You can’t tell a rickettsiosis from its spots: the expanding spectrum of spotted fever in the United States

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The findings and conclusions are those of the presenter and do not necessarily reflect the views of US Department of Health and Human Services or the Centers for Disease Control and Prevention
Rocky Mountain spotted fever: the disease

- *Rickettsia rickettsii* can infect vascular endothelial cells of every organ in the body
- Disease may involve lungs, heart, kidneys, gastrointestinal tract, central nervous system and skin
- High fever, headache, nausea, vomiting
- Macular rash starts ~3 days evolves into petechiae ~6 days, involves palms and soles
- Most deaths occurs within 9 days
### RMSF: historical case-fatality rates

<table>
<thead>
<tr>
<th>Location</th>
<th>Interval</th>
<th>Case fatality rate (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitterroot Valley, MT</td>
<td>1904-1923</td>
<td>63% (238)</td>
</tr>
<tr>
<td>Long Island, NY</td>
<td>1926-1934</td>
<td>30% (10)</td>
</tr>
<tr>
<td>Cape Code, MA</td>
<td>1955-1968</td>
<td>15% (13)</td>
</tr>
<tr>
<td>Mississippi</td>
<td>1969-1972</td>
<td>18% (49)</td>
</tr>
<tr>
<td>North Carolina</td>
<td>1966-1995</td>
<td>14% (114)</td>
</tr>
<tr>
<td>White Mountain, AZ</td>
<td>2002-2004</td>
<td>12% (16)</td>
</tr>
</tbody>
</table>
Doxycycline is **the recommended drug**

- Adults: 100 mg twice daily for 5-10 days
- Children <45 kg: 2.2 mg/kg body weight per dose, twice daily
- Therapy most effective within the first 5 days of illness
- Chloramphenicol the only other alternate drug
- Penicillins, cephalosporins, aminoglycosides, and macrolides are ineffective
New York State, 1998

- 9-year-old Labrador retriever first seen at a veterinary clinic for rapidly progressive lethargy

- Condition worsened over next several days, developed fever, stupor, and scrotal swelling and erythema

- Dog euthanized and necropsy performed

Testis showing lymphocytic vasculitis
Dog’s owner had been hospitalized the day after the death of her dog with high fever, nausea, vomiting, and thrombocytopenia.

Gradually recovered, but diagnosis unknown.

Physician contacted; patient subsequently found to have a seroconversion to *R. rickettsii*.

Testis, immunohistochemical stain for *R. rickettsii* (red)
ROCKY MOUNTAIN SPOTTED FEVER

A STUDY OF COMPLEMENT FIXATION IN THE SERUM OF CERTAIN DOGS

CHARLES C. SHEPARD AND NORMAN H. TOPPING

From the Division of Infectious Diseases, National Institute of Health, Bethesda, Maryland

During the summer of 1943 several members of the New York State Department of Health called our attention to a possible connection between a case of Rocky Mountain spotted fever and a previous illness in the patient's dog. The sequence of events was briefly as follows: On the first of May, the B's took their 4-year-old male Doberman pinscher dog from New York City to East Hampton, Long Island. On May 14, the dog became ill with fever and the

tory gave the following results:*  

Agglutination:
  Specimen 6/23
    Proteus OX-19:                 Positive 1:640
  Specimen 6/28
    Proteus OX-19:                 Positive 1:640

Complement Fixation
  Specimen 6/23
    Rocky Mountain spotted fever antigen:  Positive 1:2048
  Specimen 6/28
    Rocky Mountain spotted fever antigen:  Positive 1:2048
Young boy dies in a small community in a mountainous region of eastern Arizona with fever and petechial rash

CDC confirms the cause of death as Rocky Mountain spotted fever

14 more cases diagnosed from the same community during 2004

No *Dermacentor* ticks reported in this region

Investigations initiated by CDC to determine the cause
A dry, high-desert community in northeastern Arizona, USA: how could an epidemic of Rocky Mountain spotted fever occur here?
Free-roaming dogs were everywhere...
This is high desert and is very hot during the day. The dogs often went under the houses for shade. Children often played under the houses.
Surprisingly, we found thousands of ticks in the concrete and dirt under each of the houses, and not the tick we expected...
The brown dog tick: an unexpected vector of Rocky Mountain spotted fever in Arizona

