



Case report

Rickettsia typhi infection presenting as severe ARDS

Liem T. Tran^a, Jessica L. Helms^b, Miguel Sierra-Hoffman^c, Mark L. Stevens^d,
Rafael Deliz-Aguirre^e, Mirams T. Castro-Lainez^f, Rafael J. Deliz^{g,*}

^aTexas A&M Detar Family Residency Program, Victoria, TX, 77901, USA

^bDetar Medical Group, 605 E. San Antonio St, Suite 310E, Victoria, TX, 77901, USA

^cPost Acute Medical, 506 E. San Antonio St, 3rd Floor, Victoria, TX, 77901, USA

^d82 Bahia St Victoria, TX, 77904, USA

^eBerlin, Germany

^fBlvd. Suyapa Ciudad Universitaria Tegucigalpa, Honduras

^gUIW School of Osteopathic Medicine, Laredo Medical Center, 1700 E. Saunders St. - P.O. Box 2068, Laredo, TX, 78044-2068, USA



ARTICLE INFO

Article history:

Received 18 September 2019

Accepted 18 September 2019

Keywords:

Rickettsia

Murine typhus

Acute respiratory distress syndrome

Pneumonia

Endemic

ABSTRACT

Murine typhus, also known as endemic typhus, is a disease resulting from an infection caused by the gram-negative bacillus *Rickettsia typhi*. Murine typhus is identified worldwide, predominantly in tropical and subtropical geographic locations. Transmission occurs through direct inoculation by an arthropod vector, most commonly the rat flea, *Xenopsylla cheopis*. rickettsial infections are notorious for disseminated infections throughout the endothelial cells. The increase in permeability is an immediate consequence and has the potential of leading to non-cardiogenic pulmonary edema, otherwise known as acute respiratory distress syndrome (ARDS). Clinical manifestations are non-specific and initially mimic typical viral etiologies, obscuring early diagnosis. As a result, clinicians often do not include rickettsial infections in their differential diagnoses. Definitive diagnosis is based on clinical recognition, epidemiologic awareness, and serological testing. Here we present a confirmed case of murine typhus in a young non-immunocompromised patient who developed ARDS one week from the initial onset of symptoms.

© 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Murine typhus, also known as endemic typhus is a disease resulting from infection by *Rickettsia typhi*. *Rickettsia typhi* is an obligate intracellular gram-negative bacillus causing zoonotic infections in humans. The bacteria is transmitted by fleas, most commonly the *Xenopsylla cheopis*, and primarily affects opossums, rats, mice, and household pets. Other potential vectors include mites and lice. Humans usually become infected by contamination of broken skin or mucosal surfaces with *Rickettsia*-containing flea excrement. *Rickettsia typhi* is identified worldwide with endemic areas in North and South America, Southeast Asia, Africa, Mediterranean countries, and Australia. These geographic regions of tropical and subtropical climate are natural reservoirs for

carrying vectors of *Rickettsia*. The clinical manifestations of rickettsial infections are analogous to that of many viral etiologies; a classic example is dengue fever, which at its initial stage is clinically difficult to differentiate. Hence, rickettsial infections mimic the clinical manifestations of many viral etiologies commonly found in these regions, resulting in a delayed diagnosis.

Case presentation

A healthy 32-year-old Hispanic female without significant medical history presented to the Emergency Department with fever, chills, generalized weakness, malaise, and body aches for the past 72 h. The symptoms progressed in severity, prompting her to report to the Emergency Department on two separate occasions.

On the initial presentation after 4 days of onset of symptoms, the physical exam revealed fever with a maximum temperature of 103.3 °F, tachycardia with a heart rate of 120 beats per minute, a blood pressure of 128/82 mmHg, respiratory rate of 18 breaths per minute, and an oxygen saturation of 99% on room air. Physical exam, other than mild tachycardia, was unremarkable. The patient denied chest pain, cough, shortness of breath, and abdominal pain. The patient resided in a rural community in coastal South Texas,

Abbreviations: ARDS, Acute Respiratory Distress Syndrome.

* Corresponding author.

E-mail addresses: liemtran19@gmail.com (L.T. Tran),

jessicahelms79@gmail.com (J.L. Helms), msh.xatracho@gmail.com

(M. Sierra-Hoffman), markmd205@gmail.com (M.L. Stevens),

Rafael.deliz.aguirre@gmail.com (R. Deliz-Aguirre), Mtcastrolainez@gmail.com

(M.T. Castro-Lainez), rdeliz@uiwtx.edu (R.J. Deliz).

