Analysis of Health-Care Charges in Murine Typhus: Need for Improved Clinical Recognition and Diagnostics for Acute Disease

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Abstract. Murine typhus, caused by *Rickettsia typhi*, is an undifferentiated febrile illness with no available rapid and sensitive diagnostic assay for use during early disease. We aimed to compare the health-care charges in those diagnosed with murine typhus to those with influenza, a febrile illness with an available rapid diagnostic test. A comparison of health-care-associated charges at the University of Texas Medical Branch at Galveston demonstrated a median of \$817 for influenza versus \$16,760 for murine typhus ($P < 0.0001$). Median laboratory (\$184 versus \$3,254 [$P < 0.0001$]) and imaging charges (\$0 versus \$514 [$P < 0.0001$]) were also higher in those with murine typhus. Those receiving at least one imaging study during their illness were greater in the murine typhus group (91.3% versus 20.3%) ($P < 0.0001$). The median time needed to establish a confirmed or presumptive diagnosis was 2 days for influenza compared with 9 days for murine typhus ($P < 0.0001$). The median number of health-care encounters was greater for those with murine typhus (2 versus 1) ($P < 0.0001$). Eleven patients (15.9%) with influenza were hospitalized as a result of their illness compared with 16 (69.6%) with murine typhus ($P < 0.0001$). The estimated mortality based on disease severity at presentation by Acute Physiology and Chronic Health Evaluation II scoring was similar in the two groups—both had a median 4% mortality risk ($P = 0.0893$). These results highlight the need for improved clinical recognition and diagnostics for acute rickettsioses such as murine typhus.

INTRODUCTION

Murine typhus is caused by *Rickettsia typhi*, a Gram-negative, obligately intracellular bacterium. It is classically transmitted to humans by *Xenopsylla cheopis*, a flea that infests rats worldwide.¹ *Ctenocephalides felis* has been implicated as the vector in a suburban cycle of transmission in the United States that involves opossums.^{1,2} In the United States, murine typhus is endemic in southern California, Hawaii, and South Texas.^{2–5} Recently, there has been a reemergence in other parts of Texas^{6,7} with evidence that suggests a northward spread.⁸ Manifestations of murine typhus are generally undifferentiated and include flu-like symptoms such as fever, headache, and myalgias.⁹ Rash, often considered the *sine qua non* for consideration of a rickettsial illness, is only present in 59% of patients (data collected from 10 large case series reporting a total of 841 patients)^{9–18} and is not usually present early in the course. When the diagnosis is not apparent, diagnostic workup can be costly, time-consuming, and lead to unnecessary hospitalizations. Currently, there is no rapid sensitive diagnostic test for rickettsioses, such as murine typhus, for use during acute infection. Because the usual diagnostic method—serology—is retrospective (only 15–55% of patients have reactive antibodies in the first week of illness),^{9,16,19} clinical recognition and empiric therapy with doxycycline are imperative.²⁰ This study aimed to compare the health-care charges in those with murine typhus compared with those with influenza, a febrile illness of similar severity with an available rapid diagnostic test. We hypothesized that the cost of care for patients with murine typhus, as measured by health-care charges, would be more than those with influenza.

METHODS

A retrospective evaluation of adult patients (18 years and older) at the University of Texas Medical Branch (UTMB) with murine typhus and influenza was performed. Patients with murine typhus were identified using data collected during patient recruitment for a study of murine typhus in Galveston⁶ and using international classification of diseases (ICD)-10 diagnosis codes. The ICD-10 search was performed to query medical records from January 1, 2012 to January 31, 2016. Charts were reviewed to verify the diagnosis of murine typhus and to classify them as confirmed or probable. A confirmed case of murine typhus was defined as a compatible illness with laboratory evidence yielding IgG seroconversion against *R. typhi* (nonreactive at a cutoff titer of 1:64 to reactive at a titer of at least 1:128) from acute- and convalescent-phase sera, a 4-fold increase in serum IgG titer against *R. typhi* from acute- and convalescent-phase sera, polymerase chain reaction (PCR) detection of rickettsial DNA in acute-phase blood or tissue; or isolation of *R. typhi* from blood (each as used in a previous study).⁶ Acute-phase was defined as the time during acute illness and convalescent-phase was defined as 2–4 weeks after the onset of illness. A probable case was defined as a single IgG titer of at least 1:256 during a clinically compatible illness.⁶ Confirmed and probable cases of murine typhus were included for analysis.

For influenza cases, a data report was generated using ICD-10 diagnosis codes having “influenza with other respiratory manifestations.” The ICD-10 search was performed to query medical records from January 1, 2012 to January 31, 2016. Charts were examined to verify clinically compatible symptoms of influenza and confirmatory diagnostic testing. Consecutive eligible patients with influenza, confirmed by nasal wash PCR, were matched to those with murine typhus with respect to age (± 1 year) and gender in a 3 to 1 ratio (influenza:murine typhus).

