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The Role of Chiggers as Human Pathogens

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Abstract

Trombiculid mites (Acari: Trombiculidae) are distributed worldwide ectoparasites of a wide range of vertebrates. More than 50 species are known to bite humans, and about 20 have medical importance. The larval stages (chiggers) of the genus *Leptotrombidium* are vectors of *Orientia tsutsugamushi*, causative agent of scrub typhus. This life-threatening disease is widely endemic in Asian Pacific regions where more than one billion people are at risk of acquiring the infection and around one million new cases are estimated to occur annually. In addition, although underreported and often misdiagnosed, trombiculiasis, defined as a dermatitis caused by the salivary secretion of biting chiggers, is present in America and Europe.

Keywords: Chiggers, *Orientia tsutsugamushi*, dermatitis, vectors

1. Introduction

This chapter includes a thorough description of the main characteristics, life cycle, and distribution of chiggers. Moreover, a comprehensive review of the responsibility of chiggers as infectious disease vectors and agents of troublesome dermatitis is given. The following pages cover, for the first time in a unique chapter, the current knowledge of chigger mites.

1.1. Taxonomy and distribution

Trombiculid mites (Acari: Trombiculidae) are widespread ectoparasites of a wide range of vertebrates. More than 50 species have been recorded attacking humans, and about 20 of them are considered to be medically important because they cause dermatitis or due to their role as vectors of human pathogens. The most relevant species are *Eutrombicula alfreddugesi* in North and South America, *Neotrombicula autumnalis* in Europe, and *Leptotrombidium* spp. in Asia [1].

Trombiculidae is one of the largest families in the Acari group, including more than 3,000 species [2]. Table 1 shows the taxonomic position of these mites.

Phylum	Arthropoda
Subphylum	Chelicerata
Class	Arachnida
Subclass	Acari
Superorder	Acariformes
Order	Trombidiformes
Suborder	Prostigmata
Superfamily	Trombiculoidea
Family	Trombiculidae

Table 1. Taxonomic classification of the family Trombiculidae.

Trombiculids are distributed worldwide, but they show their greatest diversity in the subtropical, tropical and southern temperate zones [3]. Table 2 shows the main trombiculid species and their geographical distribution.

Species	Distribution	Disease
<i>Blankaartia acuscutellaris</i>	Hungary, Spain, Moldova, Ukraine, Russia, Sumatra, Malaysia, and Africa	Trombiculiasis
<i>Eushoengastia koreaensis</i>	Korea	Scrub typhus ^a
<i>Euschoengastia xerothermobia</i>	Europe	Trombiculiasis
<i>Eutrombicula alfreddugesi</i>	Canada, South of United States (except for the southwest), South and Central America (including West Indies)	Trombiculiasis
<i>Eutrombicula batatas</i>	Bolivia, Mexico, Central and South America, southwestern and southeastern United States	Trombiculiasis
<i>Eutrombicula lipovskyi</i>	United States: from Alabama and Tennessee West to Arkansas, Oklahoma and Kansas	Trombiculiasis
<i>Eutrombicula sarcina</i>	Southeast Asia, Australia and the Pacific Islands	Trombiculiasis
<i>Eutrombicula splendens</i>	Eastern United States (from the Gulf Coast North to Massachusetts, Minnesota) and Ontario	Trombiculiasis

Species	Distribution	Disease
<i>Eutrombicula wichmanni</i>	Japan, Southeast Asia, Australia, and Pacific Islands	Trombiculiasis
<i>Keptatrombicula desaleri</i>	Italia, Austria, and Bulgaria	Trombiculiasis
<i>Leptotrombidium akamushi</i>	Japan, China, Southeast Asia, Indonesia, Philippines, and New Guinea	Scrub typhus
<i>Leptotrombidium arenicola</i>	Malaysia, Indonesia, and Thailand	Scrub typhus
<i>Leptotrombidium chiangraiensis</i>	Thailand	Scrub typhus
<i>Leptotrombidium deliense</i>	China, Taiwan, Sri Lanka, Nepal, Bangladesh, India, Myanmar, Vietnam, Cambodia, Thailand, Singapore, Brunei, Malaysia, Indonesia, Philippines, New Guinea, southwestern Pacific Islands, northern Australia, Pakistan, Kazakhstan, Uzbekistan, and Afghanistan	Scrub typhus
<i>Leptotrombidium fletcheri</i>	Southeast Asia, Malaysia, New Guinea, Philippines, Indonesia, and Melanesia	Scrub typhus
<i>Leptotrombidium fuji</i>	Japan	Scrub typhus ^a
<i>Leptotrombidium gaohuensis</i>	China	Scrub typhus
<i>Leptotrombidium imphalum</i>	Thailand	Scrub typhus
<i>Leptotrombidium intermedium</i>	Japan	Scrub typhus ^a
<i>Leptotrombidium kitasatoi</i>	Japan	Scrub typhus ^a
<i>Leptotrombidium orientale</i>	Japan, Korea, and Primorye region of Russia	Scrub typhus ^a
<i>Leptotrombidium pallidum</i>	Japan, Korea, and Primorye region of Russia	Scrub typhus
<i>Leptotrombidium palpale</i>	Japan, Korea, and Primorye region of Russia	Scrub typhus ^a
<i>Leptotrombidium pavlovsky</i>	Siberia and Primorye region of Russia	Scrub typhus
<i>Leptotrombidium scutellare</i>	Japan, northern China, Korea, Thailand, and Malaysia	Scrub typhus Hantavirus ^a
<i>Leptotrombidium subquadratum</i>	South Africa	Trombiculiasis
<i>Neotrombicula autumnalis</i>	Europe (including British Isles, excluding Norway, Sweden, Finland, and northern Russia), Turkey, and Turkmenistan	Trombiculiasis

Species	Distribution	Disease
<i>Neotrombicula inopinata</i>	Spain, Czech Republic, England, Austria, Germany, Bulgaria, France, states of former Yugoslavia, Ukraine, Russia, Romania, Hungary, Slovakia, and Poland	Trombiculiasis
<i>Neotrombicula japonica</i>	Korea, Europe	Scrub typhus ^a Trombiculiasis
<i>Neotrombicula nagayoi</i>	Japan, China, and Russia	Trombiculiasis
<i>Neotrombicula zachvatkini</i>	Europe	Trombiculiasis
<i>Odontacarus</i> spp.	Southeast Asia, Australia, and the Pacific Islands	Trombiculiasis
<i>Shoengastia hanmyaensis</i>	Japan	Scrub typhus ^a
<i>Schoengastia</i> spp.	Southeast Asia, Australia, and the Pacific Islands	Trombiculiasis
<i>Trombicula toldti</i>	Austria	Trombiculiasis

^aNot confirmed.

Table 2. Distribution and diseases transmitted by the main trombiculid mite species [1,4–15].