- Sole vector of ongoing epidemic in eastern Arizona
- Strongly associated with dogs and peridomestic habitats—very resistant to desiccation
- Very common tick in the US; seldomly bites humans
- Contribution to epidemiology of RMSF may be greater in than appreciated

*Rhipicephalus sanguineus*
• Analysis of 329 archival canine serums samples from same community collected in 1996: only 2 (0.6%) with relevant titers to *R. rickettsii*.

• 2003 canine serosurvey: robust anti-*R. rickettsii* antibodies in 70 (72%) of 97 dogs

• High titers also detected in 57% of dogs from another community 60 miles away; outbreak of RMSF occurred the following year
Reported cases of RMSF, United States, 1986-2007
**Rickettsia rickettsii** in *Dermacentor variabilis* *

An epidemiologic-ecologic disconnect?

<table>
<thead>
<tr>
<th>Location, year</th>
<th>No. (% infected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD, 1951-53</td>
<td>17,649 (0.25)</td>
</tr>
<tr>
<td>NC, 1982</td>
<td>2,123 (0.05)</td>
</tr>
<tr>
<td>OH, 1984-89</td>
<td>12,631 (0.06)</td>
</tr>
<tr>
<td>MD, 2002</td>
<td>392 (0)</td>
</tr>
<tr>
<td>TN, 2007-08</td>
<td>555 (0)</td>
</tr>
<tr>
<td>DE, MD, NJ, 97-09</td>
<td>1,400 (0.07)</td>
</tr>
</tbody>
</table>

*Price, 1954; Gordon et al., 1984; Burgdorfer, 1988; Pretzman et al., 1990; Ammerman et al., 2004; Moncoyo et al., 2010; Stromdahl et al., in press.*
Tick-borne spotted fever rickettsiae in the United States

*Rickettsia rickettsii*
*Rickettsia parkeri*
*Rickettsia sp. 364D*
*Rickettsia rhipicephali*
*Rickettsia montanensis*
*Rickettsia peakockii*
“*Rickettsia cooleyi*”
“*Rickettsia amblyommi*”
*Rickettsia sp. “Tillamook”*
*Rickettsia sp. “parumapertus”*
In 1937, R. R. Parker initiates a survey of ticks in Liberty County, Texas, following an outbreak of illnesses diagnosed as “RMSF”

- Guinea pigs inoculated with *Amblyomma maculatum* ticks develop febrile illness, similar to, but milder than classical RMSF.
“An unnamed, apparently new rickettsia has been repeatedly isolated at the Rocky Mountain Laboratory during the past nine years from specimens of Amblyomma maculatum, a tick of wide distribution in the Southern States...the presumptive evidence from animal experimentation suggests that human infection might be confusingly similar to spotted fever”

R.R. Parker, 1948
Confirmed and suspected cases of *Rickettsia parkeri* rickettsiosis through 2010
Rocky Mountain spotted fever

*Rickettsia parkeri* rickettsiosis
**RMSF vs. *Rickettsia parkeri* rickettsiosis**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Rocky Mountain spotted fever (n = 208)</th>
<th><em>R. parkeri</em> rickettsiosis (n = 15)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Headache</td>
<td>72%</td>
<td>80%</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>83%</td>
<td>87%</td>
</tr>
<tr>
<td>Petechial rash</td>
<td>47%</td>
<td>13%</td>
</tr>
<tr>
<td>Vesicular rash</td>
<td>0</td>
<td>40%</td>
</tr>
<tr>
<td>Eschar</td>
<td>0</td>
<td>93%</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>78%</td>
<td>33%</td>
</tr>
<tr>
<td>Death</td>
<td>7%</td>
<td>0</td>
</tr>
</tbody>
</table>

*Clin Infect Dis 2008;47, Arch Dermatol 2010;146*
Eschars on patients with *R. parkeri* rickettsiosis
Vesicular rash of *R. parkeri* rickettsiosis
### R. *parkeri* rickettsiosis: initial diagnoses and IFA titers

