Review Article

Insect bite reactions

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ABSTRACT

Insects are a class of living creatures within the arthropods. Insect bite reactions are commonly seen in clinical practice. The present review touches upon the medically important insects and their places in the classification, the sparse literature on the epidemiology of insect bites in India, and different variables influencing the susceptibility of an individual to insect bites. Clinical features of mosquito bites, hypersensitivity to mosquito bites Epstein-Barr virus NK (HMB-EBV-NK) disease, eruptive pseudoangiomatosis, Skeeter syndrome, papular pruritic eruption of HIV/AIDS, and clinical features produced by bed bugs, Mexican chicken bugs, assassin bugs, kissing bugs, fleas, black flies, Blandford flies, louse flies, tsetse flies, midges, and thrips are discussed. Brief account is presented of the immunogenic components of mosquito and bed bug saliva. Papular urticaria is discussed including its epidemiology, the 5 stages of skin reaction, the SCRATCH principle as an aid in diagnosis, and the recent evidence supporting participation of types I, III, and IV hypersensitivity reactions in its causation is summarized. Recent developments in the treatment of pediculosis capitis including spinosad 0.9% suspension, benzyl alcohol 5% lotion, dimethicone 4% lotion, isopropyl myristate 50% rinse, and other suffocants are discussed within the context of evidence derived from randomized controlled trials and key findings of a recent systematic review. We also touch upon a non-chemical treatment of head lice and the ineffectiveness of egg-loosening products. Knockdown resistance (kdr) as the genetic mechanism making the lice nerves insensitive to permethrin is discussed along with the surprising contrary clinical evidence from Europe about efficacy of permethrin in children with head lice carrying kdr-like gene. The review also presents a brief account of insects as vectors of diseases and ends with discussion of prevention of insect bites and some serious adverse effects of mosquito coil smoke.

Key words: Arthropod, bite, insect, mosquito, papular urticaria, pediculosis, permethrin, spinosad

INTRODUCTION

Insects are a class of living creatures within the arthropods with a chitinous exoskeleton, three-part body, three pairs of jointed legs, compound eyes, and two antennae [Table 1].[1] Insects (Latin *insectum*, meaning "cut into sections") may be considered to "cut into" three sections, head, thorax, and abdomen. Bite is a wound produced by the mouth parts of an animal. Some animals have a special structure called sting through which they inflict wound and inject venom. All insects do not bite. Some non-biting insects are beetles, locusts, moths, and butterflies, although these may produce skin reactions by other means such as allergic reactions to their body parts, faeces, or body fluids. Bees, wasps, and ants also do not bite, but produce dermatological reactions by their stings.

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EPIDEMIOLOGY IN INDIA

Insect bite reactions are common, but information about their prevalence is limited. Children <14 years of age in dermatology outpatient clinic in Pondicherry had a prevalence of 5.3%.[2] Children <5 years of

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Table 1: Insects of dermatological significance[1]

- Order Diptera
- Suborder Nematocera (long-horned flies)
  - Family Culicidae (mosquitoes)
  - Family Psychodidae (sandflies)
    - Genus *Phlebotomus*
    - Genus *Lutzomyia*
  - Family Simuliidae
    - *Simulium damnosum complex* (black flies)
    - *Simulium posticatum* (Blandford fly)
  - Family Ceratopogonidae (biting midges, 'punkies', 'no-see-ums')
    - Genus *Culicoides*
    - Genus *Leptoconops*
- Suborder Brachycera (circular-seamed flies, muscoid flies, short-horned flies)
  - Family Tabanidae
    - Genus *Tabanus* (horse flies)
    - Genus *Chrysops* (deer flies)
    - Genus *Haematopota* (clegs)
  - Family Rhagionidae (snipe flies)
  - Family Chloropigae (eye flies, frit flies)
  - Family Muscidae (house flies, lesser house flies, stable flies, tsetse flies)
  - Family Hippoboscidae (flat flies, louse flies)
  - Family Calliphoridae (blow flies)
  - Family Sarcophagidae (flesh flies)
  - Family Oestridae
- Order Siphonaptera (Fleas)
  - Family Tungidae
  - Family Pulicidae
    - *Pulex irritans* (human flea)
    - *Ctenocephalides canis* (dog flea)
    - *Ctenocephalides felis* (cat flea)
    - *Xenopsylla cheopis* (tropical rat flea)
  - Family Ceratophyllidae (bird fleas)
- Order Hymenoptera (bees, wasps and ants)
- Order Phthiraptera (lice)
- Suborder Anoplura
  - Family Pediculidae
    - *Pediculus humanus humanus* (body louse)
    - *Pediculus humanus capitis* (head louse)
  - Family Pthiridae
    - *Pthiris pubis* (crab louse)
- Order Hemiptera (bugs)
  - Family Cimicidae
    - Genus *Cimex*
      - *Cimex lectularius* (common bed bugs)
      - *Cimex pipistrelli* (batbug)
      - *Cimex hemipterus* (tropical batbug)
    - Genus *Leptocimex*
    - Genus *Oeciacus* (martin bug, swallow bug)
    - Genus *Haematosiphon* (Mexican chicken bedbug)
  - Family Anthrocoridae
  - Family Pantatomidae
    - *Palomena prasina* (green shield bug)
  - Family Reduviidae (kissing bugs, assassin bugs, cone-nosed bugs)
- Order Thysanptera (thrips)
- Order Coleoptera (beetles)
- Order Dictyoptera (cockroaches)
- Order Orthoptera (locusts)
- Order Lepidoptera (butterflies, moths)