Examined data included health-care charges, disease severity, number of encounters, and the presenting health-care setting (i.e., clinic, urgent care, and emergency department). Total charges encompassed inpatient and/or outpatient

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facility, professional, laboratory, and radiologic imaging charges during all cumulative and associated health-care encounters at our institution. Charges for laboratory work (i.e., hematology, chemistry, and microbiology) and imaging charges were also examined individually. Charges from encounters at outside institutions were not obtained. The type and number of radiologic imaging studies were recorded for each patient. Disease severity at presentation was calculated by the APACHE II scoring system.²¹ As not every patient had every component of the score (e.g., arterial blood gas), an assumption was made that a value's omission was not detrimental to the score.

Records were examined to determine the time needed to either confirm a diagnosis (influenza) or establish a presumptive clinical diagnosis to initiate appropriate antibiotic treatment (murine typhus). The time was calculated in whole days, with the day of initial presentation counting as day 1, and each additional calendar day that a patient remained in the hospital (if applicable) counting as an additional day. For influenza, time to diagnosis was the number of calendar days from symptom onset to when the confirmatory influenza PCR returned positive. For murine typhus, time to diagnosis began from symptom onset to when a presumptive clinical diagnosis was made and an effective anti-rickettsial antibiotic was prescribed. An encounter was defined as a physician or health-care visit for the current illness that was documented in the electronic record. We also included encounters to non-UTMB facilities that were documented in the chart as noted by histories obtained from treating clinicians (charges from these facilities were not obtained). Records were also examined to determine if patients were hospitalized for their illness.

Total charges, laboratory charges, imaging charges, and time needed to establish a confirmed or presumptive diagnosis were considered as continuous. We report the median and interquartile range (IQR) and compare the two diagnosis groups with a Mann-Whitney *U* test as appropriate for non-normally distributed outcomes. Hospitalization (yes/no) and having zero versus at least one imaging study was considered as categorical. We report the proportion and compare the diagnosis groups with Fisher's exact test. Number of encounters and estimated mortality were considered as ordinal. We report the number of patients with each outcome and compare diagnosis groups with a Mann-Whitney *U* test. Analysis was performed using GraphPad Prism 7.0a (GraphPad Software, Inc., La Jolla, CA). The UTMB institutional review board approved this study.

RESULTS

A total of 92 patients were included: 23 with murine typhus and 69 with influenza. All of the patients with murine typhus were identified through ongoing investigations and recruitment of patients with rickettsioses in Galveston, TX, during the study period (January 1, 2012, to January 31, 2016). No additional patients with murine typhus were identified via ICD-10 search. The 69 age- and gender-matched patients with influenza were chosen from a list of 3,564 influenza patients collected by database query during the aforementioned study period.

Of the patients with murine typhus, 13 (56.5%) were confirmed and 10 (43.5%) were considered probable. Of the confirmed cases, one was diagnosed via culture and blood

PCR (as reported in detail elsewhere),⁶ one via 4-fold increase in indirect immunofluorescence assay (IFA) titer and PCR of a skin sample (as reported in detail elsewhere),²² and the remaining via 4-fold increase in the IFA titer. Among the 69 with influenza, 60 (87.0%) had influenza A and 9 (13.0%) had influenza B. Patients with murine typhus initially presented to the following settings: clinic (30.4%), urgent care (4.4%), and emergency department (65.2%) and those with influenza initially presented to the following: clinic (42.0%), urgent care (40.6%), and emergency department (17.4%).

Comparison of total charges demonstrated a median of \$817 (IQR: \$297) for influenza versus \$16,760 (IQR: \$19,582) for murine typhus ($P < 0.0001$) (Table 1). Median laboratory charges for those with influenza was \$184 (IQR: \$92), whereas that for murine typhus was \$3,254 (IQR: \$5,833) ($P < 0.0001$). Influenza patients also had less expense in regard to imaging studies. The median imaging charges were \$0 (IQR: 0) compared with patients with murine typhus, which had median imaging charges of \$514 (IQR: \$2,686) ($P < 0.0001$). Those receiving at least one imaging study during the course of their illness were greater in those with murine typhus (91.3% versus 20.3%) ($P < 0.0001$). The murine typhus group also had more patients receiving radiologic studies in the categories of chest, abdominal, and brain/neurologic imaging (Table 2).

