

AN OVERVIEW ON SCRUB TYPHUS (MITE-BORNE TYPHUS): IS IT A NEGLECTED ZONOSIS DISEASE IN EGYPT?

By

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Abstract

Scrub typhus or bush typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi*), a gram-negative coccobacillus antigenic distinct from rickettsia typhus group. Infection begins insidiously with headache, anorexia, and malaise, or start abruptly with chills, severe headache, myalgias and high fever or pneumonitis, meningoencephalitis, jaundice-meningitis and/or meningo-encephalitis or even spontaneous pregnancy risky outcomes. An Escher or dark rash may develop in a subset of patients. Severe complicated infection can range from mild and signs symptoms to multi-organ systemic failure in elderly delayed treated patients. Diagnosis includes serology, biopsy, culture, and PCR. Scrub typhus as a non-specific clinical disease must be differentiated from other vector-borne diseases as malaria, dengue, chikungunya, other rickettsia diseases, and insect bites as well as leptospirosis and enteric fever as typhoid.

Key words: Chigger bites, Pathogenesis, Diagnosis, Miss-diagnoses, Treatment, Overview

Introduction

Mites belong to small arachnids (subclass Acari, class Arachnida), a hyper-diverse group with a global distribution, and 55,000 species, but hundreds of thousands more species yet discovered (Linn *et al*, 2024). Mites parasitize plants and animals as important nuisance pests, but zoonotic mites may produce cutaneous lesions, yield allergy, or act as vectors for infectious disease (Brennan and Goff, 1977). Trombiculidae Ewing, 1944 is one of the largest parasitic mite's groups of 2000 or 3000 species (Fernandes and Kul-karni, 2003).

Chigger bites from the larvae of Trombiculidae family (or chiggers) its synonyms include the harvest mites, harvest bugs, harvest lice, Mower's mites, and redbugs (McClain *et al*, 2009). The chigger must not be confused with Chagas disease caused by *Trypanosoma cruzi* (CDC, 2021), or jigger, or jigger flea that refers to chigoe flea or *Tunga penetrans* (Elston, 2006). Also, many arthropo-

ds species (insects, arachnids, millipedes and centipedes) bite or sting humans as a defense mechanism or during their normal feeding (Morsy, 2012). The hymenopterous sting reactions of sawflies, wasps, bees and ants are large local ones causing transient pain and redness for a few hours (local reaction), exaggerated swelling last for few days (large local), and dangerous immediate one is fatal anaphylaxis (Abdel-Rahman *et al*, 2015).

Adult trombiculid mite is 1 to 2mm in length, with a bright red or red-brown color. Life cycle passes through seven active and inactive lifecycle stages, but only the larva (0.15 to 0.3mm in length) is responsible for chigger bites, after hatching, they reside on the leaves or grass stems waiting for humans or animals to pass by (Neal and Barnett, 1961). Mites reproduce rapidly during warm weather between June and September and during favorable conditions, mites develop within 7 days, with 8 to 10 generations per season (Campbell *et al*, 1974). They can att-

ach to the host's skin and remain there for up to a few days. Subsequently, the larvae drop to the ground to mature into the harmless nymph and adult male and female (Lane and Crosskey, 1993). The nymph is similar to, but smaller than the adult; both live in the soil and feed on plants, other mites and small insects, or their eggs (Mullen and O' Connor, 2019).

Review and Discussion

Chigger mites are the main causative agents of acute dermatitis (trombiculiasis, or trombiculosis) globally in man and domestic animals, including pets, livestock, birds, and amphibians (Kunz *et al.*, 1969), and also bats (Morsy *et al.*, 1985). They are specific ectoparasites for days to months on reptiles, and wild & urban rodents (rats, mice, and voles); the main reservoir hosts (Ding *et al.*, 2021). Mites display parasite preferences including ears, face, nasal cavity and anus of rodents (Matthee *et al.*, 2020). The high transovarial and/or transracial transmission rates among chigger species play a marked role in Scrub typhus incidence and prevalence in the nature (Phasomkusolsil *et al.*, 2009).

Chiggers survive best in brushy, gardens, grassy, parks, or weedy areas with moisture at daytime (Gasser and Wyniger, 1955). Scrub typhus has a global distribution, outside Tsutsugamushi Triangle in subtropical, tropical and temperate zones (Moniuszko and Makol, 2014). There are more than 3,000 species, but only about 20 chiggers always attack humans (Binh *et al.*, 2020). Nielsen *et al.* (2021) reported that Trombiculoidea superfamily includes six families; of which Trombiculidae and Leeuwenhoekiidae larvae are vectors of scrub typhus, caused *O. tsutsugamushi*. They gave checklist of 3,013 accepted species, together with their zoogeographic distribution and synonyms.

