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REVIEW ARTICLE

Bed Bug Infestation: An Updated Review

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Abstract: In the past decade, there has been a global resurgence of bed bug infestations, especially in developed countries. Proper awareness and identification of bed bug infestations are essential to guide treatment and eradication. The purpose of this article is to familiarize physicians with bed bug bites so that they can effectively diagnose, treat, and address questions about bed bug bites and infestations. Bed bug bites are often painless. Typical reactions include pruritic, erythematous maculopapules occurring in clusters or in a linear or curvilinear distribution in exposed areas of the body. A small red punctum may be visualized at the center of the bite mark. Lesions that appear three in a row and papules on the upper eyelid associated with erythema and edema are highly suggestive of bites from bed bugs. Exaggerated local reactions such as vesicles, urticarial wheals, urticarial perilesional plaques, diffuse urticaria, bullae, and nodules may occur in previously sensitized individuals. Reactions to bed bug bites are self-limited. As such, treatment is mainly symptomatic. Topical pramoxine and oral antihistamines can be used to alleviate pruritus. Topical corticosteroids can be used for significant eruptions to control inflammation and pruritus, and to hasten resolution of the lesions. Integrated pest management, an approach for the eradication of bed bugs, includes monitoring devices (active monitors include the use of heat or carbon dioxide attractants and passive monitors include the use of sticky pads for trapping), and judicious use of nonchemical and chemical treatments known to be effective. Nonchemical interventions include keeping affected areas clean and free of clutter, vacuuming, washing linens with hot water, caulking wall holes and cracks where bugs can hide, proper disposal of highly infested items, and placement of bed bug traps/interceptors at the base of beds and furniture. Chemical interventions involve the use of insecticides such as synthetic pyrethroids, silicates, insect growth disruptors, carbamates, organophosphates, neonicotinoids, diethyl-meta-toluamide, chlorfenapyr, fipronil and plant essential oils. Insecticides should be used with caution to prevent over-exposure and toxicity (in particular, cardiovascular and neurologic toxicity), especially if there are young children around. It is important to note that multiple mechanisms of insecticide resistance exist and as such, chemical treatment should only be undertaken by trained professionals who understand the current literature on resistance. Both nonchemical and chemical technologies should be combined for optimal results.

Bed bug infestations may cause diverse dermal reactions, stigmatization, poor self-esteem, emotional stress, anxiety, significant adverse effect on quality of life, and substantial socioeconomic burden to society. As such, their rapid detection and eradication are of paramount importance. Consultation with a professional exterminator is recommended to fully eradicate an infestation.

Keywords: Cimex, papular urticaria, pruritic papules, pyrethroids, urticarial wheals, bed bug infestations.

1. INTRODUCTION

Bed bugs are hematophagous arthropods that can infest human dwellings and inflict bites to humans [1]. In recent years, there has been a global resurgence of bed bug infestations, especially in developed countries [2-6]. Physicians should familiarize themselves with bed bug bites to effectively diagnose, treat, and answer questions about bed bug bites and infestations. A review of the topic is therefore in order and is the purpose of the present article. This review covers mainly literature published in the previous ten years.

2. ENTOMOLOGY

Bed bugs are obligate hematophagous ectoparasites that belong to the phylum Arthropoda, the class Hexapoda (In-

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secta), the order Hemiptera, the family Cimicidae, and the genus *Cimex* [1, 7]. *Cimex lectularius* (the common or temperate bed bug) and *Cimex hemipterus* (the tropical bed bug) are the two main species that feed primarily on humans [6, 8]. *Cimex* is derived from the Roman word for "bug" and *lectularius* from the Latin word for "bed" or "couch" [9]. While humans are the preferred host, *C. lectularius* and *C. hemipterus* can feed on other warm-blooded mammals and birds [10-13]. The term “bed bug” is a misnomer as bed bugs tend to hide not only in beds, but also in other indoor harborages that provide easy access to the human host. [14].

Adult bed bugs are reddish-brown, flat, oval-shaped, wingless insects, typically 4 to 7 mm long, with females slightly larger than males [7, 15, 16]. Latter instars and adults are easily visible without magnification. Bed bugs are usually brown in color and turn dull red or violaceous and increase in size after feeding [7, 9]. They have a “buggy” or "sickly sweet" odor [4, 17]. Bed bugs have 3 pairs of legs, a pyramid-shaped head, a retroverted, slender and elongated piercing-sucking labium (mouthparts), widely spaced compound eyes, a pair of four-segmented antennae, a small semicircular to triangular scutellum (dorsal sclerotic plate) behind the pronotum (plate-like structures covering the dorsal thorax), and an 11-segment abdomen (Fig. **1**) [1, 18-20]. Short lateral hairs can be observed along the margins of the upper thorax. Males have a pointed abdomen at the apex while the females have a more rounded abdomen [4, 11]. The female has a ventral notch or paragenital sinus on the posterior abdomen whereas the male has a paramere on only one side of the posterior abdomen [20].

