

### **Virtual Pediatric Lecture Series**



Thursday, January 23, 2025 12:30 – 1:30 PM (PST)

# Typhus

Delma J. Nieves, MD Pediatric Infectious Disease CHOC Specialists I have no financial interests or conflicts to resolve

# objectives

### Review Murine typhus clinical presentations

**Etiology and Epidemiology** 

Typhus in Orange County

Diagnosis

Treatment and management

Review Murine typhus case presentations and review of clinical presentation Green, Jennifer S. MD<sup>\*</sup>; Singh, Jasjit MD<sup>+</sup>; Cheung, Michele MD<sup>‡</sup>; Adler-Shohet, Felice C. MD<sup>+</sup>; Ashouri, Negar MD<sup>+</sup>. A CLUSTER OF PEDIATRIC ENDEMIC TYPHUS CASES IN ORANGE COUNTY, CALIFORNIA. The Pediatric Infectious Disease Journal 30(2):p 163-165, February 2011. | DOI: 10.1097/INF.0b013e3181f4cc25

- 5 cases hospitalized for evaluation of fever > 1 week and following multiple evaluations and treatments for potential alternative diagnoses.
- 4 had rashes
- Headache, abdominal pain, myalgias, and emesis were prominent symptoms.
- elevated C-reactive protein, mild hepatitis, and mild hyponatremia

Green, Jennifer S. MD<sup>\*</sup>; Singh, Jasjit MD<sup>+</sup>; Cheung, Michele MD<sup>‡</sup>; Adler-Shohet, Felice C. MD<sup>+</sup>; Ashouri, Negar MD<sup>+</sup>. A CLUSTER OF PEDIATRIC ENDEMIC TYPHUS CASES IN ORANGE COUNTY, CALIFORNIA. The Pediatric Infectious Disease Journal 30(2):p 163-165, February 2011. | DOI: 10.1097/INF.0b013e3181f4cc25

- Cases 1 and 2 → prolonged fever, rash, and headache in a teenaged child, responded rapidly to empiric doxycycline and becoming afebrile within 24 hours
- Case 3  $\rightarrow$  milder illness typically seen in the younger child
- Case 4 → rash was not present, making it more challenging. Was admitted to PICU d/t severe thrombocytopenia and concern for possible hemolytic-uremic syndrome.
- Case 5 highlights → treated for Kawasaki disease (isolated cervical lymphadenopathy) before the diagnosis of murine typhus was performed

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• All were diagnosed with murine typhus confirmed by indirect fluorescent antibody testing (IFA), with acute titers sent to commercial laboratories and convalescent titers to the Orange County Health Department.

#### TABLE 2. Laboratory Features

Case	WBC (Cell/µL)	CRP (mg/dL)	ESR (mm/h)	AST/ALT (u/L)	Sodium (mMol/L)	Acute R. typhi Titers (IgM/IgG)	Convalescent R. typhi Titers (IgM/IgG)	Treatment
Case 1	11,200 (69% neutrophil, 5% band)	11.84	16	45/60	134	1:1024/1:1024	1:5120/1:16384	Doxycycline on day 11 of illness
Case 2	6000 (85% neutrophil, 0% band)	13.8	Not done	68/60	128	1:64/1:256	1:5120/1:16384	Doxycycline on day 10 of illness
Case 3	6000 (48% neutrophil, 26% band)	7.26	23	66/40	136	1:256/1:256	1:160/1:1024	No treatment
Case 4	13,800	14.43	38	115/76	130	1:64/1:1024	Lost to follow-up	No treatment
Case 5	11,800 (60% neutrophils, 16% band)	6.06	12	754/654	133	1:256/1:256	Inaccurate due to IVIG	IVIG and aspirin, then doxycycline on day 10 of illness

WBC indicates white blood cells; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; R. typhi, Rickettsia typhi; IgM, immunoglobulin M; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin.