Biting insects are underlined. Information taken from Burns, 2010.[1]

age attending skin outpatient clinic in Calcutta had 10.6% prevalence of papular urticaria,[3] with seasonal variation (rainy season 16.7%, summer 6.7%, winter 5.8%). Variables affecting susceptibility to insect bites have been described [Table 2].[4-11]

MOSQUITO BITES

Mosquitoes belong to order Diptera, suborder Nematocera, and family Culicidae [Figure 1]. Bite reactions due to insects of order Diptera are mostly due to allergens in saliva of insect and not due to toxin. Saliva of mosquitoes contains pharmacologically active compounds inhibiting body's innate immune responses, causing anticoagulation, impaired platelet formation, vasodilation and anti-inflammatory activities.[12,13] Allergens in mosquito whole body extract and saliva have been studied for developing diagnostic tests and immunotherapy for mosquito bite allergy. These approaches are used infrequently and mosquito whole body extracts are ineffective in down regulating specific immune responses to salivary allergens and may enhance sensitization.[14] Salivary gland surface proteins are major immunogenic components.[15] Species-specific and species-shared allergens of mosquitoes have been identified, which should facilitate production of specific recombinant allergens and improvement in diagnosis and specific immunotherapy.[16]

Human sweat contains odorous organic compounds, produced by skin microflora, determining its attractiveness to mosquitoes. Variation in sweat composition causes differential attractiveness to mosquitoes within and between individuals.[6] Higher probability of mosquito bites is associated with increasing age in children,[17] male gender,[18] large body size,[19] pregnancy,[9] and alcohol ingestion.[10]

Common reaction pattern

Mellanby[20] has described 5 stages of reaction to repeated mosquito bites [Table 3].

Table 2: Variables influencing susceptibility of individuals to insect bites[4-11]

	Who are susceptible?	Insects attracted	Mechanism(s) involved
Environmental factors	Persons living in tropical areas, summer in non-tropical areas	Any	Fewer clothes and expose large areas
	Spending time in garden	Any	Increased exposure to insects
	Overcrowding and poor hygiene	Lice, fleas, bed bugs	Increased re-infestation
	Shifting to a house in which previous owner kept pets	Cat and dog fleas	Cocoons hatch and attack humans in scarcity of natural host
	Dilapidated housing	Bedbugs	Source of crevices in which bedbugs multiply
	Tourism destinations, trains, cinemas, hospital wards and clinic waiting rooms, staff and student accommodation, hotels[4]	Bedbugs	Increased transfer of insects
Host factors	Body heat and carbon dioxide in exhaled air	Mosquitoes, fleas, bedbugs	Increased attractiveness to insects
	Vibrations caused by host	Fleas[5]	Displacement of air attracts insects
	Human sweat	Mosquitoes[6]	Increased attractiveness to insects
	Human skin flora	Mosquitoes[7]	Microflora produces compounds attracting insect
	Human body odour	Mosquitoes,[7] sandflies[8]	Increased attractiveness to insects
	Pregnancy[9]	*Anopheles gambiae* complex	Increased heat and increased release of volatile substances from skin surface
	Alcohol and beer[10]	Mosquitoes	Unknown
	Lipoatrophy in patients on antiretroviral therapy[11]	Mosquitoes	Lipoatrophic subcutaneous tissue may present more accessible capillary network and increased release of volatile substances from skin surface.

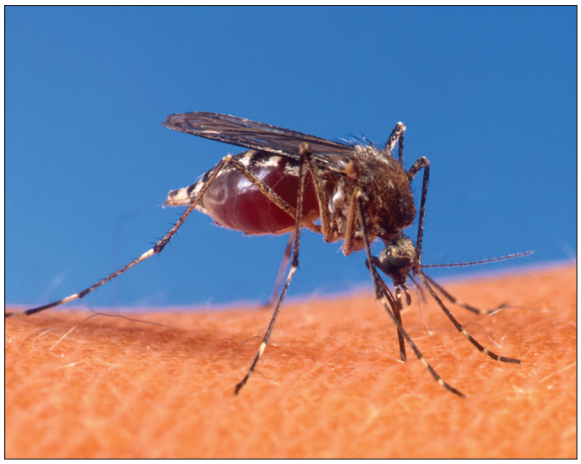

Figure 1: Aedes aegypti biting a human (source: http://commons.wikimedia.org/wiki/File:Aedes_aegypti_biting_human.jpg)

Anaphylactic reaction

Severe IgE-mediated anaphylactic reactions rarely occurs, characterized by rapid onset of skin lesions which may be associated with respiratory compromise and may result in death. It is highly recommended that individuals at risk of anaphylaxis carry an epinephrine auto-injector whenever they are likely to encounter mosquitoes.[21,22]

HYPERSENSITIVITY TO MOSQUITO BITE EPSTEIN-BARR VIRUS NATURAL KILLER (HMB-EBV-NK) DISEASE

This disease is mainly reported from Japan, Korea, and China. Persons infected with EBV may develop