Fig. (1). Appearance of a bed bug on dermoscopy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Adult females lay approximately 5 to 8 eggs per week for approximately 18 weeks when conditions are favorable (23ºC, 90% relative humidity) and with unlimited access to blood meals [4, 10]. The eggs are translucent or light cream-colored, elongated, and approximately 1 mm in length and half as wide [21]. They become progressively darker and larger as they develop [4]. Eggs typically hatch in 4 to 10 days [17, 22]. Newly hatched nymphs are pale and translucent [17]. Nymphs molt five times and mature into adults in 6 to 8 weeks [17, 23]. The female bed bug needs a blood meal to develop eggs and each nymph needs a blood meal before each molt [9].

The typical lifespan of bed bugs in temperate climates is 6 to 24 months [11, 17]. Bed bugs can survive 12 months without feeding and up to 24 months in cooler environments [17, 24]. However, males starved longer than 2 weeks will cease to mate, and females starved longer than 2 months produce fewer eggs than those starved for a much shorter period of time [24, 25].

Bed bugs are unable to fly or jump [24]. It has been shown that female bed bugs have more difficulty in climbing smooth surfaces compared with their counterparts, presumably because of the larger weight gain by female bed bugs after feeding [26]. Bed bugs are nocturnal, photophobic, live in groups, respond to aggregation pheromones when conditions are favorable and disperse when conditions are unfavorable [20, 27]. Five volatile components (dimethyl disulfide, dimethyl trisulfide, 2-hexanone, (E)-2-hexanal, (E)-2-octenal) and one less-volatile component (histamine) of bed bug aggregation pheromones have been identified [28]. The former five volatile components attract bed bugs to safe shelters and the latter less-volatile component causes their arrestment upon contact [28].

During the day, bed bugs hide in surrounding habitat in close proximity (usually within 2 meters) to where their hosts sleep or rest [29, 30]. Bed bugs tend not to live on the human body, and they return to their haborage after feeding [10, 31]. They prefer to hide along seams in the mattresses, in cracks and crevices of box springs and mattresses, upholstered furniture, backsides of headboards, between wooden floorboards, and behind loose pieces of wallpaper [20, 30, 32]. Bed bugs prefer black, blue, and red harborages more than other colored harborages [33]. They tend to avoid glossy or smooth surfaces [2]. Bed bugs can withstand temperatures from 7°C to 45°C [6]. Exposure to a much higher temperature, on the other hand, may reduce the feeding and inhibit the development of bed bugs [34]. Bed bugs have lipid-based physicochemical properties that protect them against insecticides [35].

3. PATHOPHYSIOLOGY

At night, bed bugs crawl to their host to feed, being attracted to the host by body warmth, sweat, odor, and exhaled carbon dioxide [36-42]. The peak feeding times occur between 1 and 5 am, usually while the victim is asleep or resting [4]. Each feeding typically lasts 3 to 12 minutes [15]. Usually, an adult bed bug sucks blood from the host every 2.5 to 4 days [43, 44]. During feeding, bed bugs grasp the human skin with their forelegs [20]. The mouthparts which are normally held close beneath the head and thorax, swing down before feeding [13]. The bed bugs then pierce the skin with their proboscis which is composed of two elongated extremely fine needle-like stylets. The first stylet secretes several substances including anesthetic compounds, vasodilators (such as nitrophorin), anticoagulant factors (*e.g.*, factor-X inhibitor), apyrase (*e.g.*, adenosine triphosphate-diphosphohydrolase) which is a platelet- activation and aggregation inhibitor, and pharmacologically active substances (*e.g.*, hyaluronidase, proteases, kinins) [10, 23, 45, 46]. The second stylet extracts blood either directly from the capillary or from the extravasated blood from damaged tissue [17]. Bed bugs can increase in weight by 150 to 200% and length

by 30 to 50% after a feed [9, 47]. Cutaneous reactions such as erythema and wheals are caused by the pharmacologically active substances such as various proteins found in the saliva of bed bugs [10, 48]. The type of reaction depends on the immunocompetence and sensitivity of the individual [13]. Repeated exposure may sensitize the individual, leading to more severe cutaneous or systemic hypersensitivity reactions [23, 49].