#### TABLE 1. Clinical Features

Case	Age	Duration of Symptoms at Presentation	Fever (Tmax)	Rash	Headache	Abdominal Pain	Hepatomegaly	Other Symptoms	Exposures	Presumed Diagnosis
1	15 yr	9 d	Yes (39.4°)	Yes	Yes (frontal)	Yes (severe)	Yes	Myalgias, emesis, diarrhea	Cats at home, no flea bites	EBV, constipation, mycoplasma, viral hepatitis, adenovirus
2	14 yr	10 d	Yes (39.4°)	Yes	Yes (diffuse)	Yes	No	Myalgias, emesis	Cats, brother with fever and headache but no rash	Pneumonia, EBV, CSD, Kawasaki, parvovirus
3	3.5 yr	9 d	Yes (40.5°)	Yes	Yes (diffuse)	No	Yes	Conjunctivitis, chapped lips	Kitten, recent scratch to patient	EBV, WNV, mycoplasma
4	14 yr	10 d	Yes (40.2°)	No	Yes	Yes	Yes	Myalgia, emesis, diarrhea, cough	Cats, no flea bites	EBV, CSD, toxoplasma
5	5 yr	7 d	Yes (40°)	Yes	No	No	Yes	Arthralgias, conjunctivitis, chapped lips, decreased energy, emesis, isolated lymphadenopathy	Cats, no flea bites	Pharyngitis, Kawasaki

CSD indicates Cat-Scratch disease; EBV, Epstein-Barr virus; WNV, West Nile virus.

# Typhus

- Murine Typhus AKA endemic typhus or flea-borne typhus
- First described in 1926, is a zoonotic disease
- disease can be mild in young children
- prodromal symptoms include headache, arthralgia and ill feeling, with or without a high-grade fever
- onset is characterized by persistent headache, a high-grade fever, and a rash predominating on the trunk. (rash can be mild or absent)
- Up to 50% of patients have nausea/vomiting, anorexia, and abdo pain with some tenderness

# Typhus

- complications are rare
- complete recovery occurs spontaneously in almost all cases
- severe diseases have been occasionally reported
  - ophthalmic complications, severe pneumonia, endocarditis, splenic rupture, and aseptic meningitis
  - More in the elderly and in transplanted patients

Red Book: 2024–2027 Report of the Committee on Infectious Diseases, 2024 From: **Murine Typhus (Endemic or Flea-borne Typhus)** 



Typhus

- Incubation of 1 to 2 weeks
- Rash typically presents on day 4-7 in about 50% of patients
  - discrete macular/maculopapular lesions, nonpruritic typically
  - lasts 4-8 days
  - often distributed on the patient's trunk, although extremities also can be involved
  - spares palm and soles

A healthy 8-year-old child had 5 days of fever, severe headache, and malaise before this rash began. The child had been exposed to numerous cats with fleas before the onset of illness. Courtesy of Carol J. Baker, MD, FAAP

# Typhus

- Untreated illness seldom lasts longer than 2 weeks
- Usually uncomplicated but can also be severe including sepsis or CNS involvement.
- Fatal outcomes in upto 4% of hospitalized patients
- Lab findings include
  - thrombocytopenia
  - hyponatremia
  - hypocalcemia
  - elevated liver enzymes

## Differential

- Viral syndrome
- Other more common vector borne infections, such as dengue fever, ehrlichiosis, malaria, West Nile virus, epidemic (louse borne) typhus and Rocky Mountain spotted fever
- Or non-vector borne infections such as bacterial or viral meningitis, Kawasaki disease or secondary syphilis
- Influenza
- leptospirosis
- Typhoid fever

Etiology and Epidemiology

### **Rickettsial infections**

- Rickettsiae
  - small gram-negative bacteria
  - generally obligate intracellular parasites.
    - Multiplies in the epithelial cells of the flee midgut
    - shed into the feces
    - deposited on the host skin surface while the flea is feeding
  - transmitted to humans by arthropods
    - (exception is Coxiella burnetii which is transmitted by inhalation of endospores)
- The most common rickettsial infections are Rocky Mountain spotted fever, epidemic typhus, and Q fever

https://sciencephotogallery.com/featured/rickettsia-bacteria-katerynakonscience-photo-library.html

### Typhus

- Caused by *Rickettsia typhus* or *Rickettsia felis* 
  - Gram-negative obligate intracellular bacteria
  - endothelial cells are the primary target cells → leads to a generalized vasculitis which explains the wide spectrum of clinical manifestations and life threatening complications
- Rats (who are asymptomatic) are natural reservoirs
- worldwide in distribution
- occurs most commonly in male adults
- male and female children are affected equally

Red Book: 2024–2027 Report of the Committee on Infectious Diseases, 2024 From: Murine Typhus (Endemic or Flea-borne Typhus)



A Norway rat, Rattus norvegicus, in a Kansas City, MO, corn storage bin. R norvegicus is known to be a reservoir of bubonic plague (transmitted to man by the bite of a flea or other insect), endemic typhus fever, rat-bite fever, and a few other dreaded diseases. Courtesy of Centers for Disease Control and Prevention