Members of this family are known by several names depending on their distribution (Table 3). They are often confused with other mites or insects and are mistakenly named as Mower's mites [common name of *Leptus autumnalis* (Acari: Erythraeidae)] [16,17] or jigger, chigoe, and niguas [common names of *Tunga penetrans* (Insecta: Siphonaptera)] [18,19].

Common names	Places
Harvest bug, harvest mite, harvest lice, red bug, red mite, berry mite, scrub-itch mite	North-America, Asia
Harvest mite	Europe
Aoutats, rouget, bête rouge	France
Orange tawny	Ireland
Augustelingen	Germany
Bicho colorado, coloradilla, ácaro rojo	South America
Isango	Peru
Tlazahuate	Mexico
Coloradita, chivacoa	Venezuela

Table 3. Common names given to trombiculid mites worldwide. [2,4,10,16,17,20–22]

1.2. Life cycle

Trombiculid mites undergo seven stages in their life cycle: egg, deutovum, larva, protonymph, deutonymph, tritonymph, and adult (Figure 1). This cycle is characterized by alternating active and inactive instars, being the larva, deutonymph, and adult the active ones. Active postlarval stages are soil dwellers that prey on various arthropods and their eggs. Deutonymphs look almost identical to adult mites. Both present eight legs, but deutonymphs are slightly smaller. Sexual dimorphism is not apparently evident [23]. Larvae parasitize all groups of vertebrates, except fishes, whereas the small mammals and birds are the main hosts [1,5,19,24]. There are just a few reports of chiggers feeding on invertebrates [3]. Humans are only accidental hosts. However, the question of the host specificity of trombiculids still arises. Most likely, trombiculids are associated with specific habitats and attack and feed on the first available animal within their favorite habitat, although they can have preference for a particular host among the available ones [23,25].

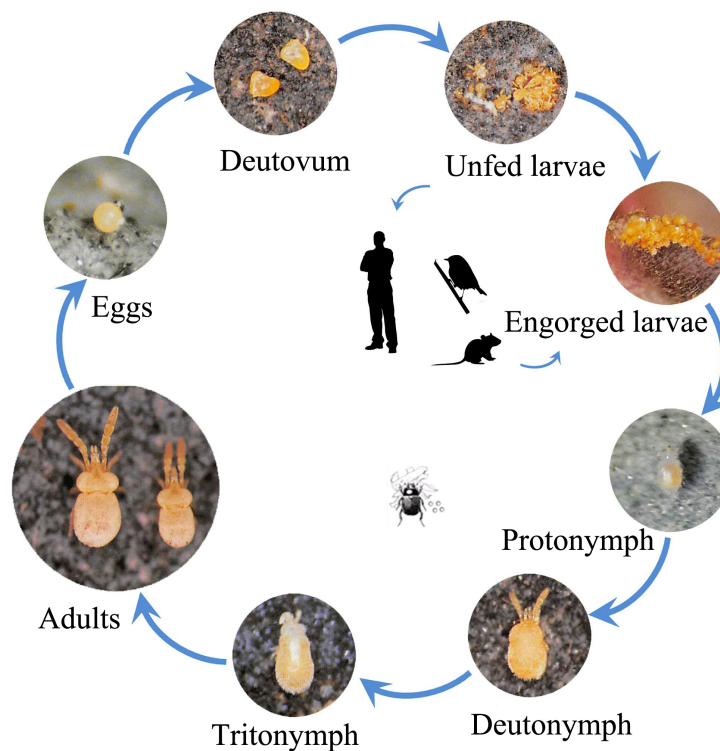


Figure 1. Schematic description of the trombiculids' life cycle. (Adapted from Takahashi *et al.*, 2003 with the permission of the author.)

During their life cycle, eggs are laid in well-drained soil, and six-legged larvae emerge from them. The general term “chigger” refers to the parasitic larval stage, and this is the name commonly given to trombiculid mites due to the importance of this instar. Chiggers are usually reddish but can vary between yellow and orange [1,26]. These tiny larvae (about 200 μm) climb onto low vegetation, where they aggregate into clusters to wait for a suitable host. On the host, chiggers mainly move to areas where the skin is especially thin and feed on lymph and tissue

fluids of the dermal layer (but not blood). Ears, head, armpits, abdomen, genitalia, and the area around the tail are preferred in animals [4,27]. In humans, bites occur mainly in body exposed areas and at sites where the clothing constricts [17,28]. Once engorged (development to subsequent stage cannot take place unless larvae have fed on the host), larvae fall to the ground and develop to the nymphal stages and subsequently to adults (900–1,200 μm).

Trombiculid mites live in moist soil covered with vegetation such as grassy and weedy areas. In general, optimal living conditions require a relative air humidity of 80% (what explains that chiggers are not typically found on vegetation higher than 30 cm off the ground) and neutral to slightly alkaline soil. The optimum activity of chiggers occurs at temperatures of 25–30°C [26,29].

Trombiculid mites often form localized “mite islands” (or “mite focus”, “larvae focus”) in suitable areas inhabited by potential hosts [30]. Therefore, chiggers have a patchy distribution on the vegetation. Mite islands are quite clearly defined, and larvae could not be detected in their immediate vicinity [26,31]. A possible explanation for this focalization may be that chiggers apparently do not move more than a few meters from where they hatched. Chiggers would temporarily disperse if a host approached. On the contrary, if physical contact were not managed or if the host were not close enough for them to drop on it, chiggers would invariably and promptly return to the cluster and would continue waiting [32].

The life cycle of trombiculid mites has been mainly studied in the laboratory. The most outstanding feature of the life cycle is the constant duration of quiescent periods and the variable duration of active stages. Trombiculid mites usually have one generation per year, but with overlapping generations, each well synchronized with the seasons because they can overwinter in most stages (egg, larva, deutonymph, and adult) and because the adult mites have a long life span [33]. In boreal species, an egg-to-egg cycle ranges from 150 to 400 days, but it is shorter in tropical species [23]. In nature, the life cycle is supposed to be completed in 2–12 months or longer, depending on the species and environmental conditions. In temperate areas, there may be 1 to 3 generations per year, whereas in tropical regions the life cycle is shorter and continuous throughout the year [1]. In Europe, the duration has been estimated in five to seven months under favorable conditions [26].

As mentioned above, trombiculid mites only act as parasites during their larval stage. Thus, the greatest attention has been paid to chiggers. In addition, adults and deutonymphs of the majority of trombiculid species have never been observed on the soil surface (in fact, their habitats are mostly unknown). Therefore, the taxonomy of trombiculid mites is based solely on their larvae [34]. It is estimated that only the postlarval stage of less than 10% of the total of Trombiculidae species are known [7]. This is the case of some tropical species in contrast to the difficulty of finding active postlarval instars in northern countries [23].