In the USA and Europe, skin disease secondary to Chigger bites is commonest in summer and fall (Toldt, 1946). The relevant species were *Eutrombicula alfreddugesi* in North and South America, *Neotrombicula autumnalis* in Europe, and *Leptotrombidium* spp.

in Asia (Arlian, 2009).

In Africa, chigger mites based on materials deposited at the Royal Museum for Central Africa (Belgium), and the Natural History Museum (London) were 443 species of 61 genera (Stekolnikov, 2018).

In the Arab Countries, Radford (1954) in Yemen identified nine species of chiggers. Stekolnikov *et al.* (2012) reported a new genus and species from Oman; and Stekolnikov *et al.* (2019) identified a diverse chigger fauna from the southwestern Saudi Arabia. Stekolnikov and Mumcuoglu (2022) in Israel detected seven species of chiggers. Stekolnikov (2023) identified the chigger mites in the United Arab Emirates based on materials collected from preserved *Acomys dimidiatus* specimens, in the museum collection.

House dust mite (HDM) causes the most important allergies and affects about 65-130 million people globally (Huang *et al.*, 2023). In Egypt, *Dermatophagoides pteronyssinus*, *Ornithonyssus bacoti*, and *Haemogamasus pontiger* were reported in Qalyobia Governorate as causing human atopic dermatitis (Morsy *et al.*, 1994). *D. pteronyssinus*, *D. farinae*, *O. bacoti* and *H. pontiger* caused respiratory rhinitis and bronchial asthma (Morsy *et al.*, 1995). In Greater Cairo, nine HDM species detected indoors were *D. pteronyssinus*, *D. farinae*, *Tyrophagous putrescentiae*, *Acarus siro*, *Cheyletus malaccensis*, *Blomia kulagini*, *Acheles graciles*, *Lepidoglyphus destructor*, and *O. bacoti* (Koraïem and Fahmy, 1999). Also, Abdelgayed *et al.* (2019) in Assiut Governorate reported 175 mite species belong to 48 families on pomegranate trees of them was four *Trombicula autumnalis* (Trombiculidae) in Manfalout City. Gazoly *et al.* (2023) in Giza and Menoufia Governorates recovered 19 predatory mite species on vegetation. Nevertheless, none have reported chigger's bites or scrub typhus on man and/or animals or even birds.

Undoubtedly, the scrub typhus is a growing and emerging disease, grossly misdiagnosed in many countries due to the unspecific clinical picture, and low awareness and/or

clinical suspicion index (Rapsang and Bhattacharyya, 2013). Bonell *et al.* (2017) reported that scrub typhus global burden with an average rate of 23.4%, but with a range of 1-96.9% among humans' fever cases.

Pathogenesis: Trombiculid mites reach human skin via areas of easy access, such as pant cuff or shirt collar (Jones, 1950). Larva widely moves on skin searching for feeding area with high local air humidity or thin epidermis (Jones, 1987). They pierce the skin with their chelicerae and inject digestive enzyme-laden saliva to liquefy epidermal cells forming of a tube-like opening or stylostome (Hase *et al.*, 1978), larvae feed upon lysed tissue and lymphatic fluid, which bites induce skin irritation, and inflammation (Shatrov, 2009).

Clinical presentation: Cutaneous inflammation and intense pruritus are the classic clinical features as larval bites are painless, papular and papulovesicular cutaneous reactions are most common; less frequently urticarial, morbilliform, and bullous eruptions occur (Baker *et al.*, 1956). Chigger dermatitis can present as a red flat or raised lesion. A vesicle or pustule may also be present (Woloski *et al.*, 2018). Itching starts within few hours and resolves within few days; but can sometimes extend as long as two weeks (Wulandhari *et al.*, 2021). Lesions usually heal within one to two weeks, but in persons with extensive involvement, intense pruritus may inhibit sleeping and skin eruption for weeks (Potts, 2001). Papules were commonly in ankles, lower legs, below knees, waistline, and even groins (Kampen, 2000). The triad of penile swelling, pruritus, and dysuria or summer penile syndrome, causes a local hypersensitivity response lasted from a few days to a few weeks (Smith *et al.*, 1998).

Nevertheless, most patients have thrombocytopenia and may show elevated levels of ALT, AST, bilirubin, and/or creatinine. Splenomegaly and hepatomegaly may also occur. Severe manifestations usually occur after the first week of untreated cases and may include multiple organ dysfunction syndromes

with hemorrhaging, acute respiratory distress syndrome, encephalitis, pneumonia, renal, or liver failure, and fatal (Seong *et al.*, 2001).