# Typhus

- Outside the US, the primary vector for transmission is the rat flea *Xenopsylla cheopis*
- Typhus has been considered an urban disease because of over-crowding and poor sanitation
- However, since around the 1970s, growing trend of typhus cases in United States suburbs
  - cat fleas (Ctenocephalides felis)
  - mouse fleas (Leptopsylla segnis)
  - fleas from opossums (often cat fleas)
  - other peridomestic species



Xenopsylla cheopis, the Oriental rat flea

https://www.cdc.gov/typhus/about/murine.html

- Opossums carry a Ctenocephalides felis aka "cat flea"
- Cat flea is ubiquitous
- Cat flea infects peridomestic animals ie. opossums, skunks, and free ranging cats and dogs
- There is an increase in *R. typhi* seropositive animals, specifically opossums, in the Los Angeles suburbs.
- C. felis can transmit R. typhi to humans
- Note *Rickettsia felis*, a recently discovered pathogen may be on the up and up



https://citywildlife.org/urbanwildlife/area-wildlife/virginiaopossums/



https://entomologytoday.org/202 2/07/14/essential-oils-untappedresource-managing-urban-insectpests/cat-flea-ctenocephalides-

felis/





https://en.wiki pedia.org/wiki/ Rickettsia



https://citywildlife.org/urbanwildlife/area-wildlife/virginiaopossums/





https://www.thedodo.com/close-tohome/kitten-adopts-orphaned-opossum



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- Infection occurs when infected flea feces are rubbed into broken skin or mucous membranes or are inhaled.
  - Infected fleas have the bacteria in their feces and can contaminate the skin surface when the flea bites.
  - If the person scratches the flea bite area, some of the bacteria in the flea feces can enter the person's blood stream.



https://familymedicineaustin.com/symptoms-of-flea-bites-on-humans/



Flea bites

Flea bites



Itchy Painful Secondary infection from scratching Papular urticaria with center blister

https://dermnetnz.org/topics/flea-bite

Flea bites

### Some Common Backyard Hosts and Their Common Fleas

		HOSTS											
		Cats	Coyotes	Dogs	House mice	Opossums	Rabbits	Racoons	Rats	Skunks	Squirrels		
	Ctenocephalides felis	AND IN COLOR						A CONTRACT		A COLOR			
	Cediopsylla inaequalis interrupta												
	Diamanus montanus					A CONTRACTOR			A MARK		A CONTRACT		
F	Echinophaga gallinacea		A CONTRACT			A CONTRACTOR	A CONTRACTOR		A CONTRACTOR	A CONTRACTOR	A CONTRACTOR		
	Hoplopsyllus anomalus						A CONTRACT		A CONTRACT	A CONTRACTOR			
E	Leptopsylla segnis				A CARACTER STATE				A CONTRACTOR				
S	Nosopsyllus fasciatus								A CONTRACTOR OF		A CONTRACTOR		
	Orchopeas howardii										A CONTRACT		
	Orchopeas sexdentatus sexdentatus												
	Pulex irritans		A A A A A A A A A A A A A A A A A A A	A BAR		A CARLER OF CONTRACT	A CARACTER OF CONTRACT			A CARACTER OF CONTRACT			
	Xenopsylla cheopis								A CONTRACT				



https://www.ocvector.org/files/7888fb751/Host-flea-List-Handout.pdf



### Murine Typhus Historical Trends

- Murine typhus was a nationally notifiable disease from 1930—1987.
- Beginning in the 1950s, cases began to decline drastically, in part due to advances in sanitation and pest management.
- By 1958, fewer than 100 cases were reported each year.
- In 1987 murine typhus was remove from the nationally notifiable disease list
- Murine typhus cases are increasing now most commonly seen in Southern California, Southern Texas, southeastern Gulf Coast and Hawaii
  - Average of 300 cases every year



Number of annual typhus group rickettsiosis cases, 1930-1987

### Human Flea-Borne Typhus Cases in California

Typhus Case Definition (CDPH working definition, 2020) • **Confirmed:** A clinically compatible case (meets clinical criteria) that is laboratory confirmed.

• **Probable:** A clinically compatible case (meets clinical criteria) that has presumptive laboratory evidence and evidence of epidemiologic link.