1.3. Feeding process

It is well known that when feeding on hosts, chiggers develop a characteristic feeding tube (stylostome) in the host’s skin. The stylostome is mostly formed of the larval salivary secretions solidifying in the host’s epidermis [7]. Larva cuts the stratum corneum with its rather short

chelicerae and stylostome allows chigger to reach the underlying connective tissue layer from which it obtains nutrients. The host's tissues around the stylostome are destroyed and necrotized. Beneath the distal end of the stylostome, an interstitial food cavity containing lymphoid and epithelioid cellular liquid elements is formed [23]. The feeding period in animal host, both in nature and reared in the laboratory, usually lasts 3–6 days [26,35]. However, feeding on humans may typically vary from 3–8 h to 1–2 days for most non-infectious chiggers, but 2–10 days for scrub typhus vectors [1,29,36,37]. It is supposed that more than 6 h are required for the transmission of the bacterium [14]. During this period, the larva remains on the skin surface. For this reason, most trombiculid larvae can be classified as ectoparasites. Larvae of some genera, however, can partly or even entirely embed within the skin of different body cavities frequently forming various types of capsules during feeding on amphibians and mammals [23]. In such cases, the feeding time is prolonged up to several weeks or even months. In lizards, specific adaptive structures of skin, known as "mite pockets", may evolve to decrease the possible damage from mite feeding [38]. It is generally thought that the organization and location of stylostome is species specific in trombiculid larvae, irrespectively of the host species and of the particular feeding site on the host, whereas the length of the stylostome is mostly a result of the width of the epidermal layer and the presence or absence of scabs at the attachment site [39].

2. Chiggers as vectors of infectious diseases

Although different microorganisms have been detected in different species of chiggers, their role as vectors of infectious diseases has been only demonstrated for scrub typhus.

2.1. Scrub typhus

Scrub typhus or tsutsugamushi disease [from Japanese words meaning disease (*tsutsuga*) mite (*mushi*) is a life-threatening arthropod-borne bacterial infection that presents as an acute undifferentiated febrile illness widely endemic in Asian Pacific regions. The disease is transmitted to humans by chiggers of *Leptotrombidium* spp. and is caused by the bacterium *Orientia tsutsugamushi*. Noteworthy are the reported cases that suggest other *Orientia* species as etiological agents of scrub typhus-like disease.

The disease was widely reported in soldiers during World War II [40] and now is an important illness for travelers to the endemic regions [41]. More than half (55%) of the world population lives in areas where scrub typhus is endemic, so over one billion people are at risk of acquiring the infection [42]. Approximately one million new cases have been estimated to occur annually [43]. However, this is surely an underestimation because recognition of the disease is difficult due to its overlapping clinical spectrum with other common causes of fever in this population, the lack of awareness among affected people, and the limitations of current diagnostic methods [44].

2.1.1. Etiology and epidemiology

The etiological agent of scrub typhus, *O. tsutsugamushi* (previously known as *Rickettsia orientalis* or *Rickettsia tsutsugamushi*), is an α -proteobacteria that was reclassified as a new genus separate from *Rickettsia* based on phenotypic and genotypic differences [45]. *Orientia* differs from *Rickettsia* in the structure of the cell wall, antigenic profile, and genome size, which is almost twice the size of the *Rickettsia* genome.

There are three prototype strains: Gilliam, Karp, and Kato; however, more than 20 antigenically distinct serotypes are present in endemic areas [46], and currently over 70 strains of *O. tsutsugamushi* are known [47]. As chigger mites are habitat specific, *O. tsutsugamushi* strains could have evolved mostly in separate biotopes, resulting in different serotypes depending on their location [48]. The general course and the prognosis of the disease is determined by the strain of *O. tsutsugamushi* implicated [49], although multiple factors such as the patient's age, genetic factors, and previous immunity are also involved [50]. It is very likely that chiggers, as it is assumed for ticks [51], have potential immunomodulatory effects in their saliva that could affect the pathogenesis, immunity, and outcome of the disease [47].

Chiggers act as reservoir and vector of *O. tsutsugamushi*, being wild rodents the main hosts. Infected mites maintain the infection through the trombiculids' life cycle by transstadial and transovarial transmission [52]. Reverse transfer from infected animals to chiggers occurs infrequently, and the bacteria transmitted in this manner are not usually passed on to the next generation [53]. Chiggers cofeeding on rodents seems to be more relevant for effective mouse-to-mite transmission of *Orientia* than feeding on rickettsemic hosts [54]. Nevertheless, the disease can only be transmitted to humans by chiggers already transovarially infected by *O. tsutsugamushi* [49].

Endemic regions are characterized by rice fields, scrubland, and the presence of primary deforestation [55,56]. Chiggers harboring the bacterium bite exposed individuals in vulnerable niches such as forests and infested undergrowth during occupational or recreational activities. *Leptotrombidium* chiggers feed on lymph and tissue fluids of the dermal layer for a period of 2–4 days [57]. Following the bite, the pathogen multiplies at the site of inoculation and subsequently induces local (eschar) and systemic manifestations of infection [58].

Several studies suggest the evidence of human infection with more than one strain of *O. tsutsugamushi* [59]. It could be explained by bites from different chiggers, each one infected with one strain or, alternatively, by the bite of individual chiggers infected with multiple strains [60].

Seasonal occurrence of scrub typhus is determined by the time of appearance of chiggers because humans are infected through bites of the larva. In temperate zones, scrub typhus season is observed mainly in the autumn but also in the spring [61]. More than 45 species of trombiculid mites are known to be infected with *O. tsutsugamushi* in nature, but only *Leptotrombidium pallidum*, *Leptotrombidium akamushi*, *Leptotrombidium scutellare*, *Leptotrombidium deliense*, *Leptotrombidium arenicola*, *Leptotrombidium imphalum*, *Leptotrombidium Chiangraiensis*, *Leptotrombidium fletcheri*, *Leptotrombidium gaohuensis*, and *Leptotrombidium pavlovsky* are proven to transmit scrub typhus [1,13,14]. Principal vector species differ according to endemic areas

(Table 2): *L. akamushi*, *L. pallidum*, and *L. scutellare* mediate scrub typhus in temperate zones, such as Japan and Korea, whereas *L. deliense* and *L. arenicola* are the principal vectors in tropical and subtropical regions or Southeast Asia and the Southwest Pacific [49] (Figure 2).

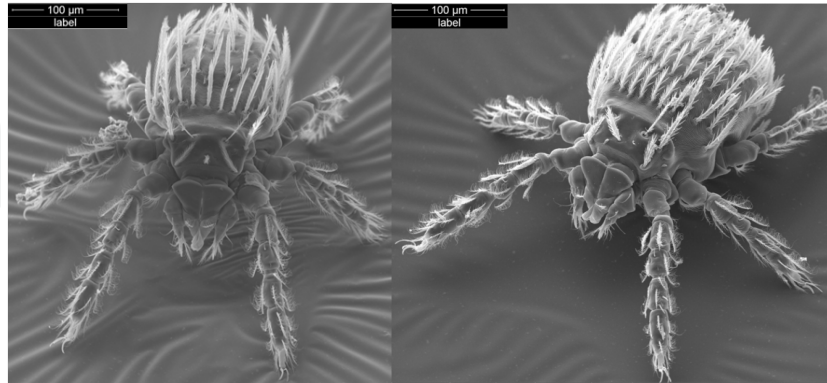


Figure 2. *Leptotrombidium intermedium* (left) and *Leptotrombidium pallidum* (right). Provided by Dr. Shatrov.