Table 3: Different stages of reaction to mosquito bites[20]

Stage of reaction	Clinical features
Stage 1	No observable reaction, period of induction of hypersensitivity
Stage 2	Pruritic papules appear after about 24 hours of bite and lasting for several days
Stage 3	Patient in addition developing an immediate wheal lasting for a few hours
Stage 4	Development of only immediate wheal without delayed papule
Stage 5	Complete tolerance with no reaction

a severe reaction to mosquito bites. In 1990, Tokura et al described a patient with HMB with 50% to 60% of peripheral blood mononuclear cells being NK cells.[23] Mean age of onset is 6.7 years without any gender predominance.[24] EBV infection immortalizes NK cells, which are activated by injection of some mosquito constituents, thereby exhibiting HMB as primary clinical manifestation.[24]

NK cell predominant mononuclear cells are infiltrated into bite sites. Typical clinical course includes three stages, initial exaggerated reaction to mosquito bites, deterioration of general systemic symptoms particularly in elderly, and the hemophagocytic syndrome (or malignant histiocytosis) with major life-threatening complications at the terminal stages.[24] A recurrent and prolonged activated state of NK cells may induce

additional genetic damage leading to leukemias or lymphomas.[25] Some patients may already have leukemia or lymphoma at first episode of HMB.[24]

HMB-EBV-NK disease is included under "T/NK cell chronic active EBV disease" (CAEBV), which also includes hydroa vacciniforme (HV), HV-like lymphoma, and systemic EBV+T-cell lymphoproliferative disease of childhood.[26]

ERUPTIVE PSEUDOANGIOMATOSIS

Millet-sized erythema or small shiny red papules of angioma-like appearance with an anaemic halo occur on exposed parts resolving within a few days.[27,28] The disease is possibly due to mosquito bites, as lesions have been elicited by *Culex pipiens* bites.[27] It overlaps with a disease known in Japan as erythema punctatum Higuchi, possibly caused by *Culex pipiens pallens*.[29] Histopathological findings are unremarkable with noticeable capillary dilation with plump endothelial cells protruding into lumen and perivascular predominantly lymphohistiocytic infiltrate without vasculitis.[29]

SKEETER SYNDROME

Skeeter syndrome is a mosquito saliva-induced large local inflammatory reaction clinically resembling cellulites.[30] Lesions are red, itchy, warm swellings appearing within minutes of bite and itchy papules, ecchymotic, vesiculated, and bullous reactions appearing 2 to 6 hours afterwards and persisting for days or weeks with or without fever.[31] Severe reactions are treated with systemic prednisone.[30]

PAPULAR PRURITIC ERUPTION OF HIV/AIDS

It is characterized by symmetrically distributed pruritic 2 to 5 mm papules on extremities and trunk sparing palms, soles, and digital web-spaces,[32] usually in advanced HIV disease, and is more prevalent in less developed regions of the world.[33] The condition, which tends to wax and wane and is resistant to oral antihistamine and topical corticosteroid therapy,[33] responds to HAART.[34] Increasing rash severity has been significantly associated with lower CD4 cell counts and higher absolute peripheral eosinophil counts.[33] Most of the patients had moderately dense to dense, superficial and deep, perivascular and interstitial infiltrates of lymphocytes and many eosinophils beneath an epidermis that was slightly hyperplastic.[33] History and histopathology suggest it to be an abnormal response to arthropod, mainly mosquito bites.[33]

BLACK FLIES

Small blood crust with surrounding ecchymosis appears at bite site. Within a few hours, small, pruritic papules develop lasting several days. Severe reactions with marked oedema of limbs and constitutional upset occasionally occur and sometimes nodules and eczematous areas persist for several months.[35]

Two patients with Simulium dermatitis from North-Eastern region of India had intense itching, excoriations, scarring, and hyperpigmentation. Histopathology showed vesicles, dermal oedema, and perivascular infiltrates rich in eosinophils and lymphocytes.[36]

BLANDFORD FLIES

Bites produce skin swellings and sometimes fever or joint pain.[37]

HORSE FLIES

Bites produce painful lesions and rarely anaphylactic reaction with generalized itching, urticaria, paresthesia, and unconsciousness.[38]

LOUSE FLIES

Deer ked (*Lipoptena cervi* L.), a haematophagous louse fly of deer, causes pruritic papules, usually in forests.[39] Lesions appear mostly on head and back, are resistant to treatment and persist for weeks to months. Direct immunofluorescence may show deposits of C3 in dermal vessel walls.[39] IgE, complement and cell-mediated mechanisms are involved.[39]

TSETSE FLY

Tsetse includes all species in genus *Glossina*, generally placed in their own family, Glossinidae.[40] Confined to Africa, tsetse flies are vectors of trypanosomiasis. Almost no information is available about lesions produced by bite. An allergen found in stinging insects (TAg5) was detected in tsetse fly saliva.[41] Anaphylactic reaction occurred following *Glossina morsitans* bites in a laboratory worker.[42]

MIDGES

Biting midges prefer certain human hosts determined by body odour, with non-attractive people producing natural "repellents".[43] In areas where midges are found, they are abundant at heights of 1 to 4 meters above ground[44] and hence bite taller people first.[45] Strong association between probability of bite and increasing height in men and body mass index in women has been shown.[45] This study found no association between bites and eating strongly flavoured foods (garlic, chilli, and onion), contrary to popular belief that garlic makes one less attractive to biting insects.

