

Murine Typhus: Endemic *Rickettsia* in Southwest Texas

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ABSTRACT

Murine Typhus is a zoonosis caused by the organism *Rickettsia typhi* and is transmitted to humans by fleas. It is endemic in several areas of Texas, California and Hawaii where the vector is supported predominantly by rodents in addition to opossums, domestic and feral cats and domestic dogs. We present a typical case in an adult from Corpus Christi, located in one of the four endemic areas in Texas. Included is an overview of the organism's pathogenicity and our host responses, both influencing the milder clinical course seen with this species of *Rickettsia*.

ABBREVIATIONS: PCR – Polymerase Chain Reaction, DDT – dichlorodiphenyltrichloroethane, CDC – Centers for Disease Control and Prevention, INF – Interferon, TNF – Tumor Necrosis Factor, NK – Natural Killer Cell, LCMV- Lymphocytic Choriomeningitis Virus, CMV - Cytomegalovirus

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INTRODUCTION

The Medical Technology Program at Texas A&M Corpus Christi came up for re-accreditation in the spring of 2011 with a new program director left to

tackle the task, an unenviable position. With just weeks before the site visit, her husband developed fatigue, muscle aches, headache and a temperature up to 105°F. Being a Medical Technologist with a PhD in Molecular Biology, diagnoses from benign to downright frightening inevitably were brought to mind. The combination of events made these few weeks exponentially stressful.

The pathogen, well known in this region, was *Rickettsia typhi* and the disease, murine typhus. This case study describes the evolution of symptoms, diagnostic tests ordered and clinical laboratory results spanning an eight day period. Following is a comprehensive discussion covering the organism's description and virulence, host symptoms and defenses, current methods for diagnosis and typical demographic and epidemiologic findings.

Case Presentation

A 54-year-old Caucasian male, self-employed in a classic car restoration shop, complained of flu-like symptoms for 3 days before presenting to his physician. He experienced fatigue, muscle aches, headache, and temperature up to 105°F. There was no neck stiffness. The patient was monitored in the physician's office for 45 minutes and was escorted to the Emergency Room following several episodes of syncope. He had some nausea and vomited once in the emergency room. He did have a cough and some congestion but only complained of the headache, fever, and body aches.

Initial lab results, with the exception of elevated liver enzymes and an increased D-dimer were unremarkable. A CT of the chest ruled out a pulmonary embolism and doppler revealed a right lower leg deep vein thrombosis (DVT). The patient has a past medical history of hypertension, diabetes mellitus type 2, DVT, basal cell carcinoma, multiple rib fractures, and Achilles tendon rupture.

Upon questioning, the patient reported that he had

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been in the McAllen area judging an outdoor car show and that he had recently been restoring a vehicle that had been removed from an old barn and had large quantities of rodent feces throughout the car.

Tamiflu was started, even though the flu test was negative, and he was placed on doxycycline which was continued throughout his workup. Viral titers for hepatitis, dengue fever, hantavirus, murine typhus, cytomegalovirus (CMV), lymphocytic choriomeningitis virus (LCMV), and influenza A and B were ordered.

Over the next 3 days, the patient continued to experience headaches, chills and fever. The patient's lab results showed a decline in his white blood cell count and platelet count for the next 3 days (Table 1) and decreased total protein, albumin, and calcium (Table 2). The most dramatic changes were visible in the patient's two major liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The patient's AST increased over 9 times the upper limit and the ALT increased over 5 times the upper limit (Table 2). A CT scan showed decreased liver density and fatty infiltration of the liver.

Table 1. Principle Hematology Findings

Date	WBC (K/mm ³)	Platelet (x10 ³)
2/18/2011	7.9	161.0
2/19/2011	4.3	119.0
2/20/2011	2.8	107.0
2/21/2011	3.0	117.0
2/22/2011	6.0	133.0
2/23/2011	7.6	162.0
2/24/2011	7.5	230.0
Normals	4.8 – 10.8	150-450

On the fourth day following admission, arterial blood gases were ordered with a chest x-ray as the patient's oxygen level had dropped and he was experiencing pulmonary complications. Bronchial washings were collected and normal findings were reported for gram stains, virus, fungal, and tuberculosis cultures. Zosyn, a broad spectrum antibiotic and Zithromax were added to the medications. Intubation was considered on day 6 if the patient's lung capacity deteriorated overnight. Multiple serology tests revealed that the patient was negative for hepatitis, infectious mononucleosis, LCMV, dengue fever, murine typhus, hantavirus, CMV, and influenza A and B.