Scrub typhus is confined to a 13,000,000-km² definite geographic region, the “tsutsugamushi triangle,” where it is widely distributed (Figure 3). It extends from northern Japan, Korea, and far-eastern Russia in the North, to northern Australia in the South and to Pakistan and Afghanistan in the West, as well as the islands of the western Pacific and Indian Oceans, including Taiwan, Philippines, New Guinea, Indonesia, and Sri Lanka [62].

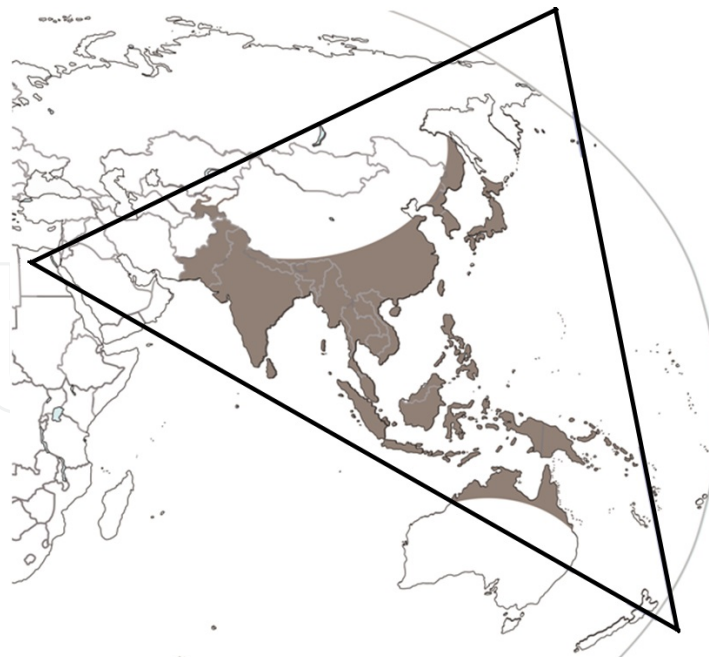


Figure 3. Tsutsugamushi triangle.

Several reports of scrub cases typhus-like infections have been described in unusual areas, indicating that a wider geographic distribution should be taken into account [47]. Thus, the recent isolation of *Orientia chuto* in a febrile patient who acquired the infection in the United Arab Emirates, the detection of another divergent *Orientia* sp. in a patient in Chile, and the serologic diagnoses of scrub typhus acquired in Africa reveal that the geographical range accepted until now may be an underrepresentation [63,64]. To date, the genetic diversity of the genus *Orientia* is being reviewed because until recently *O. tsutsugamushi* has been considered the sole species of the genus. Apart from *Leptotrombidium* spp., other trombiculid mites such as *Neotrombicula japonica* and *Eushoengastia koreaensis* have also been implicated as possible vectors of this disease [15,65].

The disease is considered rural, and the risk of infection is closely related to occupation. In areas where scrub typhus is prevalent, most cases are acquired through agricultural exposure. Most travel acquired cases of scrub typhus are associated with outdoor activities such as camping, rafting, or trekking in endemic areas [50]. Outbreaks related to military operations have been reported [66]. The impact of scrub typhus in pregnancy is less explored. Acute scrub typhus can be transmitted vertically but congenital malformation due to infection *per se* has not been demonstrated [67].

2.1.2. Clinical features and pathogenesis

Scrub typhus ranges in severity from mild and self-limiting to fatal depending on the duration of the illness, the strain of *O. tsutsugamushi*, the immune status, and other factors of the patients [14]. After an incubation period of 10–12 days (can vary between 5 and 20 days), the onset of the disease is characterized by an eschar and regional lymphadenopathy followed subsequently by fever, general malaise, headache, and myalgia. The disease is characterized by focal or disseminated vasculitis and perivasculitis, which may involve the lungs, heart, liver, spleen, and central nervous system [68]. Progression of scrub typhus is accompanied by generalized lymphadenopathy, rash, cough, and interstitial pneumonia, acute respiratory distress syndrome, gastrointestinal symptoms, meningoencephalomyelitis, myocarditis, acute renal failure, hypotensive shock, and disseminated intravascular coagulation may occur in severe cases [14,47,69].

The fever appears abruptly frequently accompanied by headache, myalgia, and malaise, with peaks on the 3rd–4th day of the disease and persists for more than 3 weeks in untreated cases. About a week after the onset of the symptoms, the eschar, which is not always present, is developed. It represents localized cutaneous necrosis at the site of mite feeding and is a typical scrub typhus marker, which is considered almost diagnostic [67]. It starts as a small papule that enlarges and subsequently undergoes central necrosis, and it eventually acquires a blackened crust with an erythematous halo that resembles a cigarette burn (Figure 4).

The common sites for finding an eschar are trunk, arms, and legs, but it also appears on the scalp, axilla, genitalia, waist, and other exposed parts of the body [14,49]. The prevalence of eschars in patients diagnosed by scrub typhus ranges from 7% to 97% [67,70]. These differences may be due to the difficulty in detecting small eschars in dark-skinned individuals and atypical appearance of eschars in areas of damp and moist skin. Multiple eschars have been



Figure 4. Eschar and erythema on the fifth day of illness in the left arm of a patient of a 36-year-old patient (photo provided by Dr. Takahashi).

reported in 0.6% to 2.2% of patients with confirmed scrub typhus [70]. Uncommonly, a maculopapular rash with centrifugal distribution may appear a week after the onset of these symptoms, starting on the chest, abdomen, or whole trunk and spreading to the limbs. Rash lasts a few days to a week [13,71]. Regional lymphadenopathy, characterized by tenderness and enlargement of the draining lymph node around the primary eschar, arises at the end of the first week after the disease onset [13]. Generalized lymphadenopathy appears 2–3 days later in some cases [72].

From the second week onwards, a proportion of patients (especially those untreated) will evidence of severe systemic infection. The extended vasculitis helps to explain the great diversity of clinical manifestations that have been described [49]. Respiratory symptoms, including interstitial pneumonia, acute respiratory distress, and pulmonary edema, are frequent. In fact, about 40% of scrub typhus patients complain of cough at the time of admission. Gastrointestinal symptoms comprise nausea, vomiting, abdominal pain, diarrhea, or gastrointestinal bleeding. Alterations in liver function and pancreatitis are also common. The central nervous system (CNS) is frequently affected. Indeed, *O. tsutsugamushi* is detected in the cerebrospinal fluid of 24% of the patients with no clinical signs of CNS involvement. Transient hearing loss, eye manifestations, confusion, neck stiffness, delirium, and mental changes occur frequently. Patients usually suffered from acute diffuse encephalomyelitis, encephalopathy, meningitis, or meningoencephalitis. Regarding the cardiovascular system, myocarditis, vasculitis, pericarditis, and rhythm abnormalities are often seen, but congestive heart failure is rare. Acute renal failure develops frequently in severe cases but may also occur in mild cases [13,14,61,62,67,69]. The case fatality rate in untreated patients is estimated in appropriately 10%, ranging from 0% to 30% [67].