Bites may manifest as IgE-mediated urticaria or as presumably delayed-type reactions with papules, ulcers, or bullae persisting for weeks[46] IFN-γ, IL-6 and TNF-α are involved in delayed reactions.[47]

BUGS

Bugs are insects of the order Hemiptera with a common arrangement of sucking mouth parts; their hindwings are smaller than forewings. All bugs of family Cimicidae are flattened, oval and have no hind wings; the front wings are vestigial, hence they do not fly. Adult bedbugs are about 5 mm long and may be confused with booklice, carpet beetles, and small cockroaches [Figure 2]. Cimicids are obligate haematophagous ectoparasites.[48] Bedbugs may survive up to a year without feeding.[49]

Bedbugs

Common species found in India are common bedbug and tropical bedbug.[1] Bedbug bites are known as cimicosis. On first exposure most individuals do not develop lesions. With further bites, most develop an obvious skin reaction and latency for previously reacting persons decreases substantially.[50] Few may not be sensitized even after repeated exposures as happened in a voluntarily-exposed researcher.[49] Three salivary proteins of bedbugs, a nitric oxide–liberating heme protein (nitrophorin),[51] a 17-kDa anticoagulant (Factor X),[52] and a 40-kDa apyrase-like nucleotide-binding enzyme, may be important immunologically.[53]

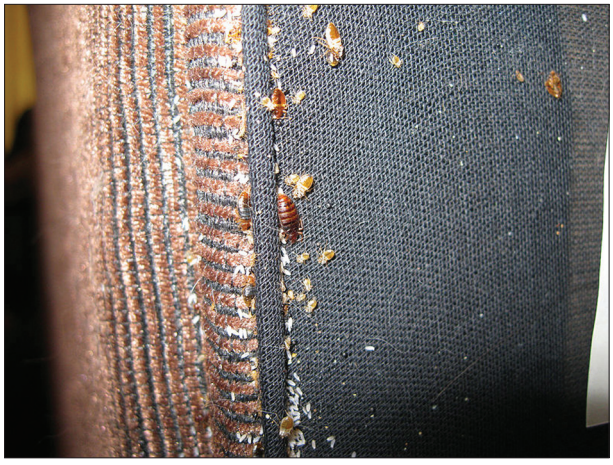

Figure 2: Bedbugs and their eggs on a mattress (source: http://commons.wikimedia.org/wiki/File:Bedbugs.jpg)

Bedbug infestation is facilitated by poor sanitation, overcrowding of residences and trade in second-hand furniture.[54] Infestation in high turnover locations (hotel rooms, school hostels) may spread the disease,[55] bedbugs being transferred with luggage to homes.

Bedbugs avoid light and feed at night.[49] Patient develops itch or a barely visible punctum.[49] This, if not abraded, resolves within a week.[56] Other lesions are pruritic, usually painless, erythematous macules, papules, nodules, urticarial wheals, and blisters.[49,57] Bullous rashes occurring days later[58] may represent late-phase response of IgE-mediated hypersensitivity to salivary protein.[57] Common sites are arms, shoulders, and legs. Bites may produce anxiety, insomnia[59] or delusions in a cured patient.[60] Heavy infestation may cause significant blood loss and anemia in children.[57]

Rare systemic reactions include generalized urticaria, asthma, and anaphylaxis.[49] Bedbugs are suspected to transmit ≥40 human pathogens,[49] however, there is no proven case.[61]

Exposing suspected infested household materials to sunlight has little effect as bedbugs move away to dark crevices.[62]

Mexican chicken bugs

Bites of Mexican chicken bugs *Haematosiphon inodorus* (haematosiphoniasis) produce polymorphic lesions (wheals, papules, vesicles, pustules, and scabs).[63]

Assassin bugs

Assassin bug bites are defensive and extremely painful.[64]

Kissing bugs

Bites of kissing bugs (*Triatoma sanguisuga*) are painless, allowing them to feed undisturbed. Initial bites produce little reaction, with repeated exposure

reactions ranging from pruritic papules with central punctum to haemorrhagic nodules and bullae may occur.[65] Patients have multiple clustered bites, especially on face, hence the name kissing bugs.[66] After additional bites, reaction may "accelerate" with local to diffuse urticaria and even erythema multiforme.[65] Rarely anaphylactic reaction may occur, usually as urticaria or angioedema.[67]

Often insects defecate while feeding, and parasite-laden faeces from infected bugs are source of *Trypanosoma cruzi* inocula, the causative organism of Chagas' disease.[66] Other insects of subfamily Triatominae may also transmit *T. cruzi*.

Kissing bug bite on face may produce Romaña sign, consisting of unilateral swelling of eye at site of initial infection with *T. cruzi* with localized lymphadenopathy. Swelling persists for weeks. Acute stage of Chagas is followed by indeterminate stage lasting ≥10 years.[66] Although considered pathognomonic of *T. cruzi* infection, the sign may occur after a bite in absence of *T. cruzi* transmission.[68]

FLEAS

Fleas are wingless haematophagous ectoparasites of birds and mammals, such as bats and humans [Figure 3]. Animal fleas bite humans coming in contact with infested animals. Flea bites produce maculopapular or papular rashes and severe pruritus (pulicosis).[69,70] Diagnosis is confirmed by examination of debris from pet's beddings[71] or presence of flea faeces, eczematous lesions or alopecia on pet's body.[1] Bites may produce psychological distress.[72] Treatment consists of eradication of flea infestation in the source animal.