Complications: The complications associated with scrub typhus spans across multiple organ systems causing severity and systemic affected on patients. These were 1- Pulmonary with cardiac complications (Rajapakse *et al.*, 2017), 2- Cardiac with uncertain pathogenesis (Jeong *et al.*, 2007), 3- Neurologic as meningitis or tuberculous meningitis (Rana *et al.*, 2017), & Meningoencephalitis leading to fatalities (Pradhan and Jindal, 2014), 4- Gastrointestinal with abdominal pain, & tenderness, indigestion, nausea, and vomiting with splenomegaly (Kim *et al.*, 2000), 5- Scrub typhus is implicated in vasculitis and perivasculitis of small blood vessels, duodenal ulcer perforation, peritonitis, and gastric ulceration (Sv *et al.*, 2017), 6- High fever can cause cranial nerve palsies, plexopathy, transverse myelitis, neuroleptic malignant syndrome and *Guillan Barré* syndrome (Mahajan and Mahajan, 2017). 7- Acute kidney injury is a predictor of mortality, and possible mechanisms include pre-renal failure due to septic shock, renal vessels vasculitis, rhabdomyolysis, and direct renal invasion (Sun *et al.*, 2014), & 8- Pregnant women with scrub typhus are at poor outcomes risk, such as preterm deliveries, miscarriages, and delivery of small-for-gestational-age babies, or even neonatal deaths (Rajan *et al.*, 2016). However, treatment for scrub typhus pregnant women should be determined in consultation with an expert in infectious diseases.

Diagnosis: Chigger bites diagnosis is supported by a history of recent outdoor activities in a chigger-infested area, and appearance of pruritic grouped papules, papulovesicles, or bullae in skin sites (Farkas, 1979).

Diagnosis relies on serologic tests, mainly IFA, whereby the illness is identified by a 4-fold increase in antibody titers in paired sera and/or a positive IgM titer in a single serum sample (Coleman *et al.*, 2002). Other serological tests included Weil-Felix test, ELISA and rapid assays (Bora *et al.*, 2018). PCR

and, serologic tests improve scrub typhus diagnosis among acute febrile patients (Tantibhed-hyangkul *et al*, 2017).

Differential diagnosis: Scrub typhus differential diagnosis includes: 1-Other arthropod/insect bites, 2- Allergic contact dermatitis (ACD) is a type 4 or delayed-type hypersensitivity response (DTH) by a human's immune system to a small molecule (<500 Daltons), or hapten contacts a sensitized human skin (Divkovic *et al*, 2005), or with an offensive chemical such as poison ivy, nickel, rubber, hair dyes, textile chemical, preservative, fragrance, and sunscreen (Vocanson *et al*, 2009), or photo allergens penetrated skin stratum corneum and engulfed by Langerhans cells (Bock *et al*, 2018), or with subsequent T-cell mediated response (Aquino and Rosner, 2019). 3- Bullous pemphigoid (in a pronounced bullae patient) is the commonest autoimmune subepidermal blistering disorder up to 80% of subepidermal immunobullous cases mainly in elderly patients >60 years spontaneously healed in a few months up to 5 years (Pezzolo and Naldi, 2019). Also, fever of unknown origin, enteric fever, typhoid fever, dengue fever, other rickettsioses, tularemia, anthrax, leptospirosis, malaria, viral hemorrhagic fevers, and infectious mononucleosis must be in the differential diagnosis (Dumler and Siberry, 2007).

Treatment: Vigorous cleaning with soap & water may help to remove mites, and managing symptoms. Itching is treated with menthol or calamine lotion or only topical corticosteroids to improve itching and inflammation (Yarbrough *et al*, 2013). Undoubtedly, early access to effective drug therapy is key in reducing disease damage. The commonly used drug is doxycycline or tetracycline, but chloramphenicol is an alternative (Kollars *et al*, 2003), and for resistant strain Rifampicin and azithromycin are alternatives (El Sayed *et al*, 2018). Lu *et al*. (2022) reported that rifampicin was associated with the highest cure rate benefit and lowest risk of deferescence time on treating scrub typhus patients, except in the tuberculosis endemic are-

as, and that azithromycin gave better in cure rate and associated with a lower probability of gastrointestinal symptoms and abnormal blood count, and may be considered in pregnant women and children treatment. They added that moxifloxacin had a much lower cure rate than other drugs and not recommended for the scrub typhus management.

