humans, and can be applied safely to the skin of children over two months of age, where >50% DEET products were available then the protection time advantage associated with the formulations reasonably considered both DEET and Picaridin as the first choice repellents (Goodyer and Schofield, 2018).

Other agents, such as citronella and lemon eucalyptus oil are less effective and relatively short-acting. Citronella may be effective for only 20 minutes, and eucalyptus oil for only two hours (Peng and Simons, 2007).

Treatment of large local reactions: Antihistamines: In randomized, placebo-controlled trials of patients bitten by mosquitoes in laboratory and field settings, prophylactic Oral daily dose with levocetirizine 5mg, cetirizine 10mg, and rupatadine 10mg by placebo-controlled trials decreased size of wheal and skin pruritus in adults (Reunala *et al*, 1993). Oral administration of a non-sedating H1 antihistamine; as loratadine, fexofenadine, or rupatadine (Karppinen *et al*, 2006), relieved itching in the early-phase allergic reaction and reduced late-phase reaction; redness, swelling, and induration (Karppinen *et al*, 2012). A non-sedating anti-histamine was suggested on a regular daily basis when mosquito exposure is inevitable and that such antihistamines must also be used to treat itching, redness, and swelling at mosquito bite sites.

Glucocorticoids are used to treat allergic inflammation associated with large local reactions to stinging insects, extrapolated to treat large local bites reactions (Golden *et al*, 2017). To relieve itching, redness, warmth, and swelling, a moderately potent topical corticosteroid cream may be used twice daily for 5 to 10 days (Kim and Lockey, 2010). For severe, ones that are distressing and/or interfere with normal vision, ingestion of

liquid or food, or ambulation, an oral glucocorticoid such as prednisone 1mg/kg to a maximum of 50mg may be given for 5 to 7 days (Zhang and Kramer, 2014). But, antibiotic treatment was not indicated for large local reactions developed within hours of the bites, because it is unlikely that bacterial infection would develop this rapidly.

Conclusion and Recommendations

Many people who are bitten by mosquitoes become sensitized to its salivary allergens but few develop mosquito allergy, which most commonly presents as large local reactions to mosquito bites. Systemic reactions, including anaphylaxis, are rare.

Large local reactions to mosquito bites are allergic/immunologic reactions to its saliva. These itchy, red, warm swellings typically develop within hours after bites and resolve with or without treatment over 3 to 10 days. Large local reactions to mosquito bites are commonest in young children who have been bitten and sensitized but, not yet developed natural immunity to mosquitoes. Sometimes these reactions are accompanied by a low-grade fever and malaise.

Diagnosis of large local reactions to bites is done clinically. Key information needed is the time elapsed, measured in hours between a witnessed mosquito bite or exposure to mosquitoes and a likely mosquito bite and the appearance of an itchy, red, warm, swollen area at the bite site. Prompt recognition and appropriate treatment helps avoid unnecessary diagnostic procedures and unnecessary antibiotic treatment.

Large local reactions to bites are frequently misdiagnosed as bacterial cellulitis. But, large local reactions to mosquito bites typically develop within hours of a bite, and bacterial cellulitis typically develops a few days later after bite sites were scratched and excoriated.

Clinical diagnosis of allergic reactions to bites is difficult to confirm because of lack of availability of high quality, standardized allergens (mosquito salivary gland or saliva extracts) for use in skin tests or in measure-

ment of serum mosquito saliva-specific IgE and IgG levels. Otherwise, in healthy children, large local reactions to mosquito bites typically cease to occur within a few years.

Environmental measures to limit mosquito breeding habitats and repellents to prevent bites are the primary means of avoiding large local reactions in patients with a history of reactions. If mosquito exposure is predictable or inevitable, a non-sedating H1 antihistamine was suggested before outdoors activities (Grade 1B).

Treatment of large local reactions is symptomatic. For patients with bothersome itching, an oral non-sedating H1 antihistamine is suggested (Grade 1B). For those with swelling and induration several centimeters in diameter, a moderate potency topical corticosteroid cream was suggested (Grade 2C). Mometasone 0.1% used twice daily for 5 to 10 days is given. For those with extensive periorbital swelling that interferes with vision, lip swelling that interferes with liquid or food ingestion, or more limb swelling that interferes with movement, an oral glucocorticoid as prednisone (1mg/kg to 50mg) once daily for 5 to 7 days was suggested (Grade 2C).

Authors' Declaration: The authors declared that they neither have any conflict of interest nor received any funds.

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Table 1: Mosquito bites: Developmental stages with repeated bites by same species

Stage	Clinical findings
I	No observable skin reaction (sensitization stage)
II	Delayed skin reaction
III	Immediate skin reaction followed by delayed skin reaction
IV	Immediate skin reaction only
V	No reactivity (natural desensitization stage)

Explanation of figures

Fig. 1: Cellulitis (CDC, June 27, 2022).

Fig. 2: Mosquito bite on the back of a boy's neck (CDC, May 24, 2023).

Fig. 3: Tick bite man (Lyme Disease Rash)