• **Suspect:** A case with presumptive or confirmatory laboratory evidence of infection but no clinical information available, OR a clinically compatible cases (meets clinical criteria) that has evidence of epidemiologic link but no laboratory testing or equivocal laboratory evidence. Reported Typhus Cases, California, 2015 – 2024 As of August 29, 2024



https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/FleaborneTyphusCaseCounts.pdf

#### Human Flea-Borne Typhus Cases by Year and County, California, 2015 – 2024

County	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	Total	Incidence
County	2010	2010	2017	2010	2013	2020	2021	2022	2025	2024	Total	incluence
Los Angeles	66	82	87	147	115	114	175	192	144	13	1,135	1.12
Orange	15	17	11	20	20	14	27	29	19	2	174	0.55
Riverside	0	1	0	1	1	1	9	5	7	0	25	0.11
San Bernardino	0	1	0	1	1	5	4	1	5	3	21	0.10

Data includes all confirmed, probable and suspect cases as of August 29, 2024.

Flea-borne Typhus Average Annual Incidence Rates by County, California, 2013-2019



Flea-borne Typhus Average Annual Incidence Rates by Age Group, California, 2013-2019



\*Potentially unreliable rate: relative standard error 23 percent or more.

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/FleaBorneTyphusEpiSummary2013-2019.pdf

# Flea-borne Typhus Cases and Population by Race/Ethnicity, California, 2013-2019



https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/FleaBorneTyphusEpiSummary2013-2019.pdf

Flea-borne Typhus Cases by Month of Estimated Illness Onset, California, 2013-2019



Month of Estimated Illness Onset

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/FleaBorneTyphusEpiSummary2013-2019.pdf

Typhus in Orange County

# Typhus

- Prior to 2006, the last reported case in Orange County was in 1993.
- According to California Department of Public Health, flea-borne typhus is considered endemic (always present) in Orange County, but cases are reported from other parts of California.



	2011	2012	2013	2014	2015	2016	2017	2018	
Total Cases <sup>1</sup>	11	28	33	16	15	17	11	18	Median of 16.5 cases/year
Hospitalized	11	26	30	16	14	11	9	18	
Sex									
Male	4	15	25	10	13	10	5	12	63% were male
Female	7	13	8	6	2	7	6	6	
Race/Ethnicity									
White	7	14	21	5	9	7	7	11	54% non-Hispanic white
Black	0	0	1	1	0	0	0	0	
Asian	1	2	2	1	0	2	0	1	
NHOPI <sup>2</sup>	0	0	0	0	0	0	0	0	
Hispanic	3	5	4	3	6	6	2	6	
Other/Unknown	0	7	5	6	0	2	2	0	
Age Group (years)									
<18	1	4	2	1	0	3	1	7	
18 - 49	7	17	16	9	10	11	5	7	55% 18-49yo
50 - 64	2	5	12	2	4	0	2	3	
≥ 65	1	2	3	4	1	3	3	1	

#### Table 1. Count of Orange County Typhus Cases by Sex, Race/Ethnicity, and Age Group, 2011 – 2018.

Table 3. Typhus Incidence Rates per 100,000 people in United States, California, and Orange County, 2011-2018.

	2011	2012	2013	2014	2015	2016	2017	2018
California	0.14	0.25	0.33	0.20	0.23	0.26	0.26	0.44
Orange County	0.36	0.91	1.06	0.51	0.47	0.53	0.34	0.56

Note: Incidence rates are only calculated for categories in which there are 5 or more cases (Table 2 and Table 3). Darker orange indicates a higher incidence rate.

Across all years, Orange County had higher incidence rates than California as a whole.



#### Figure 1. Comparison of Typhus Incidence Rates: General County, Male, and Female Populations. Orange County, 2011 - 2018.

Generally there is a higher incidence among males.



Case counts are highest in the summer months.



# Diagnosis

### Antibody titers are used for diagnosis

- peak at 4 weeks post infection and may be negative early in infection
- IgG is detected after 7-10 days from onset of illness
- A single titer of >1:128 is considered supportive of a rickettsial infection
- Fourfold change between acute and convalescent titers taken 2-4 weeks apart is definitive to confirm recent infection

- IgM assays alone is not recommended (and not routinely performed)
- Cross-reactivity can occur with other Rickettsia including *Rickettsia prowazekii* or *Rickettsia rickettsii*.
- The different Rickettsial species are so closely related that there is significant cross-reactivity (especially between R.typhi and R. felis, which are 98.5% homologous).