Other interventions: Since mites don't burrow into the skin and pruritic eruption usually starts after the mites have already detached from the skin, interventions to eradicate mites from the skin (e.g., acaricides or home remedies such as nail polish) were not indicated (Houck *et al*, 2001). Cloths worn during period of outdoor exposure to mites must be washed in hot water, or can be treated with pyrethroid to kill mites (Morsy *et al*, 2019).

Prevention: Heavily infested areas should be avoided, and trousers should be tucked in-side socks. DEET, and dimethyl phthalate applied to skin and clothing are effective repellants or pyrethroid to kill mites (Tilak *et al*, 2001). Clothing may be treated with pyrethroid such as permethrin (Fradin, 1998). Natural repellents containing aromatic oils, such as citronella oil, tea tree oil, jojoba oil, geranium oil, and lemon grass oil, are also effective (Hanifah *et al*, 2010).

Mites prefer moist areas with overgrown vegetation, so removal clippings after scalping improve Bermudagrass mite control, and limit damage on the emerging ones. Also, clippings resulting from regular mowing or scalping must be properly disposed since mites abandon desiccating host plants, and survive sufficiently long to infest the surrounding areas (Brown and Chong, 2024).

Vectors of diseases: 1- Scrub typhus, an infection caused by *Orientia tsutsugamushi*, is transmitted via the bite of the harvest mite in the rural areas of Asia and Australia (Watt and Parola, 2003). The symptoms usually start within ten days post-infection.

Signs and symptoms: Fever, chills, headache, body aches, rash, and muscle pain, as well as dark, scab-like region at its bite site or an Escher with central necrosis, mental

changes from confusion to coma, enlarged lymph nodes, and, If not treated, is fatal due to organ damage, and bleeding (CDC, 2024).

Hantavirus, *Borrelia*, and *Ehrlichia*: These zoonotic diseases were identified by Hantavirus-specific RNA, *Borrelia*-specific DNA, and *Ehrlichia*-specific DNA in trombiculid mites in Czech Republic, & Spain (Kampen *et al*, 2004), and Texas (Literak *et al*, 2008), but transmission from mites to man was not documented (Fernández-Soto, *et al*, 2001). But, Chen *et al*. (2022) in USA reported that other human pathogens, namely Hantavirus, *Bartonella*, *Borrelia*, and *Rickettsia* were detected in chiggers. Chaisiri *et al*. (2023) in Thailand reported that pathogens (Hantaan-orthohantavirus, Dabie bandavirus, and species of *Anaplasma*, *Bartonella*, *Borrelia*, & *Rickettsia*), and symbiotic bacteria (*Cardinium*, *Rickettsiella*, & *Wolbachia*) were detected in chiggers with increasing frequency.

Hantavirus pulmonary syndrome (HPS) is a rare, but risky pulmonary disease marked by pulmonary edema, hypoxia, and hypotension, presented in two clinical forms, Hemorrhagic Fever Renal Syndrome (Chandy and Mathai, 2017) characterized by fever, myalgias, and acute respiratory distress (Saavedra *et al*, 2021). Hantaviruses are transmitted by contact with body fluids of rodents, particularly saliva from bites and from inhalation of viral particles from urine and feces in aerosols. Among HCPS-causing Hantaviruses is Andes-orthohantavirus, the only virus capable of spreading from man to man (Morsy *et al*, 2022). Botros *et al*. (2004) in Cairo a hospital-based case-control study exposed to rodents, by ELISA detected anti-Hantavirus IgG in 5/350 of CRF history (1.4%), and 7/695 controls (1.0%) were 94 positive with a titer > or =1:400, but added that Hantavirus sero-prevalence was, but without CRF significant cause.

Borrelia burgdorferi is a spirochete causes Lyme disease via a tick vector that preferred natural reservoir is small mammals and birds causing a characteristic annular rash, arthritis, carditis, and ending with encephalopat-

hy (Shapiro, 2014).