<https://doi.org/10.1016/j.idcr.2019.e00645>

2214-2509/© 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

United States, and had dogs and cats at home. There is no recent exposure to communicable diseases, recent travel outside of the country, tobacco, alcohol, or illicit drug use.

Complete blood count showed white blood cells 4300 cells/mm³, neutrophils 85%, lymphocytes 11.4%, monocytes 3%, hemoglobin 12.4 g/dL, hematocrit 37.2%, platelets 230,000 per cubic mm, aspartate aminotransferase 38 U/L, alanine aminotransferase 28 U/L, and alkaline phosphatase 62 U/L. Rapid influenza A and B test, urinalysis, lactic acid, and thyroid-stimulating hormone were normal. Chest radiograph indicated mild peribronchial cuffing consistent with bronchitis (Fig. 1).

The patient received one liter of 0.9% normal saline intravenously and one oral dose of ibuprofen 800 mg. The patient was diagnosed with viral bronchitis, and discharged home.

Once at home, the patient deteriorated clinically and returned to the Emergency Department four days later with similar complaints of fever and body aches. The vital signs revealed a temperature of 101.2 °F, tachycardia with a heart rate of 125 beats per minute, a respiratory rate of 17 breaths per minute, a blood pressure of 118/56 mmHg, and an oxygen saturation of 99% at room air.

Physical examination was remarkable for diminished breath sounds to bilateral lung fields, tachycardia, dry mucous membranes, and decreased skin turgor. Laboratory data showed white blood cells 3600 cell/mm³, neutrophils 82.8%, lymphocytes 11%, monocytes 5%, hemoglobin 11.6 g/dL, hematocrit 33.2%, platelets 64,000 per cubic mm, aspartate aminotransferase 226 U/L, alanine aminotransferase 138 U/L, alkaline phosphatase 182 U/L, D-dimer >5000 ng/mL, lactic acid 2.4 mmol/L, and normal fibrinogen. Chest radiograph identified bilateral alveolar infiltrates bilaterally (Fig. 2). Computed tomographic angiogram of the chest was negative for pulmonary embolism but confirmed bilateral lower lobe consolidation.

The patient was admitted to the medical-surgical floor with a diagnosis of sepsis secondary to community-acquired pneumonia. The sepsis protocol was initiated with meropenem and voriconazole after obtaining blood and urine cultures. Despite resuscitation with 3 liters of intravenous 0.9% normal saline fluid, the patient

remained tachypneic and tachycardic. Six hours from presentation to the emergency department, the condition deteriorated, and became hypotensive with a blood pressure of 87/53 mmHg with a heart rate of 137 beats per minute, and a respiratory rate of 36 breaths per minute. Patient was transferred to the Intensive Care Unit requiring two more liters of intravenous fluid of 0.9% normal saline.

The initial impression was atypical pneumonia; thus, a serology panel for suspected zoonoses was immediately collected considering endemic microorganisms. By the second day of hospitalization, the patient developed a dry cough and quickly progressed to acute hypoxemic respiratory failure with a heart rate of 144 beats per minute and respiratory rate of 33 breaths per minute and a low oxygen saturation of 82%. An echocardiogram revealed mild right heart chamber dilatation and normal left ventricular systolic function with an ejection fraction of 65%. Arterial blood gases were obtained and showed PaO₂/FiO₂ of 102, consistent with moderately severe ARDS. This event was managed with non-invasive positive pressure ventilation. Voriconazole was discontinued due to lack of evidence to support invasive fungal infection. Meropenem and doxycycline were continued awaiting final serology panel and culture results. All bacterial cultures yielded negative results. By the fourth day, the patient had a nontender pink maculopapular rash to the bilateral lower extremities, without associated lymphadenopathy. At the seventh day, the zoonoses serology panel confirmed acute infection of murine typhus with Typhus Fever group IgM titer of 1:128 and murine typhus IgG titer of 1:258. Meropenem was discontinued, and the antimicrobials were deescalated to doxycycline monotherapy.

There was a weaning process from non-invasive positive pressure ventilation to high flow oxygen nasal cannula, then to low flow oxygen nasal cannula at 2 liters per minute. The patient was discharged home without oxygen supplementation after eight days of hospitalization. The treatment was completed with minocycline for 11 additional days, due to a nationwide shortage of doxycycline. The patient had generalized weakness at the moment of discharge from the hospital without other complaints.

