Tick-borne viral diseases in the United States

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Disclosure

The Association of Public Health Laboratories adheres to established standards regarding industry support of continuing education for healthcare professionals. The following disclosures of personal financial relationships with commercial interests within the last 12 months as relative to this presentation have been made by the speaker(s):

J. Erin Staples, MD, PhD - Nothing to disclose.
Objectives

- Describe geographic distribution and clinical features of tick-borne viral diseases
- Understand role of molecular and serologic diagnostic testing in confirming tick-borne viral infections
Colorado tick fever
Colorado tick fever (CTF) virus

- Double-stranded RNA virus
- Family: *Reoviridae*; Genus: *Coltivirus*
- Transmitted primarily by *Dermacentor andersoni* (Rocky Mountain wood tick)
- Small rodents are primary reservoir
Ecology of CTF virus

1. Small rodents such as squirrels, chipmunks, and mice are infected with CTF virus through tick bites. These animals usually do not become ill but they can pass the virus to other ticks that feed on them.

2. CTF virus is also passed from one stage of the tick life cycle to the next – from larvae to nymph to adult.

3. People are infected with CTF virus through the bite of infected ticks. People who work or play outdoors are most likely to be exposed to ticks.

4. Other animals such as elk, marmots, and deer also can be infected with CTF virus through tick bites. However, these animals probably do not play an important role in passing the virus to other ticks.
CTF epidemiology

- Endemic to mountainous regions (elevation of 4,000-10,000 feet) of western U.S. and southwestern Canada
- CTF is currently reportable in six states
  - Arizona, Colorado, Montana, Oregon, Utah, and Wyoming
- Up to 90% of cases recall tick exposure
- Blood-borne and laboratory transmission rare
Approximate geographic distribution of *Dermacentor andersoni* and counties of residence for CTF cases, United States – 2002-2012

* All cases were acquired in states where local transmission of CTF virus has been reported previously.

Number of CTF cases by year, United States – 1987-2012

Median 55 cases/year
Median 5 cases/year

Number of cases

1987 1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011
Month of illness onset for CTF cases, United States – 2002-2012
Demographics of CTF cases, United States – 2002-2012

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=75</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
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<tr>
<td><strong>Sex</strong></td>
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<td><strong>Age (years)</strong></td>
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<tr>
<td>0-19</td>
<td>11</td>
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<tr>
<td>20-39</td>
<td>13</td>
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<tr>
<td>40-59</td>
<td>30</td>
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<td>≥60</td>
<td>19</td>
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Clinical features of CTF

- Incubation period 2-3 days (range 1-14 days)
- Sudden onset of fever; can be bi-phasic
- Other symptoms include chills, headache, myalgia, and malaise
- Rare reports of meningitis, encephalitis, hepatitis, pericarditis, pneumonia, coma
- 15-30% of cases hospitalized
Clinical laboratory findings of CTF

- Some findings secondary to CTF virus infecting hematopoietic progenitor cells
- Leukopenia with relative lymphocytosis
- Atypical lymphocytes
- Moderate thrombocytopenia
Treatment and outcome for CTF

- No specific treatment; supportive therapy
- Illness duration 7-10 days but malaise can last for weeks
- Death is rare
Diagnostic testing for CTF virus infection

- Testing is available at Focus Diagnostics, Montana Public Health Laboratory, and CDC
- CTFV infects red blood cells; leads to prolonged viremia and delayed antibody production
- RT-PCR is most sensitive for acute samples; also can culture virus
- IFA or neutralization testing for antibodies may not be positive until 2-3 weeks post infection
- IHC also available for tissues
Number and proportion of samples positive for CTF virus infection by days post onset and assay