At the beginning of the infection, *O. tsutsugamushi* mainly infects dendritic cells in the eschar [58]. The systemic dissemination of *O. tsutsugamushi* is suggested to be lymphogenous to the regional lymph nodes, followed by spread to target organs via the blood. This pathway was suggested based on the early development of lymphadenopathy in the regional drainage of the eschar as well as on animal experiments and clinical observations [14,47]. Once *O. tsutsu-*

gamushi infection progresses, the main target cells are vascular endothelial cells and macrophages of the reticuloendothelial system, although cardiac myocytes can also be infected [14]. The endothelial cells seem to have a central role in the systemic inflammation because *in vitro*-infected human dermal microvascular endothelial cells are activated to express interleukin (IL)-8 and monocyte chemoattractant protein just after the infection. Moreover, soluble endothelial cell-specific adhesion molecules (sE-selectin) are highly concentrated in serum at the early stage of the disease.

The basic histopathologic findings reveal multiplication of *O. tsutsugamushi* in the endothelial cells lining the small blood vessels, perivasculitis and focal interstitial mononuclear cell infiltrations, and edema. Perivasculitis may involve the lung, heart, brain, kidneys, gastrointestinal tract, liver, spleen, and lymph node [73].

2.1.3. Diagnosis and treatment

Due to the severity of *Orientia* infection, treatment has to be started as soon as possible, even before having a conclusive microbiological diagnosis.

As in other infectious diseases, the gold standard of the diagnosis of scrub typhus is the isolation of the etiological agent by culture. Isolation of *O. tsutsugamushi* can be done in cell culture or in inoculated mice. Yolk sacs of 5- to 7-day-olds have been widely used in the past, but it was replaced by cell culture systems [74]. Currently, culture in HeLa, Vero, BHK, L929, ECV304, and HMEC-1 cell lines is the reference method for isolating *O. tsutsugamushi* from clinical samples [45,49,75,76]. These techniques are restricted to biosafety level 3 facilities and personnel with extensive experience. A positive result is given in an average time of 28 days, being inappropriate for the routine diagnosis of the disease. The shell-vial culture technique makes the detection of the microorganism possible in 48–72 h, allowing an early diagnosis before seroconversion [74,77]. *O. tsutsugamushi* can also be isolated by inoculating patient blood into mice, but results are not available in time to guide clinical management [78]. Mouse inoculation remains helpful when isolation of the organism from postmortem tissues is required [74].

The mainstay in scrub typhus diagnostics remains serology [79,80]. Nevertheless, despite their widespread use, all currently available serologic tests have limitations. The Weil–Felix OX-K agglutination reaction was the earliest serological tests used for clinical diagnosis of scrub typhus. It is inexpensive, easy to perform, and results are available overnight; however, it lacks specificity and sensitivity [46]. To date, the gold standard assay for the serologic detection of scrub typhus antibodies is the indirect immunofluorescence assay (IFA) [79]. Most frequently, IFA uses antigen from serotypes Karp, Kato, and Gilliam [46]. IFA is sensitive, and results are available in a couple of hours. Although it is accepted that a ≥ 4 -fold increase in antibody titer between two consecutive samples (acute and convalescent-phase) is diagnostic, this is a retrospective diagnosis and cannot guide initial treatment [79]. Anyway, IFA is expensive and requires a level of technical expertise and equipment that may not be available in rural areas. Indirect immunoperoxidase is an alternative that eliminates the expense of a fluorescent microscope by substituting peroxidase for fluorescein [80].

The development of PCR amplification-based approaches have been incorporated to the diagnoses of infectious diseases even in nonreference laboratories. PCR has potential benefits in detecting *Orientia*-DNA before antibody response occurs. However, the high resource costs and training required for this technique make them impractical in many areas where scrub typhus is endemic. Moreover, the most appropriate specimen to use remains unclear. The PCR of eschar material yields more sensitive results than blood and remains positive even after the initiation of treatment. However, eschar-based PCR would diagnose a small amount of the cases in a scenario with a prevalence of eschars as few as 7%. Buffy coat could improve sensitivity compared with whole blood, but the use of blood-based assays is limited to the time window of rickettsemia [81,82]. Moreover, low copy numbers is an important handicap of DNA-based approaches. The optimal PCR target for diagnosing scrub typhus stays also uncertain. A target gene enabling specific but sensitive detection as well as sufficiently broad coverage of genotypes of *O. tsutsugamushi* is needed. A nested-PCR assay targeting the 56-kDa gene is highly specific, but sequence variability of this gene may affect primer annealing and, therefore, test sensitivity [83]. 16S rDNA-based *Orientia*-specific PCR may show a broader detection spectrum than an assay based on a more variable species-specific target, such as the 56-kDa gene [47]. Real-time PCR assays targeting the 47-kDa outer membrane protein and the *groEL* genes of *O. tsutsugamushi* are also very sensitive tools for the diagnosis of scrub typhus [78,84]. Recently, loop-mediated isothermal PCR assay (LAMP) targeting the *groEL* gene has shown diagnostic accuracy similar to real-time and nested conventional PCR assays [84]. This assay is simple and less expensive and can be considered a valid molecular method for the early diagnosis of scrub typhus.

The diagnosis and subsequently the antibiotic treatment are often missed or made late due to the lack of effective commercially available diagnostic tests and the lack of specificity of the early clinical presentation. It is important to remark that treatment must begin whenever scrub typhus is clinically suspected, without waiting for microbiological confirmation. It is well known that delayed treatment leads to complications such as adult respiratory distress syndrome, disseminated intravascular coagulation, acute renal failure, meningitis, meningoencephalitis, and gastrointestinal tract bleeding [57]. Bacterial proliferation and the time of antibiotic treatment are very important predictors of lethality.

The clinical discrimination of scrub typhus from other undifferentiated fevers is often very difficult because the clinical symptoms are similar. In patients presenting an eschar and/or rash, and generalized or regional lymphadenopathy in a endemic area, scrub typhus should be considered in the differential diagnosis along with rickettsialpox, Mediterranean spotted fever, dengue, leptospirosis, and murine typhus [55,71].

Mortality in the pre-antibiotic era was variable and in some series approached 60%, but specific and effective antimicrobial chemotherapy is now available [80]. Doxycycline and chloramphenicol are both effective oral or intravenous agents against scrub typhus, dissipating fever in 24 h in most patients [71]. Although the disease can be treated effectively with these antibiotics, reinfection and relapse frequently occur due to the wide variety of antigenically distinct serotypes [85]. Azithromycin and rifampicin are alternative drugs [61].