The median time needed to establish a confirmed or presumptive diagnosis was 2 days for influenza (IQR: 1 day) compared with 9 days for murine typhus (IQR: 5 days) ($P < 0.0001$). Patients with murine typhus had more health-care encounters associated with their illness. The median number of encounters was 1 for influenza (IQR: 0) and 2 for murine typhus (IQR: 2) ($P < 0.0001$). Eleven patients (15.9%) with influenza were hospitalized as a result of their illness versus 16 (69.6%) with murine typhus ($P < 0.0001$). The estimated mortality based on disease severity at presentation (calculated by APACHE II scoring) did not show a difference between the two groups—both had a median 4% mortality risk (influenza [IQR: 0] versus murine typhus [IQR: 4%]) ($P = 0.0893$). No patient in either group died as a result of their illness.

DISCUSSION

Murine typhus is an often unrecognized cause of febrile illness throughout the world. Although once a more frequent cause of illness in the United States, effective vector control practices largely eliminated rat flea-transmitted *R. typhi* as a cause of disease.^{23,24} In areas of the United States that remain endemic and in areas where the disease is increasingly recognized, a suburban cycle of transmission involving opossums and their fleas have been implicated in the transmission of *R. typhi* to humans.^{1,7,25–27} Unfortunately, clinical signs and symptoms are relatively undifferentiated and make the diagnosis difficult to recognize. Furthermore, there is no rapid sensitive diagnostic test for murine typhus. Even PCR assays with excellent analytic sensitivity fail to detect rickettsial DNA within clinical specimens of those with typhus group rickettsioses—sensitivity of blood and skin biopsy specimens is 3% and 6%, respectively.²⁸ During investigation of murine typhus in Galveston, we noted that many patients had extensive medical workups and hospitalizations for fever of unknown origin before the consideration of the diagnosis of murine typhus. In an effort to stress the importance of early recognition, we sought to quantify these observations.

TABLE 1

Comparison of health-care charges, time to diagnosis, health-care encounters, and estimated APACHE II mortality risk in those with murine typhus vs. age- and gender-matched controls with influenza

	Influenza					Murine typhus					P value
	Median	Range		IQR-25	IQR-75	Median	Range		IQR-25	IQR-75	
		Min	Max				Min	Max			
Total charges	\$817	\$51	\$53,752	\$741	\$1,038	\$16,760	\$0	\$73,246	\$4,807	\$24,389	< 0.0001
Laboratory charges	\$184	\$0	\$5,310	\$184	\$276	\$3,254	\$0	\$16,625	\$772	\$6,605	< 0.0001
Imaging charges	\$0	\$0	\$4,996	\$0	\$0	\$514	\$0	\$7,897	\$0	\$2,686	< 0.0001
Time to diagnosis (days)	2	1	9	2	3	9	3	28	8	13	< 0.0001
Health-care encounters	1	1	3	1	1	2	1	4	1	3	< 0.0001
Mortality risk*	4%	4%	15%	4%	4%	4%	4%	15%	4%	8%	0.089

* Estimated by APACHE II scoring at presentation.

Our study demonstrates that medical charges, number of medical visits, and duration of illness until establishment of a presumptive diagnosis are greater in those with murine typhus compared with those with influenza, which has an accurate and fairly rapid diagnostic test (i.e., PCR). Although not addressed in this study, there is likely an element of heterogeneity among various clinicians treating those with murine typhus. For example, early infectious disease consultation may have contributed to an earlier presumptive diagnosis and empiric treatment in many of these patients. Furthermore, measured parameters of illness and costs for those with murine typhus may have decreased over time as local clinicians became more aware of the entity. This was the case in at least one instance where a patient with murine typhus did not have any billed charges (seen, treated, and worked up as an outpatient *pro bono* as the patient had no means to pay for medical care). The number of patients with murine typhus receiving radiologic imaging was striking when compared with patients with influenza. Pulmonary and central nervous system involvement sometimes occurs in those with murine typhus; but in this study, review of hospital courses and imaging results did not support severe complications in this group.

Texas reports the most cases of murine typhus in the United States, indicating a higher prevalence, greater recognition, or

perhaps a combination of both. Although recognition is not yet optimal in many parts of Texas, including Galveston, it is possible that the divergence of costs is even greater in other areas, where the disease may not be recognized by local physicians. It should be noted that heterogeneity in circulating strains of influenza from year to year may influence the severity of illness in those with influenza. Although no subtyping was performed for the purposes of this analysis, the predominant influenza A subtypes circulating during the time period of this study include H3N2 (2011/2012, 2012/2013, and 2014/2015)^{29–31} and H1N1 (2013/2014 and 2015/2016).^{32,33} No major antigenic shift occurred during this time period.

