Identification and Care of Patients with Hantavirus Disease

Clinician Outreach and Communication Activity (COCA) Call
June 30, 2016
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Objectives

At the conclusion of this session, the participant will be able to:

- Describe the risk factors, endemic areas, and incubation period of hantavirus infection

- Identify the clinical presentation and methods to identify a patient with hantavirus in the clinical setting

- Understand the parameters of clinical management and critical care for patients with hantavirus
Today’s First Presenter

Barbara Knust, DVM, MPH, DCAVPM
Epidemiologist
Office of Infectious Diseases
National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Today’s Second Presenter

Gregory Mertz, MD
Professor Emeritus
Department of Internal Medicine
University of New Mexico
Today’s Third Presenter

Michelle Harkins, MD
Associate Professor of Medicine
Division Chief, Pulmonary, Critical Care, and Sleep Medicine
Department of Internal Medicine
University of New Mexico
Hantavirus Overview and Epidemiology

- Hantavirus global overview
- US Epi summary
- Diagnostics
- Hantavirus surveillance in the US
Hantaviruses

- **Bunyavirus** family
- Primarily rodent reservoirs
- Human infection
  - Inhalation of excreta
  - Bites possible

- Hemorrhagic fever with renal syndrome (HFRS)
  - Old-world hantaviruses (Seoul virus likely throughout world)
  - Europe and Asia

- Hantavirus pulmonary syndrome (HPS)
  - New-world hantaviruses
  - Numerous pathogenic hantavirus species across North and South America
New World Hantaviruses

- **Sin Nombre**
  - *Peromyscus maniculatus*
- **Blue River**
  - *Peromyscus leucopus*
- **Muleshoe**
  - *Sigmodon hispidus*
- **Isla Vista**
  - *Microtus californicus*
- **Limestone Canyon**
  - *Reithrodontomys megalotis*
- **El Moro Canyon**
  - *Reithrodontomys mexicanus*
- **Calabazo**
  - *Zygodontomys brevicauda*
- **Choclo**
  - *Oligoryzomys fulvescens*
- **Río Mearim**
  - *Holochilus sciureus*
- **Anajatuba**
  - *Oligoryzomys formesi*
- **Bermejo**
  - *Oligoryzomys chacoensis*
- **Orán**
  - *Oligoryzomys longicaudatus*
- **Río Mamoré**
  - *Oligoryzomys microtis*
- **Río Segundo**
  - *Reithrodontomys mexicanus*
- **Caño Delgadito**
  - *Sigmodon alstoni*
- **Central Plata**
  - *Oligoryzomys flavescens*
- **Hu39694**
  - *Unknown Host*
- **Juquitiba**
  - *Oligoryzomys nigripes*
- **Araraquara**
  - *Necromys lasiuris*
- **Maciel**
  - *Necromys benefactus*
- **Lechiguanas**
  - *Oligoryzomys flavescens*
Rodent Reservoirs of Pathogenic Hantaviruses in the US

A. Deer mouse (Sin Nombre virus)
B. White-footed mouse (New York virus)
C. Hispid cotton rat (Black Creek Canal virus)
D. Rice rat (Bayou virus)

From: Mills et al, Vector-Borne and Zoonotic Diseases 2009
**Hanta Virus Ecology**

**Enzootic Cycle**

Many hantaviruses are known to cause hantavirus pulmonary syndrome (HPS). Each virus has a single primary host. The most important hantavirus in the US is the Sin Nombre virus, hosted by the deer mouse.

**Epizootic Cycle**

Favorable environmental conditions such as mild winters and summer rainfall may cause dramatic increases in rodent populations. More rodents become infected under crowded conditions. Deer mice may enter human structures in rural areas. Humans may become infected when they inhale airborne virus or come into direct contact with infected rodents or their urine, feces, or nests. Other mammal species (cats, dogs, coyotes) may be infected through contact with rodent hosts, but they are not known to transmit the virus.

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**A.** Local enzootic transmission of hantaviruses occurs at low levels during periods of unfavorable environmental conditions.

**B.** The virus is maintained and transmitted by host reservoir rodents by horizontal transmission (aggressive behavior, biting).
Hantavirus Pulmonary Syndrome Epidemiology

• Persons living or working in rural areas at increased risk
  – Farmers
  – Outdoor enthusiasts (camping, hiking)
  – Opening/cleaning unfrequented buildings and spaces (summer homes, sheds, attics, etc.)

• 20-40 cases reported annually, >95% exposed west of Mississippi River
  – Importance of exposure & travel history
### Hantavirus Pulmonary Syndrome
#### U.S. Descriptive Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>401 (63%)</td>
</tr>
<tr>
<td>Female</td>
<td>236 (37%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>496 (78%)</td>
</tr>
<tr>
<td>American Indian</td>
<td>115 (18%)</td>
</tr>
<tr>
<td>African American</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>127 (20%)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>229 (36%)</td>
</tr>
</tbody>
</table>

- Total of 637 cases between 1993 and 2015
- Mean age: 37 (range: 5 to 84)
Hantavirus Pulmonary Syndrome Cases in the U.S. 1993-2015
Annual HPS Cases and Fatality Rate in the U.S. 1993-2015
Cumulative HPS Cases by Month of Onset in the U.S.