4. EPIDEMIOLOGY

Both sexes are equally affected. Bed bugs are found internationally but are more prevalent in areas of lower socioeconomic status [50-52]. *Cimex lectularius* is most prevalent in temperate climates whereas *C. hemipterus* is most prevalent in tropical regions within 30 degrees of the equator. In recent years, both C. *lectularius* and *C. hemipterus* have been found outside their traditional zones of infestation [51]. Wang *et al.* [53] examined bed bug prevalence in 2,372 low-income apartments in four New Jersey cities using a combination of resident interviews, brief visual inspections, and monitoring with Climbup Insect Interceptors. Infestation rates ranged from 3.8% to 29.5%, with an overall infestation rate of 12.3% [53]. Sheele *et al*. [54] surveyed 706 patients in an emergency department in Cleveland, Ohio, about their experiences with bed bugs. Of the 706 patients, 2% had a current bed bug infestation, 37% had a history of bed bug infestation, 15% currently knew someone with an active infestation, and 59% knew someone who had bed bug infestation within 5 years. It is estimated that 1 in 5 Americans either has had a bed bug infestation in their home or knows someone who has had a bed bug infestation [4]. Areas of high occupant turnover, such as hotels (especially low budget ones), motels, hostels, nursing homes, dormitories, low-income, high-rise apartments, and shelters for the homeless are more frequently affected [17, 29, 50, 55]. Bed bug infestations are also common in refugee camps [22]. Other predisposing factors include poverty, overcrowding, homelessness, poor hygiene, and poor pest control [4, 17].

The recent resurgence in bed bugs especially in developed countries has been attributed to evolving resistance to pesticides (*e.g*., pyrethroids, carbamates, organophosphates), inadequate pest control programs, lack of public awareness, more frequent travel (especially international travel), and immigration [56-58]. Bed bugs are usually transported passively, mainly in luggage, book bags, clothing, and furniture [2, 59, 60]. Less commonly, bed bugs may spread actively from room to room in communities, such as through ventilation ducts, power outlets, and electrical wiring [61]. Skin-to-skin transfer of bed bugs is rare, owing to the nocturnal nature of bedbugs and the fact that bedbugs tend to avoid moving hosts [10].

5. HISTOPATHOLOGY

Histologic examination of a classic lesion shows epidermal spongiosis, dermal edema, and perivascular eosinophilic and lymphocytic infiltrates [4, 62]. Extravasated erythrocytes may also be noted [21].

6. CLINICAL MANIFESTATIONS OF BED BUG BITES

Typically, bed bug bites are painless [7, 63]. Clinically, bites are distributed in exposed areas of the body which are not covered by clothing, such as the arms, forearms, wrists, legs, ankles, neck and face and are often noticed upon awakening [16, 50, 64]. Bed bugs cannot bite through physical barriers such as cloth or paper [21]. Local bite reactions depend on the host's prior sensitivity. Approximately 50% of individuals react to the first bite [62, 65].

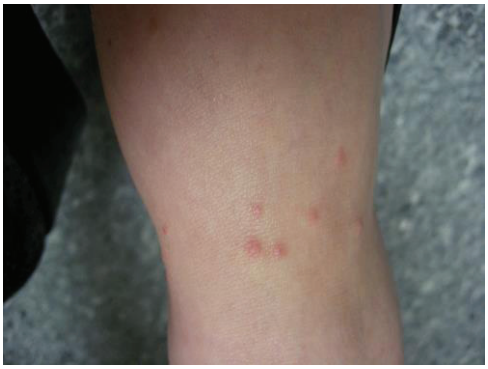

Fig. (2). Bed bug bites presenting as erythematous macules and papules (papular urticaria). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

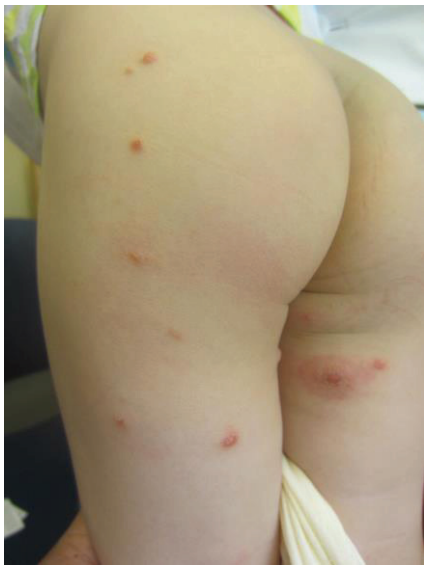

Fig. (3). Erythematous urticarial papules (papular urticaria) resulting from bed bug bites. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Typical reactions include pruritic, erythematous macules and papules, also known as papular urticaria (Figs. **2** and **3**) which are usually 2 to 5 mm in diameter [17, 66]. Bites typically occur in clusters or in a linear (Fig. **4**) or curvilinear distribution (Fig. **5**) [67-69]. Lesions that appear three in a row (Fig. **6**), colloquially referred to as the "breakfast, lunch, and dinner" sign, are highly suggestive of bed bug bites [67-71]. A small red (hemorrhagic) punctum may be visualized at the center of the bite mark [8, 16]. Some lesions may have