Figure 3: Scanning electron micrograph of a flea with false colours (source: http://commons.wikimedia.org/wiki/File:Flea_Scanning_Electron_Micrograph_False_Color.jpg)

THRIPS

Bites produce tiny puncta and small, pink macules or papules.[73,74]

PAPULAR URTICARIA

Epidemiology

Usually occurring in 2 to 10 years old children, papular urticaria occurs occasionally in adolescents and adults.[75] Sensitization takes time; hence it is not seen in newborns.[76] Higher prevalence in children may result from immune mechanisms and/or behaviours predisposing them to contact with insects. Most children outgrow the disease probably due to desensitization by repeated exposures. There are no racial or gender predilections. The disease is common in summer and spring seasons when opportunities of bites are more.

Insects

Papular urticaria results from hypersensitivity reaction to bites of mosquitoes, fleas, bed bugs, midges, biting flies, and other arthropods (mites and ticks). Some authors also consider cutaneous hypersensitivity reactions following stings and contact with body parts of arthropods (spiders, caterpillars) under papular urticaria.[77] Different insects may be responsible in different regions.

Pathogenesis

First exposure to the bites does not produce reaction. On subsequent exposures, host response to salivary or contactant proteins causes eruption.[77] Exact immune mechanism is unknown; evidence supports involvement of types I, III, and IV hypersensitivity.

Evidence supporting involvement of type I hypersensitivity includes time frame of immediate reaction, formation of wheals, elevated mosquito saliva-specific IgE in papular urticaria caused by mosquito bites, correlation of immediate wheals and flares with mosquito salivary gland-specific IgE levels, and high levels of saliva-specific IgE levels in systemic reactions.[30]

Mosquito saliva-specific IgG antibodies, mainly IgG4 and IgG1, are raised in individuals with positive mosquito bite tests and those with severe local reactions, but not systemic reactions, to mosquito bites.

Levels of mosquito saliva-specific IgG correlate with sizes of both immediate and delayed skin reactions and with saliva-specific IgE levels.[30]

Immunoglobulin and complement deposits have been detected in skin suggesting that lesions may result from vasculitis.[78,79]

Predominance of CD4+ T cells in all lesions (vesicles, wheals, and papules) after cutaneous injection of flea antigens in patients suggests delayed-type hypersensitivity.[76] Furthermore, presence of abundant eosinophils throughout dermis in all lesions, as earlier reported,[80] supported involvement of both immediate and delayed mechanisms.[76]

Peripheral blood mononuclear cells from patients with papular urticaria after polyclonal stimulation predominantly respond with Th2 cytokine (IL-4) production, indicating that patients underwent an atopic stage predisposing them to the disease.[81] Similar Th2 predominant response occurred on stimulation of dendritic cells.[82]

Type I hypersensitivity reaction may cause the wheal, while delayed papule may result from type IV hypersensitivity.

Appearance of new lesions following new bites may be accompanied by lesions appearing on previously sensitized sites, indicating role of circulating antigen(s) which stimulate cutaneous T cells in previously sensitized sites.[77]

Clinical features

Patients present with chronic or recurrent eruption of wheals and itchy papules [Figure 4]. A mnemonic SCRATCH aids in diagnosis (S, symmetric distribution; C, crops of different coloration with erythema and pigmentary changes; R, pet (rover) unnecessary for diagnosis; A, age 2 to 10 years; T, target lesions and time taking weeks to years to resolve; C, confused paediatrician or parent; and H, household with single family member affected).[76]

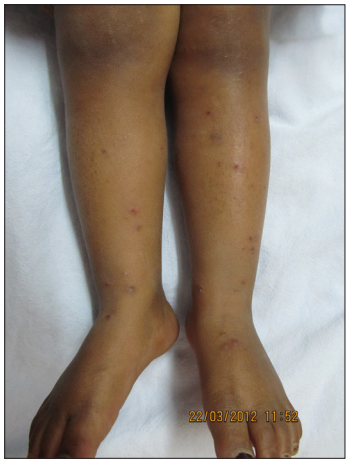

Figure 4: Lesions of papular urticaria in a 3 year old girl

Identifying culprit insect is difficult. Bullous papular urticaria, sometimes extensive, seen commonly in Iraq, may simulate serious bullous skin diseases.[83]

An eruption called harara (urticaria multiformis endemic), reported mainly in immigrants and children from Palestine after *Phlebotomus* bites, may be a form of papular urticaria.[84]

Histopathology

Mild acanthosis and spongiosis, exocytosis of lymphocytes, mild subepidermal edema, extravasation of erythrocytes, superficial and deep mixed inflammatory cell infiltrate of moderate density, and interstitial eosinophils are present. Depending on the predominant cellular infiltrate 4 subtypes (lymphocytic, eosinophilic, neutrophilic, and mixed) may be recognized.[80]

Treatment

Three "Ps" of management include protective clothing, pruritus control, and patience.[76] Treatment of insect bite reactions is symptomatic, with topical corticosteroids and antihistamines for mild reactions, short course of systemic corticosteroid for severe reactions, and management of anaphylaxis if it occurs.