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Initial diagnosis</th>
<th>Initial IFA titer to <em>R. rickettsii</em> antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>65/M</td>
<td>RMSF</td>
<td>1024</td>
</tr>
<tr>
<td>50/F</td>
<td>RMSF</td>
<td>512</td>
</tr>
<tr>
<td>83/M</td>
<td>RMSF</td>
<td>1024</td>
</tr>
<tr>
<td>40/M</td>
<td>rickettsialpox</td>
<td>1024</td>
</tr>
<tr>
<td>51/M</td>
<td>rickettsialpox</td>
<td>256</td>
</tr>
<tr>
<td>60/F</td>
<td>RMSF</td>
<td>64</td>
</tr>
<tr>
<td>53/F</td>
<td>rickettsialpox</td>
<td>32</td>
</tr>
<tr>
<td>78/F</td>
<td>RMSF</td>
<td>1024</td>
</tr>
<tr>
<td>23/M</td>
<td>spider bite</td>
<td>&lt;32</td>
</tr>
<tr>
<td>53/M</td>
<td><em>R. parkeri</em> infection</td>
<td>&lt;32</td>
</tr>
<tr>
<td>72/M</td>
<td>RMSF</td>
<td>&lt;32</td>
</tr>
<tr>
<td>30/M</td>
<td>cellulitis</td>
<td>64</td>
</tr>
</tbody>
</table>
*Rickettsia parkeri*: infection of *Amblyomma* ticks in the southeastern US

- *Amblyomma maculatum*: relatively high infection prevalence (~15% - 40%) in questing adult ticks from MS, FL, GA, and VA. 40 (28%) of 144 from NC.

- *Amblyomma americanum*: infections much less common, ~0.2% - 1% of ticks from GA, MS, KY, and TN.
How many *Ehrlichia spp.* infections are misdiagnosed as “RMSF”?

- *Amblyomma americanum*: the most common and widely distributed human-biting tick in the southeastern US; relatively high infection prevalence (~2% to 5%)

- Ehrlichiosis shares many clinical features with RMSF; rash present in ~30%

- Similar seasonal pattern, exposure history, and response to doxycycline

- Carpenter et al., 1999: 9 (56%) of 16 patients with fever and tick bite over 2 years

- Fishbein et al., 1987: 3 (10%) of seronegative ‘RMSF’ cases during 1985-86
“The American white-tailed deer… adjusts remarkably well to human activity, to cities, and to agriculture. It is a deer of ecological havoc, a survival virtuoso…”

Valerius Geist, 1998
What is the contribution of *Rickettsia amblyommii*?

- Lone star ticks frequently infected with *Rickettsia amblyommii* (~40%-60%)

- *R. amblyommii* identified in salivary glands of lone star ticks

- Multiple longitudinal studies document asymptomatic seroconversion to spotted fever rickettsiae in as many as 33% of persons exposed to *A. americanum*-infested habitats

- Apperson et al., 2008: seroconversion of symptomatic patients to *R. amblyommii*, but not *R. rickettsii* antigens
Diagnostic assays: pitfalls and problems

- Serologic methods used to diagnose >99% of all cases of spotted fever.

- Seroconversion using IFA is considered the reference standard, but not sufficient to specifically identify the causative *Rickettsia* species.

- Diagnostic levels of antibodies to spotted fever group rickettsiae occur in ~5%-10% of general US population.

- Non-quantitative assays (EIA) used increasingly; cannot be used to document seroconversion.
Changing diagnostic landscape

RMSF cases diagnosed by serologic methods other than IFA
2000-2007 (CRFs)

Change in CDC case definition
Closing comments

• Epidemiologic data for RMSF is likely confounded by other milder rickettsioses
  -change in surveillance definition in 2010 from “RMSF” to “spotted fever rickettsiosis”

• Accuracy in diagnosis imperative: molecular techniques are the key to separating similar, yet distinct, spotted fevers
  -skin biopsy
  -eschar swab
Acknowledgments

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