a central crust or erosion (Fig. **7**). Most lesions resolve within one week [16, 20]. Some authors have noted that papules on the upper eyelid associated with erythema and edema (the "eyelid sign") consistent with arthropod bites are highly suggestive of bites from bed bugs [62, 72]. Exaggerated local reactions such as vesicles, urticarial wheals (Fig. **8**), urticarial perilesional plaques, diffuse urticaria, bullae (Fig. **9**), and nodules (may be hemorrhagic) may occur in previously sensitized individuals and these lesions are usually pruritic [2, 7, 73-80]. If there are large numbers of bites, lesions can be generalized [63]. Reactions can be immediate or delayed up to 2 weeks after a bite [16]. At times, skin reactions are so minor that they go undetected, and the only evidence of a bed bug may just be a small punctum [18]. Rarely, systemic reactions such as asthma and anaphylaxis may occur [73, 81].

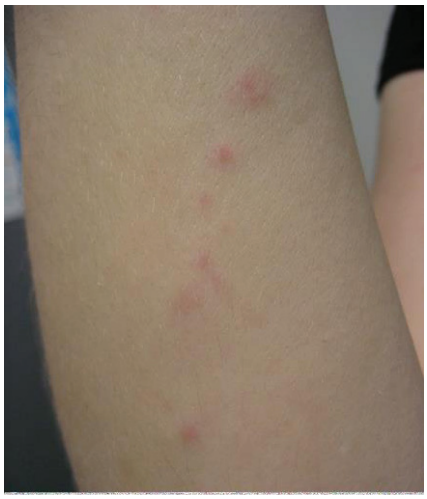

Fig. (4). Bed bug bites presenting as erythematous papules in a linear configuration. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

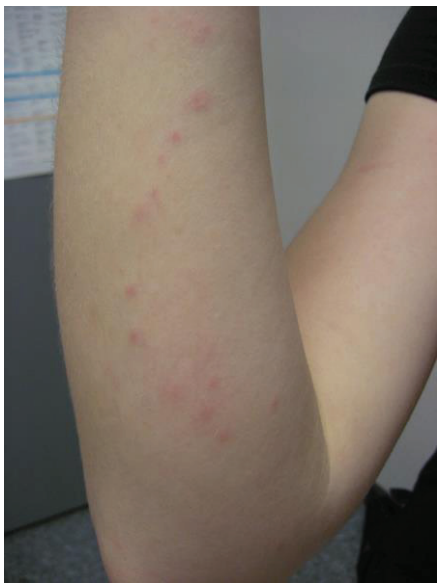

Fig. (5). Bed bug bites presenting as erythematous papules in a curvilinear configuration. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

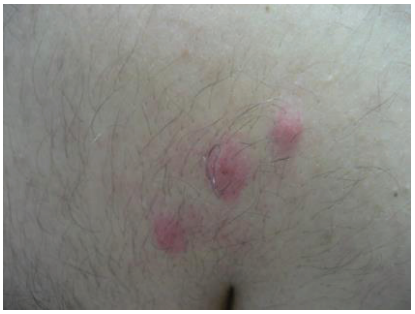

Fig. (6). Three lesions in a row, colloquially referred to as the "breakfast, lunch, and dinner" sign. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

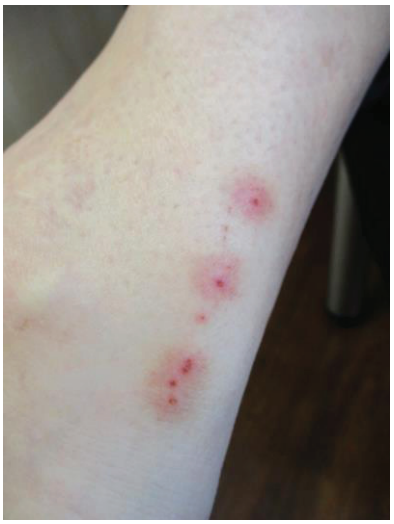

Fig. (7). Central crusts noted in some of bed bug bite lesions. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

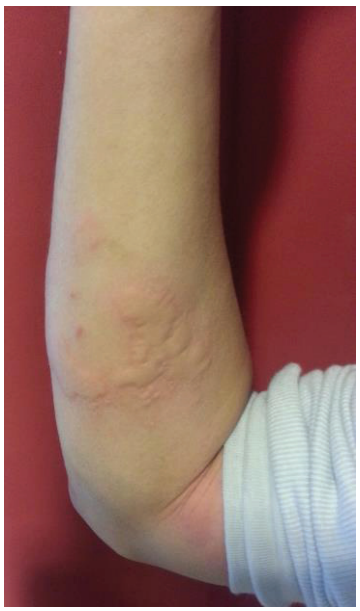

Fig. (8). Bed bug bites resulting in urticarial wheals. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