PEDICULOSIS

Head and body lice were designated *Pediculus capitis* and *P. corporis* but they are now known to belong to same species, *P. humanus*.[85] Under the body louse genome project, genome of the body louse, smallest among insects (108 Mb), has been sequenced, offering unique information and tools for understanding co-evolution among vectors, symbionts, and pathogens.[86]

Treatment

Increasing resistance and adverse effects have raised concerns about head lice treatments,[87] encouraging search for new treatments [Table 4].[88-103] No available pediculicide is 100% ovicidal, and resistance to lindane, pyrethrins, permethrin, and malathion has been reported.[100] Nits persist after the treatment and may be mistaken for active infestation [Figure 5].

Table 4: Recent research on new treatments for head lice[88-103]

Treatment	Mechanism	Comment
Ivermectin (vs. malathion)	Interrupts γ-aminobutyric acid–induced neurotransmission.	Ivermectin (400 μg per kilogram body-weight) vs. 0.5% malathion lotion, each given on days 1 and 8, showed ivermectin to be superior.[88]
Spinosad 0.9% suspension	Interferes with nicotinic acetylcholine receptors, producing neuronal excitation and subsequent neuromuscular fatigue of insects.[89]	A derivative of actinomycete *Saccharopolyspora spinosa*, a natural mixture of pediculicidal tetracyclic macrolides spinosyn A and spinosyn D,[89] ovicidal, kills both permethrin-susceptible and permethrin-resistant lice,[90] approved by the US Food and Drug Administration (FDA) in January 2011 for treatment of head lice in patients ≥ 4 years of age. Two phase III, multicenter, randomized, trials compared 0.9% spinosad to 1% permethrin in patients aged ≥6 months under actual-use conditions.[91] About 85% of spinosad-treated participants were lice free versus about 43% permethrin-treated participants ($P < .001$). Most spinosad-treated participants required 1 application, whereas most permethrin-treated participants required 2 applications.[91]
Benzyl alcohol 5% lotion	Physical	First FDA-approved non-neurotoxic lice treatment, safe and effective in children as young as 6 months, not contraindicated in pregnancy, not ovicidal, applied for 10 minutes and repeated in 7 days, resistance unlikely as it works by asphyxiating lice.[92]
Dimeticone 4% lotion	Physical	Made from high molecular weight dimeticone in cyclomethicone base, 4 randomized controlled trials have shown its high efficacy.[93-96] 15-minute application also effective.[97] Lice unlikely to develop resistance due to its physical action.
Isopropyl myristate 50% rinse	Physical	Assessed in two phase II trials (a non-randomized trial without a comparator and a randomized trial comparing 50% IPM rinse with pyrethrin 0.33%, piperonyl butoxide 4%), found to be a safe and effective. Mechanical mechanism of action makes development of resistance unlikely.[98]
Suffocant (vs. malathion)	Physical	A randomized multicentre, phase IV trial compared a suffocant [paraffinum liquidum, isopropyl myristate, lauretth-3, butylenes/ethylene/styrene copolymer, ethylene/propylene/styrene copopymer, carthamus tinctorius (safflower oil) and butylated hydroxytoluene] with malathion for head lice in children, suffocant more effective than malathion and with low incidence of mild adverse events.[87]
Essential oils pediculicides vs. suffocant	Mechanism of action of essential oils unclear	A randomized trial comparing efficacy of melaleuca oil (tea tree oil) and lavender oil pediculicide (TTO/LO); eucalyptus oil and lemon tea tree oil pediculicide (EO/LTTO); and a "suffocation" pediculicide (containing benzyl alcohol, mineral oil, polysorbate 80, sorbitan monooleate, Carbopol 934, water, and triethanolamine) showed these to be ovicidal in 44.4%, 3.3%, and 68.3%, respectively.[99]
Hot air	Desiccation	A non-chemical treatment using a machine producing controlled hot air,[100] 30-minute application of hot air used to desiccate the lice. One study demonstrated nearly 100% mortality of eggs and 80% mortality of hatched lice,[101] another showed overall mortality of lice and eggs as 94.8% and no adverse effects.[102] Head lice are unlikely to evolve resistance.
Egg-loosening products	None	Eggs difficult to remove because they are fixed to hairs by a proteinaceous secretion that hardens within seconds,[103] persistent eggshells harmless but unsightly and mistaken for active infestation, no evidence found that egg-loosening products have any efficacy.[103]

A recent systematic review on pediculosis capitis including articles published till June 2010 concluded: malathion lotion may increase lice eradication compared with placebo, phenothrin, or permethrin; current best practice is to treat with two applications 7 days apart, and to check for cure at 14 days; studies comparing malathion or permethrin with wet combing have given conflicting results, possibly because of varying insecticide resistance; oral ivermectin may be more effective than malathion in people with previous failed treatment with insecticides; although tested in a clinical trial, oral ivermectin is not currently licensed for treating head lice, and generally its likely usefulness has been superseded by introduction of physically