In Egypt, Haberberger *et al*. (1989) reported Lyme disease, and its tick vector. Ham-mouda *et al*. (1995) in Alexandria University Hospitals detected four Lyme disease positive children among chronic/recurrent arthritis and skin lesions suggested erythema chronicum migrans by IgG antibodies against *B. burgdorferi* antigen and *R. sanguineus* infested pets. Adham *et al*. (2010) by PCR identified *B. burgdorferi* (s.l.) of Lyme borreliosis *B. burgdorferi* was 28% among soft and hard ticks. High infection (66%) was in nymph and adult of *Ornithodoros savignyi*, but low one (0-50%) was in hard ticks; with sequence of *B. burgdorferi* s.l. PCR was identical to Gen-Bank species. Ghafar and Eltblawy (2011) in the Nile Delta by DNA reported *B. burgdorferi* in two male farmers. Elhelw *et al*. (2014) reported that animals associated with patients suffered from febrile illness proved Lyme borreliosis zoonosis. Besides, Elhelw *et al*. (2021) in Cairo, Giza, and Qualyobia Governorates reported that *B. burgdorferi* isolated from dog's blood associated with pools of *Rhipicephalus sanguineus* was typically identical with *B. burgdorferi* isolated from *Ixodes pacificus* in USA. Ashour *et al*. (2023) by PCR identified *Borrelia afzelii*, and *B. miyamotoi* in camels and ticks. Pukhovskaya *et al*. (2019) in Russia reported that *B. miyamotoi* as a genetically related to *B. burgdorferi* transmitted by *Ixodes* spp. caused febrile disease accompanied with fatigue, headache, chills, myalgia, arthralgia, and nausea, with fatal meningoencephalitis.

Ehrlichiosis (*Ehrlichia chaffeensis*, *E. ewingii*, *E. canis*, *E. ruminantium*, & *E. muris*) is a tick-borne bacterial disease was detected globally in man and animals (Rar and Golovljova, 2011).

Botros *et al*. (1995) in Egypt reported that 3/374 dogs with epistaxis had *E. canis* antibody titres > 1:320 were infested with *R. sanguineus*. Ismail *et al*. (2010) added that human disease called monocytotropic ehrlichiosis is caused by *E. ewingii*, *E. chaffeensis*, &

An. phagocytophilum, but in infected dog called canine monocytotropic ehrlichiosis is caused by *E. canis* and *An. phagocytophilum*, and *R. sanguineus* its vector. Nasr *et al.* (2020) by PCR and sequencing for *Anaplasma* and *Ehrlichia* spp. identified two bacterial species; *A. platys* in two kennel dogs tick pools (1.32%) and *E. canis* in two tick pools of pet dogs and one from kennel dog (1.98%). *E. canis* phylogenetic analysis showed genetic relatedness with those isolated from human cases. New species; *E. chaffeensis*, *E. ovina*, *E. minasensis*, and *E. rustica* were isolated from *Hyalomma excavatum* and *R. annulatus* collected from live stock in Alexandria, Dakahlia, Siwa, Fayoum, Assiut, and New Valley Governorates (Lofitis *et al.*, 2006; Al-Hosary *et al.*, 2021). Moreover, Abdelbaset *et al.* (2022) reported that favorable climatic and environmental conditions, along with the imported animal from neighboring countries, ticks & tick-borne diseases were introduced into Egypt. They added that up-scaling of border inspections of imported animals is a must to stop cross-ing arthropod-borne zoonotic diseases.

Conclusion

Chigger bites are infestation with larval of trombiculid mites, in areas such as grasslands, forests, gardens, around lakes and streams. Bites are painless but typically become intensely pruritic within a few hours, with papules or papulovesicles at the bites' sites, and urticarial, macular, or bullous eruptions also may occur. Pruritus usually resolves within a few days, but cutaneous eruption usually resolves within one to two weeks and symptoms persist for longer time.

Diagnosis of chigger bites is by a history and clinically by pruritic grouped papules or papulovesicles on ankles, waistline, or other areas where clothing contacts the skin.

Prevention includes avoidance of chigger-prone areas, tucking trousers inside of socks, and applying repellent to skin and clothes.

Vigorous washing with soap and water will easily displace any attached larvae. Chiggers don't burrow into the skin. Treating sympto-

matic lesions are with topical antipruritic or potent topical corticosteroids.

Sedating antihistamines may help with pruritus when indicated. Clothing worn during the exposure period to mites-infested areas must be carefully washed in hot water or treated with pyrethroid insecticides.

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Recommendations

Scrub typhus is a mild, but fatal disease if disseminated vasculitic and perivascular inflammatory lesion cause in end-organ injury.

Early diagnosis and proper treatment alleviate symptoms, and prevent severe or fatal complications. Chigger bites complications include secondary cellulitis, summer penile syndrome, and transmission of other diseases such as scrub typhus.

Doxycycline prophylaxis showed promise before exposure to chiggers infested areas.

Clinicians must be aware about scrub typhus in acute undifferentiated febrile illness.

More studies on chigger bacteria and others (parasites, fungi, and viruses), intimately associated with chiggers vector competence, and population dynamics of *Orientia* in the trombiculid mites are urgently indicated.

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Explanation of figurers

Fig.1: Eschar at site of chigger bite (after CDC)

Fig. 2: Scrub typhus (after CDC).

Fig. 3: Chigger larva feeding.

Fig. 4: Lyme disease (after CDC).