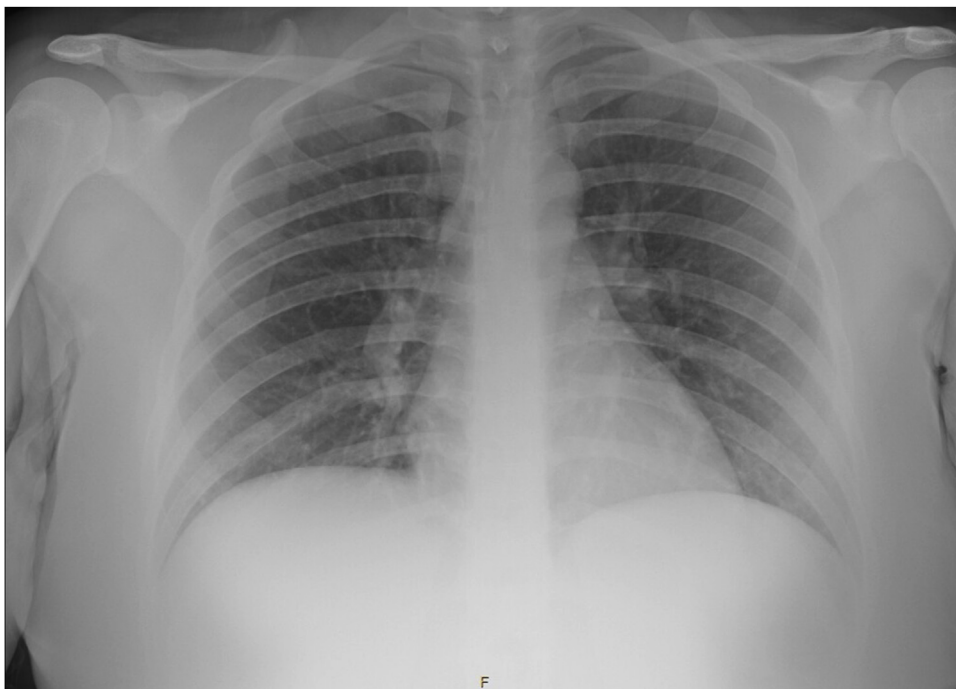


Fig. 1. Mild peribronchial cuffing opacities without pulmonary consolidations, consistent with bronchitis.

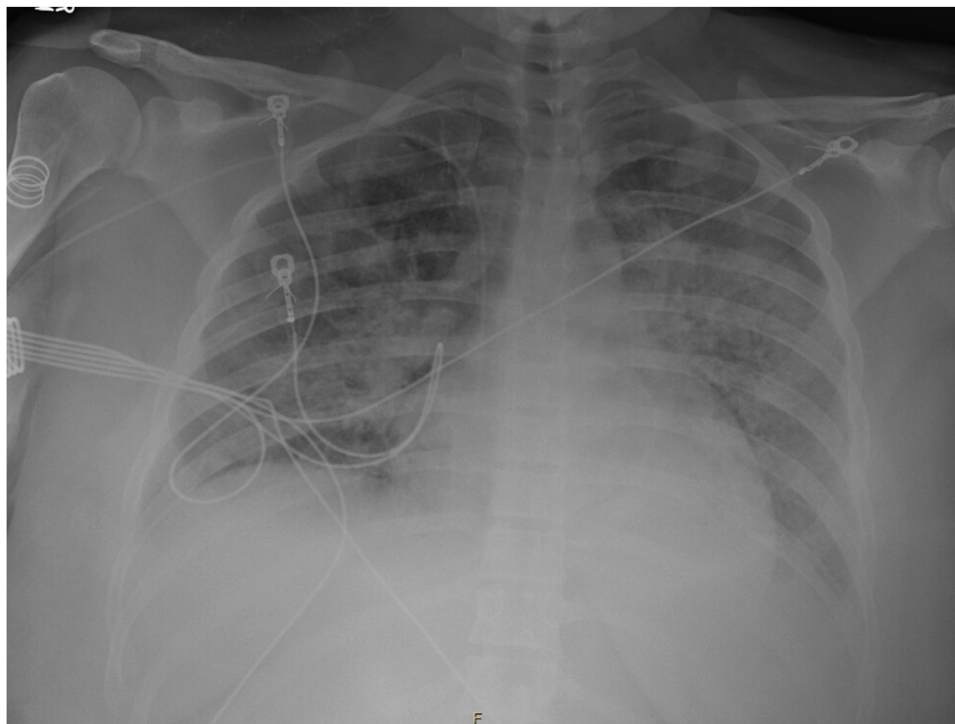


Fig. 2. Second day. Bilateral diffuse alveolar infiltrates with consolidations.