The infectious disease specialist was consulted on day 5 and provided a diagnosis of murine typhus, regardless of the reported titer of < 1:64, based on the patient's history and symptoms. Titers for murine typhus take between 5 and 10 days to return positive if infected. The patient was continued on doxycycline alone and one dose of ceftriaxone, and a short course of prednisone.

Table 2. Principle Chemistry Findings

Date	Total Protein (g/dL)	Albumin (g/dL)	Calcium (mg/dL)	AST (U/L)	ALT (U/L)
2/18/2011	7.5	3.5	8.7	72	91
2/19/2011	6.6	3.0	8.4	103	112
2/20/2011	6.2	2.8	8.2	227	197
2/21/2011	6.3	2.8	8.5	354	347
2/22/2011	6.0	2.6	8.6	203	303
2/23/2011	6.7	2.6	8.8	107	257
2/24/2011	6.3	2.4	8.5	50	177
Normals	6.4–8.2	3.4–5.0	8.7–10.5	15-37	30-65

The patient was significantly better the next day and the lab values showed improvement after day six. He continued to improve and was dismissed from the hospital on day 8 following admission with a diagnosis of murine typhus with pulmonary complications. No additional titers were drawn. Regular follow ups with the patient continued to show improvements in his physical state.

What the patient experienced including symptoms, lab values and recovery times after the administration of doxycycline was typical of patients with murine typhus. The days leading up to the diagnosis are frightening but luckily, we are in an endemic area where the local physicians are always on the lookout for this zoonotic pathogen. With the vague symptoms, diagnosis would likely be delayed elsewhere.

Etiological Agent and Mode of Transmission

Rickettsiae are obligate intracellular organisms that are Gram negative and generally rod shaped, and highly pleomorphic, ranging in size from 1 to 4 microns. Most have a polysaccharide rich slime layer. Taxonomically, they are part of a diverse gram-negative group called alpha-proteobacteria which also contains the pathogen *Brucella*. The phylogeny within the genera Rickettsia identifies four groups based on whole-genome analysis; Ancestral, Transitional, Spotted Fever and Typhus.¹

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These groups differ in their surface-exposed protein, lipopolysaccharide antigens and their ability to stimulate host cell actin polymerization for movement within and out of the cell. The tail of the actin filaments creates a propulsive force allowing this movement. Both Rocky Mountain spotted fever (*R. rickettsiae*) and epidemic typhus (*R. prowazekii*) are associated with a higher rate of morbidity and mortality than murine or endemic typhus (*R. typhi*) and differences in actin polymerization may be responsible for some of the difference in pathogenicity between the organisms.^{2,3}

As a group, rickettsiae live in eukaryotic cells and have parasitic or mutualistic association with vertebrates or arthropods.⁴ They are believed to have lost genes needed for essential biosynthetic pathways. This loss forces them to depend on host cells to provide needed nutrients.³ Though unable to use glucose, they are able to oxidize amino acids and use intermediate products generated by the Krebs cycle, such as glutamic acid and succinic acid, in order to generate ATP. Many live exclusively in and obtain these products from the host cytosol.⁵

Members of the family Rickettsiaceae are found in ectoparasitic arthropods such as ticks, lice, fleas, mites, and chiggers that feed on blood. The mammals may serve as an infected reservoir host or simply a blood meal. These organisms become zoonotic pathogens in humans because they are transmitted via feces or bites.⁵

As the name murine typhus indicates, fleas have been classically associated with infected rodents and this has been the most common enzootic cycle responsible for transmission of *Rickettsia typhi*, the cause of murine typhus. The urban and Norway rats, *Rattus rattus*/*Rattus norvegicus*, and their ectoparasite the oriental rat flea, *Xenopsylla cheopis*, make up this cycle. Recent field work in areas endemic for murine typhus indicate that it may be more commonly linked to opossums, feral and domestic cats and transmitted via the cat flea, *Ctenocephalides felis*.^{6,7,8} The organism *R. felis* is found in overlapping areas and is likely to infect the cat flea.