Weaknesses of this study include its retrospective design and inclusion of relatively few patients with murine typhus. Because of the low apparent incidence of murine typhus, these limitations are inherent. Another weakness is the exclusion of children. At the time data were collected for this study, no children had been diagnosed with murine typhus at our institution—a surprising finding that will likely change with increased efforts aimed toward physician education. We chose to use influenza as a comparison because of the similarity in regard to many of its signs and symptoms, availability of rapid diagnostics, and high incidence. The last attribute allowed us to compare three influenza patients to each with murine typhus. Although the prevalence of influenza allowed us to control for age and gender, we were not able to locate enough patients to match by raw APACHE II score. Therefore, to avoid bias by selecting a cohort of uncomplicated influenza patients, we chose the first eligible age- and gender-matched influenza cases as a method of selection. In the end, the estimated mortality based on APACHE II scoring did not show a significant difference between the two groups, but it must be noted that other factors related to these diseases (e.g., potential for neurologic complications with murine typhus or bacterial superinfections in those with influenza) may not be captured by using this scoring system at presentation.

Despite matching, these two infections remain fundamentally different. In Texas, murine typhus occurs year round but increases as the weather warms, with a peak in late spring to early summer.^{8,9} An uptick in cases of murine typhus has also been noted in the winter.⁸ Although influenza has a clear winter seasonality, a clue that may help clinicians recognize the flu, overlap with sporadic cases of murine typhus is possible. The case fatality of murine typhus has been reported to be 0.3% and 0.4% in a review of 1,801 patients reported in the literature³⁴ and in 3,048 patients reported to the Texas Department of State Health Services, respectively.³⁵ Based on CDC estimates of mortality and the number of cases of

TABLE 2

Number of patients receiving diagnostic imaging: murine typhus vs. influenza

Radiologic studies	Influenza n (%)*	Murine typhus n (%)†	P value
Any imaging	14 (20.3%)	21 (91.3%)	< 0.0001
Chest imaging	14 (20.3%)	21 (91.3%)	< 0.0001
X-ray	14 (20.3%)	21 (91.3%)	—
Multiple X-rays	2 (2.9%)	9 (39.1%)	—
CT chest	2 (2.9%)	6 (26.1%)	—
Abdominal imaging	3 (4.3%)	11 (47.8%)	< 0.0001
Acute abdominal series	1 (1.4%)	2 (8.7%)	—
US abdomen	0	4 (17.4%)	—
US kidneys	1 (1.4%)	1 (4.3%)	—
CT abdomen/pelvis	1 (1.4%)	8 (34.8%)‡	—
Brain/neuroimaging	3 (4.3%)	7 (30.4%)	0.002
CT head	3 (4.3%)	6 (26.1%)‡	—
MRI brain	1 (1.4%)	2 (8.7%)	—
MRA head	0	1 (4.3%)	—
MRA neck	0	1 (4.3%)	—
Other imaging	1 (1.4%)	1 (4.3%)	0.44
CT sinuses	1 (1.4%)	0	—
MRI lumbar spine	0	1 (4.3%)	—

CT = computed tomography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; US = ultrasound.

* Number and percentage of 69 patients with influenza receiving specified imaging studies.

† Number and percentage of 23 patients with murine typhus receiving specified imaging studies.

‡ CT abdomen/pelvis was performed twice in one patient and CT head was performed twice in another.

influenza since 2010, the case fatality of influenza is between 0.12% and 0.16%,³⁶ but in some situations can be much higher. Estimates of the case fatality rate during pandemics range from 0.5% to 5.3% (depending on the age range of the population),³⁷ and in a study of nursing home patients in the late 1990s, the case fatality rate was 3.8%.³⁸

In addition to the winter seasonality of influenza, the presence of respiratory symptoms may also clue a clinician toward the diagnosis of influenza. Symptoms of influenza such as rhinorrhea (73%), sore throat (65%), and nonproductive cough (49%)³⁹ have been documented to occur more frequently than they do in murine typhus, where sore throat and nonproductive cough occur in 14% and 27%, respectively.³⁴ Despite the frequency of upper respiratory symptoms, these are often overshadowed by the systemic complaints⁴⁰—the latter of which are more similar to those of murine typhus. Fever is almost universal and occurs in 98% in both groups.^{9,39} Other similar symptoms (influenza versus murine typhus) include headache (91% versus 81%), myalgias (61% versus 52%), abdominal pain (14% versus 18%), and nausea/vomiting (33% versus 27%).^{34,39}

In conclusion, the inability to recognize and differentiate murine typhus from other febrile diseases, as demonstrated in a cohort of patients in Galveston, translates to high cost, time lost in those afflicted, and prolonged illness. These results highlight the need for rapid and accurate diagnostics for acute rickettsioses such as murine typhus, which are not provided by serologic investigation. Indeed, diagnostic techniques with the ability to offer accurate and timely results can aid in clinical decision-making, which leads to efficient and effective patient care.^{41,42} Furthermore, recognition by clinicians, and thus effective empiric antimicrobials, can make great strides toward speedy recoveries and savings in health-care expenditures.

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