Currently, effective chemoprophylaxis or vaccination approaches for dealing with *O. tsutsugamushi* infection are still not available [42]. A prophylactic vaccine to scrub typhus is a public health priority because of its high incidence, high mortality, nonspecific clinical presentation, lack of sensitive diagnostic tests, and emergence of antibiotic resistance. The development of an effective and safe vaccine has to be strongly focused on T cell-mediated immunity, empirical testing of the immunogenicity of proteins encoded by conserved genes, and assessment of protection in relevant animal models that truly mimic human scrub typhus resistance [57]. Therefore, prevention of scrub typhus is based mainly on avoiding the chigger bites and the use of repellents during travel in rural areas of endemic countries [61]. Wearing protective clothing and self-examination after visiting arthropod-vector infested areas are also recommended [86].

2.2. Other chigger-borne infectious diseases

Nowadays, *O. tsutsugamushi* remains as the unique agent whose transmission by chigger bites has been confirmed. Nevertheless, trombiculid mites inhabit areas where the presence of several arthropod-borne microorganisms, their vectors, and reservoirs has been demonstrated. Thus, the vector competence of chiggers has long been investigated worldwide.

There are a lot of references in the old scientific literature that associate chiggers with the transmission of several pathogens, being *N. autumnalis* the most reported species. However, the majority of them correspond to secondary anecdotal information and present poor or no details [87]. In the 2000s, *Anaplasma phagocytophilum*-DNA was detected in unfed *N. autumnalis* chiggers collected on vegetation in a mountainous area from the North of Spain [88]. This finding remains doubtful taking into consideration that the infection occurred in unfed larvae, so chiggers are speculated to be true carriers of the bacteria and inherited it through transovarial transmission. The presence of rickettsiae was also investigated in chiggers of the same mountainous area of Spain. Amplicons compatible with infection by *Rickettsia* spp. were detected by molecular techniques in *Neotrombicula inopinata* collected over vegetation [89]. Up to date, these results remain unconfirmed. The vector competence of *N. autumnalis* chiggers for the transmission of *Borrelia burgdorferi* sensu lato (s.l.) has been also investigated. This bacterium was screened by PCR and further DNA hybridization in questing larvae collected on vegetation and feeding larvae removed from trapped micromammals in Germany [87]. Borrelial DNA was amplified in chiggers from 1 larva feeding on a white-toothed shrew (*Crocidura russula*), from a pool of 4 larvae feeding on a *Borrelia garinii*-infected laboratory mouse, and from 1 nymph that had previously fed as a larva on a *Borrelia afzelii*-positive laboratory gerbil. Therefore, the vector competence of *N. autumnalis* remains unclear. The presence of *B. burgdorferi* s.l. and *A. phagocytophilum* DNA was also been investigated by PCR and reverse line blotting in chiggers found on wild birds captured in the western Carpathian Mountains (Czech Republic) [24]. *B. garinii* and *B. valaisiana* were found in a pool of 5 chiggers from the genus *Neotrombicula* collected from a Eurasian Blackcap (*Sylvia atricapilla*). Regarding *A. phagocytophilum*, DNA was detected in none of the samples [87]. Trombiculid mites have also been associated to *Bartonella* spp. A new strain of *Bartonella* sp. was isolated from the gray squirrels *Sciurus carolinensis* in Georgia [90]. Then this bacterium was studied in ectoparasites

removed from gray squirrels by PCR. None of the mites tested (*Eutrombicula splendens*, *Myiatrombicula cynos*, and *Neotrombicula whartonyi*) were positive, whereas 6 *Bartonella* spp. strains were detected, 2 in fleas and 4 in lice [91]. Furthermore, *Leptotrombidium* mites have been reported as carriers of *Bartonella tamiae* [92], species isolated from patients from Thailand [93].

Several rickettsiae previously found in humans as *Rickettsia akari*, *Rickettsia japonica*, *Rickettsia conorii*, *Rickettsia felis*, *Rickettsia typhi*, and *Rickettsia* sp. closely related to TwKM02, *Rickettsia australis*, and Cf15 were detected using molecular methods in trombiculid mites removed from wild rodents collected in Korea [94]. Although the rickettsial DNA was detected in mites, it has yet to be determined whether the DNA was amplified from the meal of an infected animal or from the mite tissue itself. Tsui *et al.*, (2007), identified TwKM02 and TwKM03 closely related to *R. australis* and *R. felis* URRWXCa2, respectively, in *Leptotrombidium* chiggers collected in Taiwan [95].

Chiggers are also suspected to be vectors of viral diseases [96]. The role of *L. scutellare* as possible vector of a Hantavirus causing epidemic hemorrhagic fever with renal syndrome (HFRS) in China was hypothesized [97]. The authors suggested that this mite could be naturally infected by HFRS virus and transmitted to vertebrates by biting and to its offspring via transovarian transmission. On the other hand, although the spread of Hantavirus had been thought to be exclusively by rodent excrement and urine, Hantavirus-RNA was detected in *Leptotrombidium* mites from Texas (2 larvae and 1 free-living predatory stage), suggesting a possible role in the transmission of Hantavirus pulmonary syndrome [98].

3. Chiggers and dermatitis

“Trombiculiasis,” also called “trombiculosis,” “trombidiosis,” “chigger dermatitis,” “scrub itch,” or “seasonal dermatitis” is defined as an skin allergic reaction (dermatitis) caused by the salivary secretion of biting chiggers [1,99]. In our experience, as well as it is described in the literature, trombiculiasis is a common but underreported ectoparasitosis that is probably often misdiagnosed [100]. In many cases, trombiculiasis was primarily confused with a plant allergy [29], as it was the case in our country. The better understanding of trombiculid mites’ life cycle and their interaction with humans have made possible a proper knowledge of this disease.

3.1. Etiology and epidemiology

Although not often reported in the literature, trombiculiasis is prevalent all over the world, except for the Arctic region [20]. However, it can be easily missed because it is normally transient and no systemic signs are present.

In nontropical areas, bites are particularly common in the late summer and early autumn, when outdoor activities are maximal and the peak of abundance of chiggers occurs [19,20,26,28,101]. Thus, trombiculiasis is also an important threat to travelers that visit infested areas being unaware of chiggers [37].

Mite islands are usually found in cleared land and scrub bush with grassy vegetation, warm soil temperatures, and high humidity. Suitable habitats also require the presence of potential hosts [31]. Trombiculids are also found in parks, gardens, lawns, and moist areas alongside lakes and streams [1]. Clusters of chiggers are usually waiting at elevated points of the ground-level vegetation, such as the end of grass stalk or on dried tree branches, until an animal or human passes by [8] (Figure 5).



Figure 5. Cluster of unfed chiggers. Original contribution.