For *Rickettsia typhi*, after feeding on an infected host, the midgut intestinal epithelium of the flea is infected and the organisms are excreted in the feces. The organism can also infect the flea's reproductive organs, enabling transovarian transmission.^{5,3} Contamination of

the flea bite site by flea feces containing *R. typhi* is the cause for contraction of the pathogen rather than the bite of the arthropod. Because the flea salivary glands are not infected, as is seen with *R. rickettsiae* and the tick, transmission is unlikely to develop from the bite. Contraction through respiratory or conjunctival routes with feces is also likely because bacteria remain infective in dried feces and dead parasites.⁵ Some species of *Rickettsia* are pathogenic for the arthropod and this plays a role in the overall incidence rates seen in humans, *R. typhi* does not shorten the life span of the infected flea.^{1,3}

R. typhi has been found in hard ticks that pick it up when they take blood meals from infected vertebrates. Co-infection in arthropod vectors is not uncommon.⁹ *R. felis* is a species which is found in the same geographic area as *R. typhi* and shares reservoir host and vectors. Its symptoms and serological results are very similar. Studies indicate that it is more prevalent in the opossum and cat population than *R. typhi* making a definitive diagnosis harder.¹⁰

Pathophysiology

For murine typhus, endothelial injury and the accompanying immune response associated with vascular inflammation are responsible for the most frequent symptoms patients report which include the clinical triad of fever, headache and rash. After entering the skin through breached epithelium, the organism spreads via the bloodstream or lymphatics. *Rickettsia* are one of a small group of organisms which have a predilection for vascular endothelium.⁵ Brain, lungs and other visceral organs and skin are affected to various degrees depending on the dose and species.

Initial binding to the endothelial membrane is believed to be between an endothelial surface protein called Ku70 and the bacterial membrane protein OmpB.³ The organism is able to enter the cell through induced endocytosis or phagocytosis following binding and it escapes from the endosomes into the cytoplasm following production of an exoenzyme. They divide by binary fission and stay in the cell until it bursts.¹¹ Organisms re-infect new endothelial cells either adjacent or distant. Unlike *R. rickettsia* that replicates minimally before exiting, *R. typhi* fills the cell to capacity before leaving or being release due to cell rupture.¹² The organisms' ability to harness and

polymerize host cell actin determines its range of movement within the cell and through the membrane. Organisms such as *R. rickettsia* trigger more directional motility allowing them to more freely leave one cell to re-infect another, a feature that likely increases pathogenicity of this and other species.

Studies suggest that some *Rickettsia* have the ability to inhibit internal and external apoptotic signals in order to prolong their survival within the host cell and thereby allowing them to multiply and re-infect neighboring cells.³ It appears that they are activating the transcriptional factor NF- γ B which slows the triggering of apoptosis even though the cell is being targeted by immune cells, inflammatory cytokines and its own internal stress signals.¹² Another important factor affecting an organisms overall pathogenicity involves its ability to affect the magnitudes and kinetics of host cell-signaling.²

Symptoms

Murine typhus falls into a large group of conditions which cause vague symptoms often resembling the flu. If the patient also presents with a rash, lives in an endemic area and recalls a recent flea bite, there should be no problem getting them on doxycycline immediately. Many cases though lack one or more of these clues and for this reason, even in endemic areas, diagnosis presents challenges. For patients presenting with the clinical triad of fever, headache and rash, a prompt diagnosis can be expected.

Dr. Rachel Civen and Van Ngo from the Los Angeles County Public Health Department reviewed case studies in literature from the United States, Greece, Spain and Thailand in an attempt to globally describe the presentation of murine typhus. Table 3 represents a summary of the frequency of symptoms experienced by patients confirmed to have murine typhus. Keep in mind that most cases present as an acute, self-limited illness after an incubation period of between 7-14 days and most occur without complications.⁸

Our patient presented with classical symptoms but lacked the rash as is common early in the infection. When present, it may present as fine erythematous papules on the abdomen and tends to spread centrifugally to the extremities but is rarely seen on the face, palms or soles.⁷

Table 3. Range of percentages for symptoms seen at presentation for confirmed cases of murine typhus.

Clinical Findings	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/or vomiting	3-48
Abdominal pain	11-60
Confusion	2-13

Data derived from Clinical Practice, 2008 and with the permission of Dr. Rachel Civen.

Whiteford et al. reported that in children, the symptoms were mild to moderate and the median duration was 12 days.¹³ This value was significantly related to initial diagnosis but the length of time until defervescence or abatement of fever was related to appropriate therapy. Though adult cases are also generally described as clinically mild, in his study, up to ten percent of adults required intensive care and mortality approached four percent for some of the years reviewed.¹³ Most reviewed references list this value around one percent.

Fever is a direct response to cytokines that act as endogenous pyrogens causing the release of prostaglandin E2 with subsequent hypothalamic activity. The cytokines can be produced by the infected cell, immune cells responding to the pathogen or pathogen lipopolysaccharide-binding protein which triggers immune cells to produce cytokines. Fever is the most commonly seen symptom and it is typical for the temperature to incrementally rise to a relatively high level then stabilize rather than fluctuate.