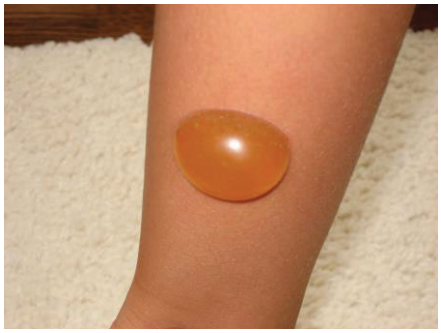

Fig. (9). A bullous eruption resulting from a bed bug bite. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

7. DIAGNOSIS

The diagnosis is suggested by the history (recent travel to infested areas, poor home environment, residence within building with known bed bug infestation, concurrent infestation among cohabitants, use of previously owned furniture), clinical findings of bites (tiny hemorrhagic punctum, pruritic erythematous maculopapules and wheals in clusters or linear pattern in exposed areas of the body), and findings of flecks of blood on bed linen, dark brown insect fecal droplets, exoskeleton casts, and identification of bed bugs in cracks and crevices of mattress seams, box springs, and upholstered furniture [16, 30]. Dermoscopy is a useful tool to observe the tiny hemorrhagic punctum (bite spots) in a background of diffuse erythema [82-84]. With heavy infestation, a pungent "sickly sweet" malodor may be detected. In the majority of cases, the diagnosis can be confirmed by visual identification of the bed bug.

From a public health perspective, use of a trained bed bug-detection dog is gaining popularity [80, 85-87]. In one study, the diagnostic accuracy was 96.3% with a positive predictive value of 83.3% and a negative predictive value of 99.1% [85]. Lateral flow strip tests for detecting specific proteins in biological samples can be used for the detection of the bed bug specific proteins in the sample, thus allowing the diagnosis of bed bug infestation to be made without the expertise of an entomologist [88]. Proper identification of bedbug infestation is essential to guide treatment and eradication.

8. DIFFERENTIAL DIAGNOSIS

Swallow bugs (*Cimex vicarius*) and bat bugs (*Cimex adjunctus*) may incidentally bite humans although humans are not the preferred host [22]. These bugs may produce bites similar to bed bug bites. Examination of the insect by an entomologist can aid in the diagnosis. In general, swallow bugs are smaller than bed bugs, are grayish in color, have long, fine body hairs, and visible antennae. Swallow bugs infest the nests of swallow birds. Bat bugs have longer lateral hairs (longer than the diameter of the eye) on the upper thorax than in the bedbugs (shorter than the diameter of the eye) and they stay close to their bat hosts and only wander to other hosts when abandoned [22].

Bed bug bites should be differentiated from scabies and other arthropod bites. Scabies, an infestation of the skin caused by the mite *Sarcoptes scabiei var. hominis*, is characterized by burrows, an erythematous papular eruption, and intense pruritus typically worse at night [89, 90]. Burrows which are pathognomonic of the disease, appear as serpiginous grayish, whitish, reddish, or brownish lines several millimeters long in the upper epidermis usually in the intertriginous regions and the interdigital web spaces. Finding the mite, ova, or scybala on microscopic examination of scrapings taken from skin lesions confirms the diagnosis. The use of dermoscopy in patients with scabies reveals a sinuous burrow with a brown jet-shaped triangular structure ("delta wing jet" or "mini triangle" sign) composed of the pigmented head and anterior legs of the mite. Flea bites are characterized by irregular groups of multiple erythematous pruritic wheals with a central punctum on the lower legs (especially ankles) and are more often seen in pet owners [6, 91]. Mosquito bites present as urticarial papules and wheals and occur on exposed areas only. Tick bites present as an asymptomatic papule which may evolve into an annular lesion at the site of a tick bite (in exposed areas of the body) in the case of Lyme disease [91]. Central clearing of the lesion as the lesion expands, gives rise to "bull's eye" or "target" appearance [91]. Tick bites are more commonly seen in pet owners and hikers especially during the spring and summer.

Other differential diagnoses include drug eruptions, food allergies, urticaria, chickenpox, contact dermatitis, erythema multiforme, dermatitis herpetiformis, pityriasis lichenoides et varioliformis acuta, prurigo nodularis, lymphomatoid papulosis, Grover disease, Sweet syndrome, Gianotti-Crosti syndrome, and delusional parasitosis [92-104]. The distinctive features of each condition usually allow for a straightforward differentiation from bed bug bites.

9. COMPLICATIONS

Post-inflammatory pigmentary changes may occur but are usually transient [62]. Scratching can lead to secondary bacterial infection including impetigo, cellulitis, folliculitis, ecthyma, and lymphangitis usually caused by *Staphylococcus aureus* or group A streptococci [13]. Scratching may lead to excoriation and may increase the severity of existing skin conditions, such as atopic dermatitis and psoriasis. Itching may lead to sleep deprivation, reduced ability to concentrate, tiredness, and somnolence [105].