People are usually bitten during outdoor activities for recreational or professional purposes such as hunting, hiking, mushroom picking, forestry work, etc. [8,28,101]. Although the rate of people bitten is very high, apparently some persons are preferred by the chiggers, resulting in massive parasitization, while others remain unmolested even in highly infested areas [26,28].

More than 3,000 species of chiggers are known, but about 15 frequently bite humans and domestic animals causing cutaneous reactions [102] (Table 2). Species currently considered as the most frequent cause of trombiculiasis are *E. alfreddugesi* in the Americas, *N. autumnalis* in Europe, *Eutrombicula batatas* in South America, and *Eutrombicula wichmanni* in Southeast Asia, Australia, and the Pacific Islands [4,28,37,103].

E. alfreddugesi is the most common and widespread trombiculiasis-producing species in the New World. The larvae are present in the late summer and early autumn in temperate regions

of its geographical range and throughout the year in the tropics and subtropics. It is particularly common in areas of secondary growth, along margins of swamps, and ecotones between woodlands and open fields or grasslands [1]. *E. splendens* is the second most common chigger attacking human in North America. This species is especially abundant in moist habitats such as swamps, bogs, and low-lying areas with rotting stumps and fallen trees. The seasonality is similar to *E. alfreddugesi* ones [1]. In addition, another mite causing trombiculiasis in the United States is *Eutrombicula lipovskyi*. It is present in moist habitats, generally characterized by an abundance of decaying logs and stumps bordering swamps and streams [1].

E. alfreddugesi and *E. batatas* are the main species implicated in South-America. However, trombiculiasis attributed to *N. autumnalis* (isango) is well-known in Peru [21]. Recently, a “pest” called “Qhapa,” with the same clinical features than trombiculiasis, has been associated with *E. batatas* in Bolivia [104]. In Venezuela, it is possible that a high percentage of the diagnosed scabies may actually be trombiculiasis [22]. Recently, *E. alfreddugesi* was implicated in a case of trombiculiasis in a tourist after a vacation in Brazil [20].

Seven chigger species are proven to cause trombiculiasis in Europe: *N. japonica*, *Neotrombicula zachvatkini*, *Euschoengastia xerothermobia*, *N. autumnalis*, *Kepkatrombicula desaleri*, *Blankaartia acuscutellaris*, and *Trombicula toldti* [6,29,105]. Recently, *N. inopinata* has been reported as a possible causative agent of trombiculiasis in Spain [8]. As stated above, it is generally accepted that *N. autumnalis* is the most common cause of trombiculiasis in Europe and the British Islands [1]. However, in many cases, the role of “harvest mite” has been attributed to *N. autumnalis* without enough taxonomic criteria. Therefore, other species may be causative agents of trombiculiasis, as occurred with *N. inopinata* in Spain [8] (Figure 6).

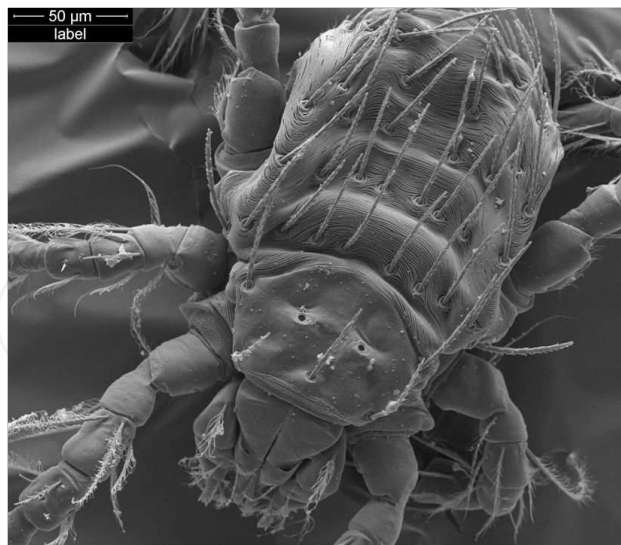


Figure 6. *Neotrombicula inopinata* (photo provided by Dr. Stekolnikov).

Although well known in many European regions, the scientific description of trombiculiasis cases have been only reported from Italy [36] and Spain [28]. Moreover, four different cases suspected of trombiculiasis caused by *N. autumnalis* were described in Croatia [106], and one

case attributed to harvest mites was informed in the United Kingdom [107]. In Europe, trombiculiasis is associated with the late summer and early autumn [26,28,36,101]. In fact, *N. autumnalis* is known as the “European harvest mite” due to the seasonality of the disease [87]. Nevertheless, in the last years, trombiculiasis-like skin reactions have been reported in Germany not only in summer and autumn but also in early spring and in winter [31].

In Southeast Asia, Australia, and the Pacific Islands, the main involved mite is *E. wichmanni*. Nevertheless, *E. sarcina* and species of genera *Odontacarus* and *Schoengastia* are also causative agents of trombiculiasis [4]. In addition, *Neotrombicula nagayoi* was involved in human trombiculiasis in Japan [5].

A single case of trombiculiasis has been reported in Africa. *L. subquadratum* was described as a cause of severe itching and dermatitis in humans and dogs in South Africa [108].

It is generally accepted that to suffer from trombiculiasis, the antecedent of direct contact with vegetation is required. Nevertheless, it is important to remark that one of the patients reported in Guarneri *et al.*, 2005 [36] was not in contact with vegetation but presented similar clinical features than the one that was hunting with the dogs. The authors speculated that trombiculiasis was transmitted by direct contact with the infected dogs. The hypothesis is supported in the fact that the dogs were frequently allowed to sit on the legs of the patients, and the patient’s lesions were concentrated on the abdomen and thighs. Dogs can be affected by chigger bites and suffer neurological and digestive forms that may be fatal. In our experience, massive infections are more frequent, and untreated dogs finally die. Dogs usually began with diarrhea, irritation, and ataxia. The precedent of visiting infested areas and the presence of “red points” in the dog’s eyes are essential clues to guide the diagnosis [25]

Another example of disease caused by chiggers but without direct contact to vegetation is also a case of conjunctivitis induced by *N. autumnalis*, reported in a patient with no history of travelling, hill walking, gardening, or contact with vegetation [109]. There, the authors suggested mite infestation occurred by direct contact with the patient’s cat. Nevertheless, there is no data about the cat in the manuscript. These cases suggested that close human contact with infected pets should be considered as an unusual route of trombiculiasis, so chigger transmission is possible without direct contact with infested soil or vegetation [36,109].

Previously, patients were rarely referred for dermatologist review unless symptoms were severe. Over the last 15 years, cases of severe trombiculiasis have increased in western Germany and in the United Kingdom [31,107]. The influence of climate and environmental variations, changes in leisure habits, and broader environmental awareness in the population have been speculated as possible explanations of this increase [26].