Discussion

The *Rickettsia* genus, found worldwide, necessitates a vector to infect its definitive host; among these are ticks, lice, mites, and fleas [1,2]. In the United States, the most common regions that report murine typhus are Southern California and South Texas [3]. In these areas, the vector is usually the cat flea, *Ctenocephalides felis*, with opossums being the usual host [4,10]. Cases are no longer isolated to the coastal territory during the last decade in the state of Texas, but have been reported further inland in northern regions as well [8]. The diagnosis is often initially elusive due to the non-specific symptomatology and physical findings in the early clinical stages. Lack of awareness of rickettsial infections may ultimately be associated with poor outcomes, including death [3,4]. Current statistics support the concept that murine typhus is no longer a rare disease in Texas. The reported cases have drastically increased by fivefold between the years of 2004–2017 [5].

The *Rickettsia* genus consists of small (0.3 - 0.5 by 0.8–2.0 micrometer) obligate intracellular Gram-negative bacilli. In 1906, Howard Ricketts, an American pathologist, successfully identified and isolated the causative organism from human serum through inoculation from guinea pigs. In his honor, the genus *Rickettsia* was established. In 1910, Ricketts died of epidemic typhus while studying an outbreak in Mexico City. To date, *Rickettsia* encompasses at least 27 species in which over 60% are pathogenic to humans [2,6]. Their classification is complex and has evolved. Currently, they are classified into four groups: The Ancestral group, Spotted Fever group, Typhus group, and Transitional group [1]. The first three groups are all recognized human pathogens [7]. There was a revolution in recognition of new *Rickettsia* species in the 21st century.

The typhus group remains limited to *Rickettsia prowazekii* and *Rickettsia typhi*. *Rickettsia prowazekii* is the cause of epidemic typhus. As its name implies, historically, it has been involved in severe epidemics especially in wartime and in refugee camps. Conversely, *R. typhi* is the cause of endemic typhus or murine typhus [2]. *R. typhi* is present worldwide and hence the name

endemic. *R. typhi* has the highest prevalence in tropical and subtropical areas, typically near warm coastal waters [8]. The primary reservoir of *R. typhi* is the *Rattus* genus. The rat flea, *Xenopsylla cheopis*, acts as the most common vector [2,9]. The fleas acquire the bacteria when their host rats go through bacteremic episodes. Humans acquire infections when infected fleas attach to human surfaces such as an open wound, mucosal surface, or through a direct bite [2,3].

The pathophysiology of rickettsial infections has several commonalities. Most significantly, they are acquired by direct inoculation as the bacteria attach directly to human target cells, usually to the endothelium [10]. This explains the universal clinical features of rickettsial infections, as they are a disseminated infection of the endothelium cells, with the ability to produce vascular permeability. Hence, causing non-cardiogenic pulmonary edema, otherwise known as ARDS, which we speculate occurred in our case.

Prior studies have identified the most common symptoms (Table 1). In general, typhus as a group presents with a triad of sudden onset of fever, headache, and myalgias [2,3].

Table 1
Signs and Symptoms. Adapted from Civen and Ngo [3].

Clinical finding	Range of occurrence %
Fever	98–100
Headache	41–90
Rash	20–80
Arthralgia	40–77
Hepatomegaly	24–29
Cough	15–40
Diarrhea	5–40
Splenomegaly	5–24
Insect bite	0–39
Nausea and vomiting	3–48
Abdominal pain	11–60
Confusion	2–13

Table 2
Previous Reported Cases of *R. Typhi* Meeting Criteria for ARDS.