With heavy infestations, iron deficiency anemia may result from chronic blood loss [43, 106-108]. Otitis externa has been reported as a result of bed bug infestation in the ear canal [82]. Rarely, bed bug bites may result in anaphylaxis especially in individuals with a history of atopy [22].

Bed bug infestation can also lead to social stigmatization, poor self-esteem, anxiety, nervousness, psychological distress, nightmares, hypervigilance, flashbacks, avoidance behaviors, depression, and posttraumatic stress disorder [45, 109-112]. One case of suicide resulting from bed bug infestation has been reported [113].

Bed bug bites can have a significant adverse effect on quality of life [6]. Also, the economic burden in the eradication of bed bug infestation can be substantial [6]. Although pathogens such as hepatitis B virus, hepatitis C virus, human immunodeficiency virus, *Leishmania* parasites, *Francisella tularensis*, *Borrelia burgdorferi*, *Bartonella quintana*, *Wolbachia*, *Rickettsia parkeri*, and *Trypanosoma cruzi* have been detected in bed bugs, thus far, there is insufficient evidence that bed bugs are involved in the transmission of these infectious diseases to humans [114-119].

10. MANAGEMENT OF BED BUG BITES

Reactions to bed bug bites are self-limited and usually spontaneously resolve within one to two weeks [22]. As such, treatment is mainly symptomatic. Patients should be advised to maintain good dermal hygiene and to avoid scratching the lesions to reduce local reactions and to prevent secondary bacterial infection. Topical pramoxine and oral antihistamines (*e.g.*, diphenhydramine, hydroxyzine, loratadine, desloratadine, cetirizine, bilastine, rupatadine) can be used to alleviate pruritus and can help with urticarial reactions [23, 47, 120]. Topical corticosteroids can also be used, if the eruption is significant enough, to control inflammation and pruritus, and to hasten resolution of lesions [23]. In general, the least potent corticosteroid that can control symptoms should be used. Oral corticosteroids should be considered for severe or diffuse bullous lesions [73]. Secondary bacterial infection can be treated with topical antibiotics (*e.g.*, mupirocin, fusidic acid) and, in severe cases, with systemic antibiotics [17, 23]. Severe systemic reactions such as anaphylaxis may require treatment with intramuscular epinephrine, oral antihistamines, and oral corticosteroids [17, 20, 47]. Psychologic support should be offered if needed, especially for individuals with severe anxiety or secondary delusional parasitosis [22].

A recent study on 20 children with recurrent papular urticaria due to bed bugs unresponsive to multiple treatments (such as oral antihistamines, topical corticosteroids, eradication of bed bugs through application of insecticides in their homes) treated with subcutaneous specific immunotherapy (using whole body bed bug extract) showed significant improvement of papular urticaria [121]. The authors of the study suggested that immunotherapy has a protective effect against subsequent reactions to exposure to bed bugs by increasing IgG4 [121]. Further studies are necessary to confirm or refute the above findings.

11. ERADICATION OF INFESTATION

Bed bugs are difficult to eradicate because they breed quickly and are quite elusive [14]. In addition to the infested rooms, the adjoining areas should be inspected and treated meticulously. For eradication of bed bugs, integrated pest management (IPM) may be an effective approach. The IPM includes monitoring devices (active monitors include the use of heat or carbon dioxide attractants and passive monitors include the use of sticky pads for trapping), canine detection, and judicious use of nonchemical and chemical treatments known to be effective [122-124]. It has been shown that blood deprivation combined with heat stress increases the rate of eradication [125, 126]. Eradication of bed bug infestation requires the expertise of a professional exterminator [14]. Patients should refrain from initiating control measures themselves. Confirmation of live bed bugs two weeks after appropriate treatment indicates continued infestation [78].

11.1. Non-chemical Interventions

Generally, nonchemical interventions have a more immediate effect in reducing the number of bed bugs and are less hazardous than chemical interventions [4]. Nonchemical interventions include keeping affected areas clean and free of clutter, vacuuming, use of equipment to heat room to a lethal temperature (60°C) for bed bugs, steam treatment of furniture, washing linens with hot water, placing infested items into a freezer (temperature -17°C for at least two hours), caulking wall holes and cracks where bugs can hide, mattress encasements, proper disposal of highly infested items (sealed in plastic), and placement of bed bug traps/interceptors (*e.g.*, the "pitfall" style) at the base of beds and furniture [127-132]. Most traps use heat or semiochemicals (*e.g.*, carbon dioxide, kairomones) to attract bed bugs.