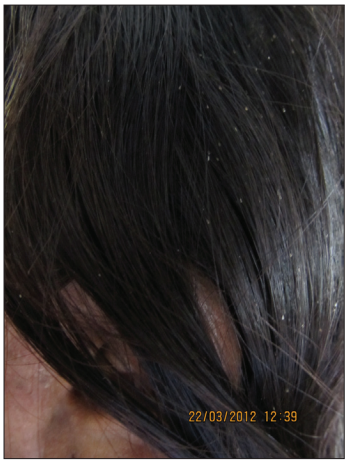

Figure 5: Numerous nits in a 15 year old girl with pediculosis capitis

acting chemicals that are not affected by resistance and are considered safer; permethrin may be more effective than placebo or lindane; eradication may be increased by adding trimethoprim–sulfamethoxazole to topical permethrin, although this increases adverse effects; we don't know whether combinations of insecticides are beneficial compared with single agents or other treatments; dimeticone may be more effective compared with malathion or permethrin; dimeticone and phenothrin have produced similar results, but this may be because of varying insecticide resistance and formulation of phenothrin used; we don't know whether pyrethrum is beneficial compared with other insecticides; some herbal and essential oils may be beneficial compared with other treatments but this likely depends upon the compound(s) or extracts used; isopropyl myristate may be more effective than permethrin; benzyl alcohol may be more effective than placebo, however, we don't know whether benzyl alcohol is more effective than insecticides or other treatments; and spinosad may be more effective at eliminating lice than permethrin.[104]

Permethrin resistance

Permethrin acts by its agonist action at voltage-gated sodium channels (VGSC) in nervous systems of insects. Selective point mutations in α-subunit gene of VGSC result in nerve insensitivity, resulting in resistance known as knockdown resistance (kdr).[105,106] For efficient monitoring of head lice resistance in field based on kdr genotype molecular tools (quantitative sequencing, real-time PCR amplification of specific allele, serial invasive signal amplification reaction) have been developed.[105]

Surprisingly, a recent report from Germany has questioned that kdr gene is responsible for treatment failure.[107] Kdr–like gene was detected in up to 95% of head lice in Europe, which contrasts with reported low rates of treatment failure with permethrin. Treatments with 0.5% permethrin and 0.3% pyrethrin were effective in 93% and 74% of children, respectively, whose head lice carried kdr-like gene. Authors concluded that in *Pediculus capitis* populations examined, the kdr-like gene did not correlate with failure of permethrin or pyrethrin treatment and that further studies are necessary to identify all possible contributors to pyrethroid resistance, including attributes of head louse and host factors.[107] It may be possible that permethrin is acting by some hitherto unknown mechanism or its vehicle is acting as a suffocant.

INSECTS AS VECTORS OF DISEASES [TABLE 5]

Prevention of insect bites

This is achievable by protective clothing, insecticide sprays, residential insecticides, repellents, or by physical means using nets which may be insecticide-treated. Major classes of insecticides used to control mosquitoes are pyrethroid, organophosphate, carbamate and dichloro-diphenyl-trichloroethane (DDT).[108] Repellents are substances applied to skin preventing insects from biting. Most efficient repellents are diethyl-m-toluamide (DEET) and dimethylphthalate (DMP),[109] others being N, N-diethylphenylacetamide (DEPA),[110] para-Menthane-3, 8-diol (PMD),[111] picardin (icaridin, KB 3023),[112] and IR3535.[113] Neem oil has been found to have larvicidal activity in field conditions,[114] and has been shown to possess weak mosquito repellent activity.[115]

Rational repellent prescription for a child must take into account: age, active substance concentration, topical substance tolerance, nature and surface of the skin, number of daily applications, and the length of use in a benefit-risk ratio assessment.[113] The 4 repellents currently recommended by the WHO for their long lasting efficacy and tolerance are PMD, DEET, icaridin, and IR3535.[113] Minimum effective concentration of each of these agents for 3 hours efficacy against most arthropods is 20%.[113] Although the toxicity of topical repellent used sub-chronically and chronically is not well studied in paediatric age groups, current French recommendations are as follows: once daily use of topical repellent in infants above 6 months, 2 applications daily from ages 1 to 12 years, and 3 applications daily after 12 years.[113]

Synthetic pyrethroids are now commonly used as they cause less ecological problems and are available as sprays, vaporizing mats, mosquito coils or in combination with physical means such as bed-nets.[109] Although ineffective against mosquitoes, systemic vitamin B1, acoustic devices and so-called electrocuting light traps are still sold and used.[109]

Pyrethroids resistance among insects is increasing, necessitating study of its implications for insect bites and insect-borne diseases.[116,117]

Long-term exposure to mosquito coil smoke (MCS) might induce asthma and persistent wheeze in children.[118] Mosquito coils containing pyrethroid insecticides, particularly d-allethrin, may contain