Abnormal chemistry values are evidence of systemic involvement. In the liver, elevation of enzymes such as alanine transaminase, aspartate transaminase, lactate dehydrogenase and alkaline phosphatase are indicative of hemolysis, possible bile duct damage, injury to adjacent tissue or inflamed microvasculature.¹³ Hypoproteinemia, hypoalbuminemia and hyponatremia are related to the loss of integrity, increased vascular permeability and edema associated with systemic

vasculitis. Our patient displayed an initial leukocytopenia and thrombocytopenia which recovered by day six. Thrombocytopenia is seen in many patients and is due to the attempts to plug damaged areas in the vascular wall.⁵ Leukocytopenia may be due to cytokine induced extravasation in areas with vasculitis. As has been noted with other patients, it took a little longer for liver enzymes to return to normal.

Rarely patients exhibit some peripheral nerve involvement in the form of reversible hearing loss or facial paralysis.¹⁵ Other rare complications are splenic rupture, endocarditis and meningitis.⁸

Host Defenses

Even though patients develop antibodies to several surface epitopes, the humoral arm plays a minor role in our initial response to the infection. Antibodies do coat and help clear organisms that are released from ruptured cells but as with most infections involving intracellular organisms, the cell mediated response dominates until the adaptive response can help resolve the infection.

Infected endothelial cells are capable of secreting many inflammatory mediators, increasing their expression of adhesion molecules and acting as antigen presenters.¹¹ Billings et al. propose that the endothelial cellular response starts by the recognition of these signals by immune cells and includes the production of IL-12 and TNF- α by macrophages and activation of NK cells with subsequent production of IFN- γ .¹⁷ These cytokines help to trigger anti-rickettsial activity in the infected endothelial cell. This activity involves the production of nitric oxide, hydrogen peroxide and possibly tryptophan depletion to decrease replication or kill the intracellular organisms.^{15,16}

In addition, production of cytokines, especially IFN- γ and TNF- α trigger the cell mediated activity of CD8 T cells.^{3,11,17} Both CD8 and NK cells are capable of cytotoxic activity but rather than lysing the cell, they initiate apoptosis. *Rickettsia* contained in the apoptotic bodies are phagocytized rather than being released into the bloodstream to re-infect new cells.^{15,17} By this time, the adaptive immune response is in full swing involving macrophages and CD4 T cells and B lymphocytes.

It may take several weeks to develop an antibody titer high enough to be considered positive by current

methods but many can be detected after 7-10 days. The patient develops antibodies to several surface epitopes and some have been shown to crossreact with other rickettsial species. This cross-reactive protective immunity was demonstrated between the spotted fever and typhus groups through work at the University of Texas Medical Branch in Galveston.¹⁸

Demographic and Epidemiologic findings

It is difficult to know the exact prevalence of murine typhus in the United States because it is not a reportable disease in most states. California, Hawaii and Texas account for the vast majority of cases. Among the Rickettsiae, *R. rickettsia* is reported more frequently nationwide. Compared to the early 1900s, the number of cases of murine typhus has dramatically decreased due to the use of DDT by municipalities and the successful institution of rodent control measures in many counties.⁵

In Texas, cases are reported to Texas Department of State Health Services and are investigated at a county level. Hospitals report cases to the local health department through the National Electronic Disease Surveillance System within 1 week of detection.¹⁹ Cases increase in late spring and early summer and most are clustered around just three southeast counties; Nueces County (Corpus Christi seat), Hidalgo (Edinburg seat) and Cameron (Brownsville seat). In California, an endemic area exists in Los Angeles County with most cases reported in summer and fall.⁸ Our patient resides in Nueces County where the incidence of cases was near or below 20/year until 2004 when they increased and have remained relatively stable in the 40 +/- 10 range since (Table 4).

Table 4. Cases of Murine Typhus in Nueces County, Texas

2004	2005	2006	2007	2008	2009	2010	2011
35	29	48	57	47	44	40	59

*Data derived from personal communication, Nueces County Health Department and Texas Department of State Health Services 1/2012

Following a local epidemic of typhus in Travis County (Austin seat), the CDC worked with the Texas Department of Health in an environmental investigation to determine the cause. Fleas were collected from domestic animals, feral cats, captured opossums, rats and raccoons at or around the homes of patients confirmed with murine typhus.⁶ Of the 57

animals assessed, 33% had evidence of active murine typhus using serology and none were positive by PCR. Previous studies had shown a higher percent of seropositive animals. Though no definitive cause could be assigned to the local epidemic, county officials initiated programs to increase public awareness and they worked with the local medical community to help local physicians better recognize the signs of fleaborne rickettsiosis.¹⁸ Because the organism is now firmly established, Travis county is watched carefully for spikes in its murine typhus cases.