<table>
<thead>
<tr>
<th>Days post illness onset</th>
<th>RNA No. pos/No. tested (%)</th>
<th>Neutralizing antibodies No. pos/No. tested (%)</th>
<th>IgG antibodies No. pos/No. tested (%)</th>
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</thead>
<tbody>
<tr>
<td>0-6</td>
<td>14/14 (100)</td>
<td>0/12 (0)</td>
<td>1/8 (13)</td>
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<tr>
<td>7-13</td>
<td>8/8 (100)</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
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<td>14-20</td>
<td>1/1 (100)</td>
<td>2/4 (50)</td>
<td>5/6 (83)</td>
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<tr>
<td>≥21</td>
<td>0/0 (0)</td>
<td>16/16 (100)</td>
<td>3/3 (100)</td>
</tr>
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</table>
Summary of CTF virus and disease

- Likely under-recognized cause of febrile illness in spring and early summer in Western U.S.
- Majority of cases recall tick exposure
- Samples collected in first 14 days of illness should be tested for viral RNA
- Antibody testing not reliably positive until 3 weeks after illness onset
- Defer blood donors for 6 months
References for CTF

Powassan (POW) virus

- Single-stranded RNA virus with two lineages
  - POW virus or Lineage I POW virus
  - Deer tick virus (DTV) or Lineage II POW virus

- Family: *Flaviviridae*; Genus: *Flavivirus*
  - Member of tick-borne encephalitis group

- Transmitted primarily by *Ixodes* spp.
  - Lineage I: *I. cookei*, *I. marxi*, and *I. spinipalpus*
  - Lineage II: *I. scapularis*, *I. dammini*, *D. andersoni*

- Small to medium mammals (rodent, woodchucks, skunks) are main reservoirs
POW virus disease epidemiology

- Endemic primarily in northeastern states and Great Lake region
- POWV disease is nationally notifiable
- No other modes of transmission documented
  - Theoretical risk for blood and \textit{in utero} transmission
  - Tick-borne encephalitis virus transmitted via ingestion of milk from infected ungulates
Geographic distribution of POW virus neuroinvasive disease cases, United States – 2004-2013
Number of POW virus disease cases by year, United States – 1970-2013

Median 0 cases; Northeast US

Median 6 cases; NE and North Central US
Month of illness onset for POW virus disease cases, United States – 2004-2013
## Demographics of POW virus disease cases, United States – 2004-2013

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (74)</td>
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<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>0-19</td>
<td>10 (15)</td>
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<tr>
<td>20-39</td>
<td>8 (12)</td>
</tr>
<tr>
<td>40-59</td>
<td>15 (23)</td>
</tr>
<tr>
<td>≥60</td>
<td>32 (49)</td>
</tr>
</tbody>
</table>
Clinical features of POW virus disease

- Incubation period range 8-34 days
- Asymptomatic or mild disease may occur
- Fever, headache, vomiting, and weakness are initial symptoms of neuroinvasive disease
- Progresses to altered mental status, aphasia, paresis, movement disorders, nerve palsies
- 88% of cases hospitalized
Clinical laboratory and imaging findings of POW virus disease

- CSF with lymphocyte pleocytosis though neutrophils can predominate early
- Normal or mildly elevated CSF protein
- Normal CSF glucose
- Brain MRI with demyelinating disease or micro-vascular ischemia in parietal or temporal lobes
Treatment and outcome for POW virus disease

- No specific treatment; supportive therapy
- Roughly half of cases have long-term neurologic sequelae
- 10-20% of cases are fatal
Diagnostic testing for POW virus infections

- Testing is available at Minnesota and New York state public health laboratories and CDC
- Viremia rarely detected early in illness and usually only with nested RT-PCR
- Antibody measured by IgM and IgG EIA and neutralization testing
  - Cross-reactivity can occur in EIA with related flaviviruses
  - Antibody testing can not differentiate between lineages
- IHC also available for tissues
Summary of POW virus and disease

- Likely under-recognized cause of neuroinvasive disease during tick season
- Occurs predominantly in northeastern and north central United States
- Neutralizing antibody testing needed to confirm diagnosis due to flavivirus cross-reactivity
References for POWV