- Routine blood cultures are not suitable for culture of R typhi.
- Nucleic acid amplification tests (NAATs) can detect R typhi and distinguish murine and epidemic typhus and other rickettsioses.
  - acute whole blood, serum, and skin biopsies
  - sensitivity is lower during the first few days of illness or following 48 hours of antibiotic treatment
- They can be differentiated via PCR technology (not widely available)

Treatment and management

- Treatment should be started early based on clinical suspicion and epidemiology. (not be withheld because of a negative laboratory result or while awaiting laboratory confirmation)
- Treatment is given for at least 3 days after defervescence and evidence of clinical improvement
- Total course is 7 to 14 days

- Treatment of choice is doxycycline regardless of age
  - children <45 kg (100 lb) 2.2 mg/kg per dose IV or PO twice a day (maximum 100 mg/dose)</li>
  - adults 100 mg/dose, twice daily
- Fluoroquinolones are alternative medications
  - may not be as effective
  - not approved for this use in children <18 years

### Reportable disease

- California Code of Regulations (CCR), Title 17, Section 2500:
  - requires health care providers to report suspected cases of typhus to their local health department within 7 calendar days of identification.
- Laboratories
  - required to report lab results suggestive of Rickettsia infection to either the CA Reportable Disease Information Exchange (CaIREDIE) via electronic laboratory reporting or the local health department
  - reporting must occur within 1 working day after the health care provider has been notified
- The organism isolated from the suspected typhus patient should be submitted to the California Department of Public Health (CDPH) Viral and Rickettsial Disease Laboratory or another public health laboratory for definitive identification.

### prevention

- Do not leave food outdoors accessible
- Cover trash containers
- Trim vegetation around buildings
- If you see live or dead opossums, feral cats or other animals on your property, contact your local Animal Control agency
- Use flea control products on pet dogs or cats
- keep cats indoors

#### Protect Yourself & Your Neighbors from Flea-Borne Typhus

Flea-borne typhus is a disease that infected fleas can spread to humans. Several cases of flea-borne typhus were found recently in your area. Fleas can come from many types of animals including cats, rats, and opossums.

#### Follow these steps to keep your family and pets safe from flea-borne typhus.





### Communities working together to get rid of flea-borne typhus.

Los Angeles County Department of Public Health http://publichealth.lacounty.gov/acd/VectorTyphus.htm



### **FLEA-BORNE TYPHUS**



Los Angeles County Department of California Department of Public He U.S. Centers for Disease Control a Google Images – Used with Permi

#### What is flea-borne typhus?

Flea-borne typhus is a bacterial disease that can spread from some animals to humans by fleas and make people sick. Typhus is endemic (always present) in Los Angeles County.

	What animals can carry the bacteria that causes typhus?	ļ	Prevention		
	Opossums, cats, and rodents (rats) can carry the bacteria that causes typhus. Fleas living on these animals can become infected and then snread the disease to humans	Avoid contact with fleas:			
	Flea-borne Typhus Transmission	•	Use flea control products on pets		
- 1	the second se	•	Keep pets indoors		
		•	Do not leave pet food or trash outside that may attract animals		
11		•	Seal holes and openings in the home where rodents can enter		
-		•	Do not feed or try to touch free- roaming cats or		
	Who is at risk of getting flea-borne typhus?		wild animals		
	People who touch, pet, or come in contact with rats, opossums, and free-roaming cats in areas where typhus is present are at risk of getting typhus from infected fleas.	•	Keep trash cans covered at all times		
	People living outdoors or in housing infested with rats or other rodents are also at risk of getting typhus from fleas.		Trim and remove plants near the outside of the		
	What are the common symptoms of typhus?		house		
	Common symptoms include: fever, headache, chills, muscle aches, and rash on or around the chest, sides, and back.	•	Use insect repellent when		
	If you have these symptoms, see your health care provider right away. Tell your health care provider if you have had contact with fleas or rodents.		outside		
Public He Ith www d Preven sion	alth—www.publichealth lacounty gov/acd/vectortyphus.htm w.cdph.ca.gov.search "Typhus" non—www.cdc.gov, search "Murine Typhus"		PublicHealth		

http://www.publichealth.lacounty.gov/acd/docs/FleaBorneTyphusFlyer.pdf

# When should you think about *R.typhus*?

- Child with prolonged fever, rash and headache. Commonly with abdominal pain
- Elevated sedimentation rate, elevated transaminases
- Hyponatremia
- Leukopenia with a left shift
- They have pets (with fleas) or spend time outdoors



# Thank you for your attention!

### References

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# **Practice Contact Information**

### **CHOC Infectious Disease**

CHOC Specialty Care Clinic CHOC Clinic Building 1201 W. La Veta Ave. Orange, CA 92868

#### To refer patients, please call:

• Phone: 888-770-2462

Specialty Care Physician Concierge Service

• Phone: 714-509-4013

Medical professionals available via Telehealth

For Provider-to-Provider calls, please call our office 714-509-8403