Because symptoms may be relatively mild in some patients there is little doubt that the incidence is under reported. Several retrospective studies have looked at the seropositivity of both adults and children in areas around or on the fringes of endemic populations in an attempt to determine the true prevalence of this disease. Archived serum samples or newly drawn specimens are tested for IgM antibodies to *R. typhi*.^{19,20,22,24}

Diagnostic Testing

The classic Weil-Felix assay for rickettsia depended on the crossreactive pattern of the patient's serum with *Proteus* surface antigens. With improved technology we have seen the development of assays using specific surface antigens provide us with much better results. The IFA (Indirect Immunofluorescence Antibody) is considered the gold standard and it determines the level of IgM or IgG antibodies in serum directed against purified *R. typhi* antigen.

Acute serum samples are drawn when the patient is first seen and convalescent samples are drawn at greater than or equal to three weeks later in order to detect a classical four-fold increase in titer between these two samples.²¹ A single diagnostic IgG titer of 1:64 or higher can be accepted as confirmation with some kits but many times the titer has not reached that level when the patient first presents with symptoms and the acute serum sample is drawn. It takes between 7 and 10 days for the IgG titer to reach a positive level. A diagnosis is made from symptoms and confirmation must wait on the convalescent sample.²¹

Other tests available are the latex agglutination, the EIA using antigen coated wells in microtiter plates, immobilized antigen on nitrocellulose in the forms of dots and microimmunofluorescence.¹⁹ County and state

health departments use PCR and sequence analysis when investigating outbreaks. These methods help them distinguish between infections with *R. typhi* and the cause of cat flea rickettsiosis, *R. felis*. This murine typhus-like disease of humans possesses patient symptoms, serological results and host vector systems that overlap with *R. typhi*.¹⁰

Control and Treatment

The key to controlling local epidemics and reducing the incidence in endemic areas lies with reducing fleas and its predominant host reservoir, the rat. This means killing rats, reducing their access to food and encouraging flea infestation control measures in homes.⁵ Safety and environmental issues associated with the use of DDT in spraying programs has stopped its use but these programs were initially responsible for the reduction in murine typhus cases starting in the mid-1940s. Pesticide related illnesses have been associated with the occupational use of flea and other vector control products. Several newer products are encouraged now that include selected insecticides, insect development inhibitors and insect growth regulators, a combination that kills adult fleas and affects the development of both eggs and larva.

The recommended treatment for murine typhus is the tetracycline-class antibiotic doxycycline. A course of 7-10 days is recommended and this should include at least three days after the fever has subsided.¹⁹ Tetracycline, chloramphenicol, ciprofloxacin and azithromycin have also been used. A study from Greece compared the use of these drugs alone and doxycycline paired with ciprofloxacin or chloramphenicol. The time elapsed until defervescence was shortest in patients treated with doxycycline and did not improve when paired with any other drug.²³

CONCLUSION

For students that don't understand why they need to learn about all those exotic diseases which rarely occur in their area, this case is an eye opener. Every few days, somewhere in the U.S., someone is diagnosed with murine typhus, Rocky Mountain spotted fever, ehrlichioses, *Coxiella*, *Bartonella* or epidemic typhus. Most cases are investigated in an attempt to identify the infected vector and prevent further cases. Take a look at the Mortality and Morbidity Weekly Reports on the CDC web site to see areas of increasing incidence.

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It is essential to understand and acknowledge common risk factors associated with typhus including travel to endemic areas and flea bites. Fever, severe headache, and joint pain are vague findings for diagnosis, but coupled with elevated liver enzymes, a recent exposure to fleas and rat feces, and living in an endemic area, provide cumulative information that aid in a patient's diagnosis and successful treatment.

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ERRATA: In the Spring 2011 Volume 24:2 of *Clinical Laboratory Science* the name of the first author in the Table of Contents for the manuscript entitled "Immunoglobulin Light Chain Levels Can Be Used to Determine Disease Stage in Children with Juvenile Idiopathic Arthritis" and on page 93 in the header is misspelled. It should be Necil Kutukculer.