3.2. Clinical manifestation

Chigger bites are initially painless, and frequently the only sign of exposure is a severe itching. Then small, red bite like lesions appears on the skin [1,19]. Typical 1–2 mm diameter, pruritic, erythematous papules appear at the sites of the bites 3–24 h after exposure (Figure 7). [10,28,37,101,103].



Figure 7. Typical papules of trombiculiasis in a patient bitten in La Rioja, Spain. Original contribution.

The presence of papulovesicles, which may gradually progress to pustules, crusty, scabby, eczematous, and ulcerated confluent forms of skin lesions, has also been described [17,26,103]. The pruritus is very intense, especially at night in bed. Although the chigger is not present, the papules and discomfort may persist up to 2–3 weeks, but regression of localized itching is generally observed in 1 week [26]. Since trombiculid mites share habitat with hard ticks, people may result coinfecting. In fact, a patient suffering from trombiculiasis and having an “erythema migrans” (related to Lyme disease) was treated in our hospital. Furthermore, during an episode of trombiculiasis, two affected people and their dog had *R. felis* infection, possibly transmitted by fleas [110].

Chiggers usually “attack” in large numbers due to the clustering phenomenon, resulting in multiple grouped bites on infested hosts [32]. Given their preference for attaching where the skin is thin or in tighter contact with clothes, the bites tend to be concentrated around the knees, antecubital fossae, and ankles, thighs, axillary region, groins and genitalia, and wrists, and in areas constricted by clothing, such as along the belt line or the elastic borders or undergarments [1,17,26,28,101].

Trombiculiasis-causing chiggers do not survive more than 1–2 days feeding on humans due to the adverse host reaction and because they are removed by scratching [1,23]. The irritant effect of chiggers’ saliva seems to induce both dermal inflammatory reaction of moderate intensity and an adaptive immune response. These salivary components generally reveal relatively moderate lytic properties and weak immunological characters [111]. The type of skin inflammatory response during the feeding of trombiculid larvae is determined by concomitant factors such as the site of the parasite localization, condition of the host’s skin, among others [39]. Repeated exposures result in a more rapid and intense adaptive immune response [102]. Anyway, permanent or long-term human residents in an infested area increase their immunity as a result of continued bites, and some people can develop a high degree of tolerance to the antigenic substances injected by chiggers. However, the occurrence of unusual outbreaks of urticaria, increasingly severe pruritus or bulla formation, are indications of hypersensitivity to such antigenic substances [5]. It is clear that the natural hosts of trombiculids have to be

sensitized with respect to parasites that may lead the development of the strong specific inflammatory response [39, 111].

3.3. Diagnosis and treatment

Diagnosis is based on the clinical manifestations, taking into consideration the history of being in contact with vegetation and the seasonality. As the etiological agent of the trombiculiasis is rarely found in the skin of the patients, these reactions are often misinterpreted and has been wrongly associated to plant allergies, flea or mosquito bites, or even scabies [26]. Cutaneous findings are nonspecific, so clinical examination would probably lead to a wrong diagnosis of a nonspecific itchy dermatitis, leading to use inadequate or needless medications. Then an accurate anamnesis is essential for making such challenging diagnosis. Chigger bites should be considered whenever any unexplained skin eruption is presented to the physician.

Chiggers are not easily seen on human's skin with the naked eye, and common magnification lenses and even dermoscopy ($\times 10$ magnifications) have some limitations. Recently, videodermatoscopy ($\times 150$ magnification) has been used to diagnose trombiculiasis caused by *N. autumnalis* in a man with a well-documented diagnosis of scabies [100].

Differential diagnosis includes infestations with other mite species (e.g., the itch mite *Sarcoptes scabiei*), or blood-sucking ectoparasites, such as bed bugs, fleas, ticks, and mosquitoes. Also, hypersensitivity to chemical substances or photoallergic skin reaction to contact with a plant (*Meadow dermatitis*) should be taken into consideration [26].

Treatment is primarily symptomatic and consists of antipruritics, antihistamines, and topical corticosteroids [112]. In our medical consultation, supportive measures such as oatmeal baths are also highly recommended. Antibiotics might be needed in case bacterial superinfection resulting from repeated scratching occurs.

After being in known areas of chigger activity, the dermatitis can be minimized, and the recovery time can be significantly shortened, by taking a hot soapy shower or bath and washing clothes with soap and hot water. These good practices are recommended immediately after exposure, in order to remove both unattached and attached chiggers, before they have firmly anchored to the skin (generally within 3–6 h following attachment) [1,26]. Once the papules are present, scratching should be avoided in order to prevent to excoriate the lesions and the infection.

Patients should be advised on preventive measures, including avoidance of high-risk areas when larvae are active. Since in many cases these results are unreasonable and contact with trombiculid mites is unavoidable, chigger infestation may be minimized by wearing protective clothing and soaking socks and trouser legs with insect repellents [112]. Usually, the use of repellent sprays and lotions containing benzyl benzoate or diethyltoluamide has been recommended [29]. Permethrin was successfully used as a clothing treatment for personal protection against chigger mites [113]. However, the active ingredient is no longer available for this purpose in the European Union [10,26].

Although better than before, our contemporary knowledge on the biology and ecology of these mites is still extremely limited. Currently, no reliable recommendations for the control of mites, except from personal protection, can be given [26].

4. Other human diseases associated to chiggers

Apart from trombiculiasis, chiggers are responsible for other less frequent conditions. The summer penile syndrome is a seasonal acute hypersensitivity reaction attributed to chigger bites [114,115]. It occurs in young boys with a history of bites or outdoor exposure, and it is characterized by the rapid onset of edema and pruritus of the penile skin. It has been described most commonly in the spring and summer in different regions of United States [114,115]. Another example is the unique case of conjunctivitis induced by *N. autumnalis*, reported in United Kingdom [109]. The patient had a 2-week history of a painful, gritty, red left eye, which failed to improve with a liquid paraffin eye ointment. On examination, her conjunctiva was found to be mildly red and she had normal visual acuity. On close inspection, a live mite was identified in contact with the left upper eyelid margin.

5. Conclusions

Chiggers are worldwide distributed ectoparasites that have to be taken into account as human pathogens. Their medical importance is based on their role as vectors of scrub typhus and as causative agents of trombiculiasis.

Scrub typhus remains as one of the most life-threatening infection in Asian Pacific regions. The development of a prophylactic vaccine against *O. tsutsugamushi* is of great interest in endemic regions. In addition, special attention should be paid on recent reports of scrub cases typhus-like infections in unusual areas, and on reviewing the genetic diversity of the genus *Orientia*.

More research studies are necessary in order to clarify the relationship of chiggers with other bacterial or viral infections.

Trombiculiasis is an extended but underreported condition that should be considered when pruritic dermatitis in people exposed to vegetation occurs. In risky areas, personal protection is the unique recommendation to reduce the parasitisation. A deeper understanding of chiggers' life cycle, epidemiology and seasonality of trombiculiasis is required for a correct management of this annoying dermatitis.

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