11.2. Chemical Interventions

Chemical interventions involve the use of insecticides such as synthetic pyrethroids (*e.g.*, permethrin, cyperpermethrin, alpha-cyfluthrin, beta-cyfluthrin, deltamethrin, lambda-cyhalothrin, bifenthrin), natural pyrethrins, silicates (mostly diatomaceous earth dust [DED]), insect growth disruptors, formerly termed insect growth regulators, (*e.g.*, lufenuron, novaluron, hydropene, methoprene, pyriproxyfen), carbamates (*e.g.*, propoxur, carbaryl, bendiocarb, metoxadiazone), organophosphates (*e.g.*, malathion, dichlorvos [2,2-dichlorovinyl dimethyl phosphate] [DDVP], diazinon, fenitrothion, trichlorfon, propetamphos, pirimiphos-methyl), neonicotinoids (*e.g.*, acetamiprid, clothianidin, fenthion, dinotefuran, imidacloprid, nitenpyram, thiocloprid, thiamethoxam), diethyl-meta-toluamide (DEET), chlorfenapyr, fipronil and plant essential oils [2, 62, 133, 134]. Application of residual insecticides remains the primary choice for eradicating bed bug infestations [133]. Insecticides can be applied to cracks in furniture, seams and buttons of mattresses, walls, and floors to eliminate bed bug infestation.

Insecticides should be used with caution to prevent overexposure and toxicity (in particular, cardiovascular and neurologic toxicity), especially if there are young children or pets around [135, 136]. One may want to note that DEET may modify the feeding behavior of bed bugs, in the sense that bed bugs exposed to DEET may take multiple blood meals instead of a single blood meal [13]. Also, extensive use of insecticides has resulted in resistance in bed bug populations.

By far, pyrethroids are the most commonly used insecticide for bed bug control [4]. Presumably, pyrethroids work by blocking sodium channel repolarization of the neuron of bed bugs through cell membrane channels with resultant

paralysis and eventual death [137-139]. Resistance to pyrethroids is increasing and is a growing global concern [140-148]. An important resistance mechanism against pyrethroids is resistance of target site caused by point mutations in voltage-gated sodium channel (*VGSC*) gene that results in substitutions of the amino acid sequence of the VGSC protein (also known as knockdown resistance) [141-151]. Other resistance mechanisms include increased activities of detoxication enzymes (such as hydrolytic esterases and microsomal oxidases) and cuticle thickening as a result of overexpression of cuticle depositing protein [152-154]. The addition of piperonyl butoxide may increase the efficacy of permethrin by overcoming the resistance mechanisms of some strains of bed bugs [4]. Natural pyrethrins have been found to be less effective.

Silicates work by absorbing lipids on the waxy surface of the epicuticle of the bed bug [4]. Bed bugs exposed to silicates can no longer maintain moisture and may die of dehydration [4]. Silicates are available in an aerosol or dust formulation. Several studies have shown dust-based formulations provide longer residual protection than aerosols and are therefore more efficacious [155, 156]. The advantages of using silicates are very low mammalian toxicity, long shelf-life, long residual life, and low possibility of resistance [4]. The main disadvantage is that silicates are slow acting and may take up to 6 days to achieve 100% mortality in bed bugs [4].

There are two main kinds of insect growth disruptors, namely, chitin synthesis inhibitors (*e.g*., lufenuron, novaluron) and juvenile hormone analogs, also known as juvenile hormone mimics (*e.g*., hydropene, methoprene, pyriproxyfen) [157]. Chitin synthesis inhibitors interfere with the formation of chitin. Juvenile hormone analogs work by disrupting the metamorphosis of nymphal stages of bed bugs, particularly at juvenile stages [4, 158]. Nymphs so treated tend to die during subsequent molts [4]. Female nymphs are more susceptible than male nymphs [158]. Although insect growth disruptors are slower acting than neurotoxic insecticides, they have a favorable safety profile, including low mammalian toxicity [153].

Carbamate insecticides are N-methyl carbamates derived from carbamic acid that cause reversible carbamylation of acetylcholinesterase at neuromuscular junctions and neuronal synapses [159, 160]. The resultant elevated acetylcholine may lead to increased neurotransmitter signalling, hyperpolarization, paralysis of nerves and muscles, and ultimate death of bed bugs [160]. An amino acid substitution mutation F348Y at an acyl-binding site of the paralogous acetylcholinesterase gene accounts for carbamate resistance in bed bugs [161].

Organophosphate insecticides work by causing irreversible inhibition of acetylcholinesterase at neuromuscular junctions and neuronal synapses [161]. In many countries, organophosphate insecticides are no longer available except in impregnated strips [4]. DDVP, a volatile organophosphate often formulated into resin strips, can be used for fumigation of infested items which are placed into sealed plastic bags with the strips [4, 162]. The efficacy can be increased with the use of heat and air circulation which will increase the volatility of DDVP [4, 162]. Substitution mutation of F348Y of acetylcholinesterase gene contributes to organophosphate resistance in bed bugs [161]. Penetration resistance through remodelling or thickening may also contribute to resistance to organophosphate insecticides [133, 152].