Initial Heartland virus disease cases

- In June 2009, two adult males seen at hospitals in northwestern Missouri

- Both relatively healthy; one reported recent diagnosis of Type II diabetes mellitus

- Symptoms and signs were similar for both
  - Fever, fatigue, anorexia, and diarrhea
  - Leukopenia and thrombocytopenia
Exposures for initial cases

- Both farmers who resided and worked land
- Both reported multiple tick exposures prior to their illness onset
- No recent travel, vaccinations, or other recent illnesses
Hospital course for initial cases

- Both were admitted and received doxycycline for presumptive ehrlichiosis
- Failed to improve and laboratory parameters worsened during hospitalization
  - Thrombocytopenia became more significant
  - Moderately elevated liver transaminases developed
- Both patients discharged home after 10-12 days
- Laboratory testing for etiology was negative
Identification of novel virus

- Acute samples were sent to CDC to culture for *Ehrlichia chaffeensis*
- Both showed cytopathic effects
  - Characteristic morulae were not seen
- Electron microscopy performed identified bunyavirus-like particles
- In 2011, next generation sequencing identified virus as novel phlebovirus, Heartland virus
Entomologic evaluation

- Ticks and mosquitoes collected from farmers’ residences and local areas to test for HRTV
- Heartland virus recovered in 10 *Amblyomma americanum* (Lone star tick) pools
- *Amblyomma americanum* likely vector
Identification of additional Heartland virus disease cases

- Epidemiologic investigation implemented with MO Dept of Health and Senior Services in 2012

- Prospect study with participants enrolled in 7 medical facilities throughout MO

- Enrollment criteria includes fever, leukopenia, and thrombocytopenia
  - Excludes non-infectious etiologies

- In 2013, cases tested from other locations
Epidemiology of Heartland virus disease cases

- From 2012-2013, 6 additional cases identified from Missouri and Tennessee
- All patients were males
- Median age is 58 years (range: 50-80 years)
- Illness onset was in May (n=3), July (1), and September (2)
Clinical features and outcome of Heartland virus disease

- Of 5 patients where symptoms were collected, all reported fatigue and anorexia
- Other symptoms included headache, nausea, myalgia, or arthralgia
- Four (67%) of 6 patients were hospitalized
- One (17%) died
Reported exposures for Heartland virus disease cases (N=6)

- All patients reported spending >1 hour per day outside
- 5 (83%) reported tick bites in 14 days prior to illness onset
Diagnostics testing for Heartland virus infections

- Testing currently available at CDC; several academic centers performing RT-PCR
- RT-PCR on acute serum is often positive for Heartland viral RNA
- Neutralization test used for determining antibody titers in acute and convalescent samples
- IgM MIA and IFA and IgG MIA and ELISA have been developed but need further validation
- IHC available to test tissues
Summary of Heartland virus and disease

- Previously unrecognized human pathogen, likely transmitted by *A. americanum*
- Clinically similar to ehrlichiosis/anaplasmosis
- Consider diagnosis in patients with fever, leukopenia, and thrombocytopenia who test negative for tick-borne pathogen or do not improve on doxycycline
- Serologic and molecular testing can be used to diagnosis Heartland virus infections
References for Heartland virus


Prevention of tick-borne viral diseases

- No vaccines to prevent tick-borne viral diseases in United States
- Tick-borne encephalitis vaccine available in Canada and Europe
- Avoid tick bites
  - Use insect repellent
  - Wear long sleeves and pants
  - Avoid wooded or bushy areas with high grass
  - Perform thorough tick checks after spending time outdoors to remove ticks before they attach
CDC websites and downloadable information on tick-borne diseases

- Colorado tick fever
  - http://www.cdc.gov/coloradotickfever/

- Powassan virus disease
  - http://www.cdc.gov/powassan/

- Heartland virus disease

- General tick-borne disease information

  - Free app in Apple App store (“cdc tickborne”); android version anticipated by May 2015
Questions

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov  Web: http://www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.