Table 5: Insects as vectors

Name of vector	Human disease caused	Causal organism
Mosquitoes	Malaria (exclusively by *Anopheles* species)	*Plasmodium* sp
	Filaria	*Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*, *Loa loa* (the African eye worm), *Mansonella streptocerca*, *Onchocerca volvulus*, *Mansonella perstans*, *Mansonella ozzardi*
	Fever and/or encephalitis	Dengue virus, Chikungunya virus, Yellow fever virus, West Nile virus and others
Sandflies (*Phlebotomus*)	Cutaneous and visceral leishmaniasis in Old World	*Leishmania* sp.
	Sandfly or papatasi fever	*Vesiculovirus* and *Phlebovirus*
Sandflies (*Lutzomyia*)	Cutaneous and visceral leishmaniasis and bartonellosis in New World (Carrión disease)	*Leishmania* sp.
Blackfly (family Simuliidae)	Onchocerciasis	*Onchocerca volvulus*
	Tularaemia	*Francisella tularensis*
Tabanid/horse flies (family Tabanidae, *Tabanus* sp.)	Tularaemia	*Francisella tularensis*
Deer/mango flies (family Tabanidea, *Chrysops* sp.)	Loa loa filariasis	*Loa loa*
Tsetse fly (family Muscidae)	Human African trypanosomiasis (sleeping sickness)	*Trypanosoma brucei* sp.
Cat fleas (*Ctenocephalides felis*)	Cat-scratch disease and bacillary angiomatosis	*Bartonella henselae*
	Bubonic plague	*Yersinia pestis*
	Endemic typhus	*Rickettsia typhi*
	Flea-borne spotted fever	*Rickettsia felis*
Tropical rat flea (*Xenopsylla cheopis*, *X. brasiliensis*)	Bubonic plague	*Yersinia pestis*
Bugs (Triatomines, subfamily Triatominae, family Reduviidae)	Chagas' disease (American trypanosomiasis)	*Trypanosoma cruzi*
Body lice	Epidemic typhus	*Rickettsia prowazeki*
	Louse-borne relapsing fever	*Borrelia recurrentis*
	Trench fever/endocarditis	*Bartonella quintana*

octachlorodipropyl ether (S-2, S-421). Their use likely exposes individuals to an extremely potent lung carcinogen bis(chloromethyl)ether (BCME) formed from combustion of coils.[119] Prolonged exposures that recur in homes must be studied. Use of mosquito coils containing S-2 is illegal in US.[119] Case control studies have linked exposure to MCS to lung cancer[120] and nasopharyngeal carcinoma.[121] It may be prudent to instead use physical means such as bed-nets and window-nets for prevention of insect bites.

Topical ivermectin and 1,2-octanediol for head lice

Two studies, reporting 3 randomized controlled trials, have shown about 74% cure rate with a single 10-minute application of 0.5% ivermectin lotion.[122,123] Another randomized controlled trial showed that two 8-hour 7 days apart applications of a physically active surfactant, 5% 1,2-octanediol lotion, cured around 80% patients with superiority over 0.5% malathion liquid.[124] Octanediol is the first surface active chemical to be tested for head lice.[124]

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Multiple Choice Questions

1. All of the following insects bite except:
   a. Mexican chicken bugs
   b. Assassin bugs
   c. Deer keds
   d. Beetles

2. Which of the following statements is incorrect about mosquito bites?
   a. The skin reaction is due to toxins injected during the bite.
   b. Salivary gland surface proteins are immunogenic.
   c. Patient develops only wheals in stage 4.
   d. Human sweat attracts mosquitoes.

3. Which of the following set of variables is not associated with higher probability of being bitten by mosquitoes?
   a. Increasing age in children, male gender, large body size.
   b. Pregnancy, alcohol intake, increasing age in children.
   c. Lipoatrophy in a patient on antiretroviral therapy, male gender, darker skin colour.
   d. Beer ingestion, large body size, body heat.

4. Peripheral blood lymphocytes and dendritic cells in patients with papular urticaria have been shown to predominantly respond to stimulation by
   a. Production of Th1 cytokines
   b. Production of Th2 cytokines
   c. Increased expression of CD 14
   d. Increased expression of CD 19

5. Which of the following evidences does not suggest involvement of type I hypersensitivity in papular urticaria:
   a. Correlation of immediate wheals and flares with mosquito salivary gland-specific IgE levels.
   b. High levels of mosquito salivary gland-specific IgE levels in individuals with systemic reactions.
   c. Correlation of mosquito saliva-specific IgG with saliva-specific IgE levels.
   d. Time course of reaction and formation of wheals.

6. Haematosiphoniasis is caused by:
   a. Assassin bugs
   b. Kissing bugs
   c. Blandford flies
   d. Mexican chicken bugs

Contd...

7. Which of the following agents used for treating head lice is neurotoxic:
   a. Spinosad
   b. Isopropyl myristate
   c. Benzyl alcohol
   d. Dimeticone

8. Permethrin acts as an insecticide by:
   a. Its action on nicotinic acetylcholine receptors.
   b. Its action on voltage-gated sodium channels.
   c. Asphyxiating lice.
   d. Its egg-loosening property.

9. Which of the following statements is incorrect?
   a. kdr resistance results in lice nerve insensitivity to permethrin.
   b. kdr-like genes are commonly detected in head lice.
   c. Permethrin is now generally ineffective in treatment of head lice.
   d. There is an emphasis on developing pediculicide which act by physical mode.

10. Which of the following methods of preventing insect bites has been found to increase risk of serious diseases?
    a. Pyrethroid insecticides
    b. Mosquito coils
    c. Vaporising mats
    d. Insect repellents

Answers:
1. d, 2. a, 3. c, 4. b, 5. c, 6. d, 7. a, 8. b, 9. c, 10. b