Neonicotinoids act selectively on the nicotinic acetylcholine receptors in the central nervous system of bed bugs, leading to depolarization and continuous firing in post-synaptic neurons, resulting in spastic paralysis and ultimate death of bed bugs [163]. Although neonicotinoids are less efficacious than some pyrethroids, they are efficacious against some pyrethroid-resistant bed bugs [4, 164]. Commercial formulations that contain a combination of a neonicotinoid and a pyrethroid are more efficacious in the treatment of bed bug infestation than either neonicotinoid or pyrethroid alone [165, 166].

Diethyl-meta-toluamide (DEET), a synthetic chemical repellent, works by blocking the neuronal responses within the olfactory receptor neurons or odorant receptors of bed bugs to specific human odors [167]. In addition, DEET may function as a stimulus that triggers avoidance behavior of bed bugs in response to human odors [167]. The product provides a high level of repellency against bed bugs [168, 169]. Pyrethroid resistance is associated with a decreased DEET repellency [170].

Chlorfenapyr is a pro-insecticide derived from a class of microbially produced compounds known as halogenated pyrroles. The pro-insecticide is converted to an active toxic metabolite (AC-303268) by cytochrome P450 monooxygenases of the insect [171, 172]. AC-303268 disrupts oxidative phosphorylation in the mitochondria, preventing the formation of adenosine triphosphate (ATP), which is vital for the survival of the insect [171, 172]. The product is available in aerosol and liquid spray formulations. Although chlorfenapyr is slow acting and does not cause quick knockdown, it has a long residual life and activity (up to 4 months) [164, 171, 173]. Chlorfenapyr is a nonrepellent and is effective against all bed bugs strains including multiple insecticide-resistant bed bugs [134, 172, 174]. The insecticide is particularly effective against first-instar nymphs [175]. Studies have shown that bloodmeal feeding increases the survival time of bed bugs exposed to topical application and fresh or aged residual deposits of chlorfenapyr [176, 177]. Chlorfenapyr has a relatively low toxicity to humans [164, 178] and resistance of bed bugs to chlorfenapyr is low [164].

Fipronil, a phenylpyrazole, works by blocking the ligand-gated ion channel of the gamma aminobutyric acid (GABA) receptor and glutamate-gated chloride channels of the bed bug. This causes hyperexcitation of nerves and muscles with eventual death of the insect. Fipronil, available as a spray and powder, is highly effective against bed bugs [164, 179]. Synergism with piperonyl butoxide increases the susceptibility of bed bugs to fipronil [163].

Many essential oils from plants (such as coconut oil, clove oil, tea tree oil, peppermint oil, lemongrass oil) have

insect repellent effects and insecticidal activities [180, 181]. Plant-derived essential oils have a favorable safety profile and have been used for the control of bed bug infestations [182-186].

12. PREVENTION

While awaiting eradication of bed bugs, it is reasonable to apply permethrin 5% cream or 40% DEET before going to bed to prevent bed bug bites [9].

Avoidance is the best means in the prevention of bed bug bites. Individuals should carefully inspect unfamiliar sleeping areas such as hotel rooms for bed bugs or their fecal droplets prior to use, with particular attention to mattress seams, crevices in box springs, and behind headboards [18, 20, 187]. Items purchased at second-hand stores or at garage sales should be carefully inspected for bed bugs before these items are brought into homes. Improving sanitation and increasing public health education, along with improved pest control strategies, can improve the control of bed bug populations [80].

13. PROGNOSIS

The overall prognosis is excellent as the local reactions usually resolve within one to two weeks assuming bed bugs have been eradicated from the sleeping areas of the patients [20, 23].

CONCLUSION

In recent years, there has been a global resurgence of bed bug infestations. As the infestations may cause diverse dermal reactions, stigmatization, emotional stress, significant adverse effect on quality of life, and substantial socioeconomic burden to society, their rapid detection and eradication are of paramount importance. Consultation with a professional exterminator is recommended to fully eradicate the infestation.

AUTHORS' CONTRIBUTIONS

Professor Alexander K.C. Leung is the principal author. Dr. Joseph M. Lam, Dr Benjamin Barankin, Dr Kin Fon Leong and Professor Kam Lun Hon are coauthors. All the authors contributed to drafting and revising the manuscript and approved the final version submitted for publication.

LIST OF ABBREVIATIONS

ATP	=	Adenosine Triphosphate
C.	=	Cimex
DDVP	=	2,2-Dichlorovinyl Dimethyl Phosphate
DED	=	Diatomaceous Earth Dust
DEET	=	Diethyl-meta-toluamide
GABA	=	Gamma Aminobutyric Acid
IPM	=	Integrated Pest Management
MALDI-TOF MS	=	Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry
VGSC	=	Voltage-gated Sodium Channel

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