First Author	Year	Age (y)/Sex	Location	Comorbidi-ties	Risk Factors	Presenting Symptoms	Treatments	Outcome
Vaart [14]	2012	40/M	Netherlands	none	Travel Insect Bites Exposure to Fresh Water	Fever Headache Sweating Nausea	Doxycycline	Survived
Malheir [15]	2017	38/F	Portugal	none	Travel Insect Bites	Fever Chills Malaise Myalgia Conjunctival Congestion	Ceftriaxone Doxycycline Oseltamivir	Survived
Sakamoto [16]	2012	56/M	Japan	none	Travel	Fever Headache Fatigue	Minocycline Ceftriaxone Ciprofloxacin	Survived
Chang [17]	2012	not reported	Taiwan	none	not reported	Fever Hyperbili-rubinemia	Moxifloxacin Minocycline	Died

Unfortunately, this clinical presentation is non-specific, which makes it a challenge for the most experienced clinicians. Previously published case reports frequently report laboratory abnormalities of elevated transaminases, thrombocytopenia, and moderate leukocytosis [3]. These abnormalities mimic a myriad amount of infectious and noninfectious febrile syndromes.

Knowledge of the genus epidemiology and patient's travel and exposure to vectors are important to recognize rickettsial infections [7]. Contrary to most systemic infections, diagnosing the infection by conventional culture is rarely performed and only available in specialized laboratories. Diagnosis by serology remains the mainstay and most widely used method of confirmatory assay worldwide. Initially, serology is not helpful to execute a diagnosis considering patients are rarely seropositive during the first week of their illness.

Immunohistochemical detection performed through cutaneous biopsy can serve as diagnostic confirmation of the rickettsial antigen in the acute stages of the disease. This is rarely performed in a daily clinical setting but can serve as a confirmatory test in autopsy specimens. However, the validity of this technique fails if antimicrobial therapy has been administered for longer than 48 h. For this reason, immunofluorescence assay (IFA) remains the mainstay for diagnostic serologic testing with surpassing sensitivity and specificity in comparison to prior testing methods [7].

Immunofluorescence assay is available in the Unites States for *Rickettsia typhi*. [11]. Contrary to most immune responses, the immunoglobulin IgM does not increase significantly earlier than the IgG isotype. Hence, testing for IgM does not yield higher sensitivity and specificity during acute early illness. A fourfold IgG titer increase from the baseline is conventionally accepted as confirmatory diagnosis of rickettsial illness [2].

With all these difficulties in regards to clinical presentation and confirmatory testing, early diagnosis in the acute care setting is challenging and often overlooked. Misdiagnosis and delayed empirical treatment can lead to complications, including meningoencephalitis, shock, and multiorgan failure. Lack of recognition is associated with greater than 4% mortality [9]. Therefore, clinical suspicion, early recognition, and empirical treatment are integral.

Adult respiratory distress symptom, ARDS, has been rarely reported as a complication of *R. typhi* infection as in this case (see Table 2) [12].

The presentation was critical enough to warrant a broad panel of laboratory tests. *Rickettsia typhi* was included in the differential diagnosis due to its high prevalence in coastal South Texas with the empirical use of doxycycline. The initial therapy included meropenem and voriconazole. Voriconazole was initiated initially due to our high local rates of histoplasmosis in comparison to other states as well as geographical areas within our state.

Histoplasmosis thrives best in regions with environmental elements that consist of open water reservoirs and have high soil humidity [13].

Reevaluation of imaging studies, lack of mediastinal lymphadenopathy, and negative HIV status made histoplasmosis less likely, and voriconazole was discontinued. Meropenem and doxycycline were continued pending cultures and serology; until a positive serum titer for *Rickettsia typhi* was reported on the seventh day, with a fourfold increase in titer. At that point, meropenem was discontinued, and doxycycline monotherapy was continued for the rest of the hospitalization. The patient was reevaluated one month after discharge and was asymptomatic.

Conclusion

Rickettsial diseases are relatively common in tropical and subtropical locations but often emulate benign viral etiology deterring early diagnosis and workup. ARDS is an infrequent complication of *Rickettsia typhi* infection. Clinical manifestations and initial zoonoses serology are non-specific and can delay accurate diagnosis. A high index of suspicion with rapid identification and appropriate treatment are crucial in tropical and subtropical regions. For this reason, epidemiologic awareness coupled with high clinical suspicion is instrumental for empirical treatment, early diagnosis, and prevention of severe complications secondary to rickettsial diseases.

Consent

The patient signed an informed consent to publish this article.

Declaration of Competing Interest

The authors do not have any financial or other conflicts of interest to disclose.

Acknowledgement

The authors declare that the study was unfunded and was the result of volunteer work.

References

- [1] Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. Update on tick-borne rickettsioses around the world: a geographic approach. *Clin Microbiol Rev* 2013;26:657–702, doi:http://dx.doi.org/10.1128/CMR.00032-13.
- [2] Fang R, Blanton LS, Walker DH. Rickettsiae as emerging infectious agents. *Clin Lab Med* 2017;37:383–400, doi:http://dx.doi.org/10.1016/j.cll.2017.01.009.

- [3] Civen R, Ngo V. Murine typhus: an unrecognized suburban vectorborne disease. *Clin Infect Dis* 2008;46:913–8, doi:<http://dx.doi.org/10.1086/527443>.
- [4] Azad AF, Beard CB. Rickettsial pathogens and their arthropod vectors. *Emerg Infect Dis* 1998;4:179–86.
- [5] Shuford J, Hunt P, Mayes B. Changing epidemiology of murine typhus in Texas. *Open Forum Infect Dis* 2018;5:S242, doi:<http://dx.doi.org/10.1093/ofid/ofy210.676>.
- [6] Howard Taylor Ricketts – building for a long future – The University of Chicago Library. 2019. . n.d. (accessed July 29, 2019) <https://www.lib.uchicago.edu/collex/exhibits/building-long-future/howard-taylor-ricketts/>.
- [7] Blanton LS. The rickettsioses. *Infect Dis Clin North Am* 2019;33:213–29, doi:<http://dx.doi.org/10.1016/j.idc.2018.10.010>.
- [8] Peniche Lara G., Dzul-Rosado K.R., Zavala Velázquez J.E., Zavala-Castro, J. Murine typhus *Colomb Médica CM* n.d.;43:175–180.
- [9] Murray KO, Evert N, Mayes B, Fonken E, Erickson T, Garcia MN, et al. Typhus group rickettsiosis, Texas, USA, 2003–2013. *Emerg Infect Dis* 2017;23:645–8, doi:<http://dx.doi.org/10.3201/eid2304.160958>.
- [10] Walker DH, Ismail N. Emerging and re-emerging rickettsioses: endothelial cell infection and early disease events. *Nat Rev Microbiol* 2008;6:375–86, doi:<http://dx.doi.org/10.1038/nrmicro1866>.
- [11] Abdad MY, Abou Abdallah R, Fournier PE, Stenos J, Vasoo S. A concise review of the epidemiology and diagnostics of rickettsioses: *Rickettsia* and *Orientia* spp. *J Clin Microbiol* 2018;56;. doi:<http://dx.doi.org/10.1128/JCM.01728-17>.
- [12] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–33, doi:<http://dx.doi.org/10.1001/jama.2012.5669>.
- [13] Maiga AW, Deppen S, Scaffidi BK, Baddley J, Aldrich MC, Dittus RS, et al. Mapping *Histoplasma capsulatum* Exposure, United States. *Emerg Infect Dis* 2018;24:1835–9, doi:<http://dx.doi.org/10.3201/eid2410.180032>.
- [14] van der Vaart TW, van Thiel PPAM, Juffermans NP, van Vugt M, Geerlins SE, Grosbush MP, et al. Severe murine typhus with pulmonary system involvement. *Emerg Infect Dis* 2014;20:1375–7, doi:<http://dx.doi.org/10.3201/eid2008.131421>.
- [15] Malheiro L, Ceia F, Alves J, Sobrinho-Simoes J, Rousa R, Sarmiento A, et al. Severe interstitial pneumonia due to murine typhus in a patient returning from Bali. *ID Cases* 2017;9:17–20, doi:<http://dx.doi.org/10.1016/j.idcr.2017.05.006>.
- [16] Sakamoto N, Nakamura-Uchiyama F, Kobayashi K, Takasaki T, Ogasawara Y, Ando S, et al. Severe murine typhus with shock and acute respiratory failure in a Japanese traveler after returning from Thailand. *J Travel Med* 2013;20:50–3, doi:<http://dx.doi.org/10.1111/j.1708-8305.2012.00678.x>.
- [17] Chang K, Chen Y-H, Lee N-Y, Cy Lin, Tsai JJ, Lu PL, et al. Murine typhus in southern Taiwan during 1992–2009. *Am J Trop Med Hyg* 2012;87:141–7, doi:<http://dx.doi.org/10.4269/ajtmh.2012.11-0465>.