Hantavirus Diagnostics

- **Serology**: Most common means of diagnosis in US; detects IgM & IgG
  - Testing available through commercial and public health labs (state/federal)
- **PCR**: Detectable virus during acute phase
- **Immunohistochemistry**: Postmortem detection of hantavirus antigen
Hantavirus Antibody Testing

• IgM & IgG develop rapidly after onset of symptoms—detectable at first test in nearly all HPS patients

• Cross-reactivity between different hantavirus species

• Commercial assay:
  – False positive results possible; important to interpret results carefully

• CDC ELISA:
  – Available through state & federal labs; highly sensitive & specific
HPS Surveillance

• HPS and hantavirus infection without pulmonary symptoms are nationally notifiable conditions
  – Providers should contact local or state health department for awareness & assistance with diagnostic testing
  – Environmental investigations may occur at exposure sites
HCPS: Incubation Period, Clinical Presentation and Course

Gregory Mertz, M.D.
Professor of Internal Medicine
University of New Mexico
June 30, 2016
Site of initial HCPS case cluster
New Mexico, May 1993
Incubation period, Andes virus (ANDV) Infection, Chile
11 patients with 24-48 hrs of exposure in rural area

Mean: 18.3 days
Range: 10-34

2012 Yosemite Sin Nombre Virus outbreak
Incubation: median 30.5 (range 20-49) days

Detection of Andes virus (ANDV) RNA by reverse-transcription polymerase chain reaction (RT-PCR) in peripheral blood cells obtained from household contacts who were asymptomatic and seronegative at study entry

<table>
<thead>
<tr>
<th>Additional household case patient no. from table 3 (sex, age in years)</th>
<th>Viral level in first positive sample, ANDV copies/mL of sedimented peripheral blood cells</th>
<th>Days from first positive RT-PCR to</th>
<th>Days from onset of symptoms in index case patient to positive RT-PCR in contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 (M, 47)</td>
<td>28,244</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>15 (M, 34)</td>
<td>33,000</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>13 (F, 48)</td>
<td>18,342</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>10 (F, 2)</td>
<td>1,181,551</td>
<td>NA(^a)</td>
<td>12</td>
</tr>
<tr>
<td>14 (M, 50)</td>
<td>116,754</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>9 (F, 47)</td>
<td>3882</td>
<td>NA(^c)</td>
<td>7</td>
</tr>
</tbody>
</table>

**NOTE.** NA, not available.

\(^a\) Case patient 10 was afebrile, asymptomatic, and seronegative when ANDV RNA was detected by RT-PCR, but the day of onset of prodromal symptoms could not be determined because of the subject’s age.

\(^b\) First positive PCR result on 1 June; the index case patient died on 21 May after several days of symptoms, but the exact date of the onset of symptoms was not known.

\(^c\) Case patient 9 was seronegative when enrolled 7 days before the day of the onset of symptoms, but cells were not collected for analysis by RT-PCR at the enrollment visit.

Infection with Hantavirus

- **infection**
- **illness**

- **viremia**
- **virus in cells**
- **IgG**
- **IgM**
Neutralizing Antibody Titer in HCPS

At hospital admission, patients who have a mild course of HCPS have significantly higher anti-Sin Nombre virus (SNV) neutralizing antibody titers when compared to patients who have or progress to severe or fatal disease. (Bharadwaj M, et al, J Infect Dis, 2000; 182(1):43-8. PMID: 10882580.)
HCPS Presentation

- Fever
- Respiratory failure
- Shock
- Hematocrit
- Platelets
- Immunoblasts
- Leukocytosis
- Liver enzymes
- Diuresis

Prodrome 2-6 d  Cardiopulmonary phase 5-6 days  Convalescence months
Deaths by hospital day among 104 hospitalized HCPS cases in Chile
Presumptive diagnosis in cardiopulmonary phase

After the onset of pulmonary edema, the presence of 4 of 5 findings has a sensitivity of 96% and specificity of 99%

- Thrombocytopenia
- Myelocytosis
- Lack of significant toxic granulation in neutrophils
- Hemoconcentration
- More than 10% lymphocytes with immunoblastic morphologic features

Immunoblasts in HCPS appear early in cardiopulmonary stage
Presumptive diagnosis of HCPS in the CASG IV ribavirin trial

- In 24 subjects with suspected HCPS in the cardiopulmonary phase (with bilateral infiltrates and hypoxia), SNV infection was confirmed in 23 (96%) with a presumptive diagnosis based on smear evaluation.
- In 12 subjects with suspected HCPS in the febrile prodrome (with fever and thrombocytopenia), none had SNV infection.

Hantavirus: A Tale of Mice and Men

Michelle Harkins, MD
Diagnostic Dilemma

- Patients may present with vague symptoms
- Return for CBC in 8-12 hours
- If platelet count is falling, call 1-800-272-2000 (at UNM Med Center), ask for Medical Critical Care or ID physician on call to discuss
Triage and Treatment

- **Key point:** transfer patient prior to cardiopulmonary phase to tertiary care center, preferably one with ECMO
- Don’t wait to stabilize
- AVOID fluid resuscitation
- Inotropes early
- Oxygen, try to avoid intubation
- Arrange air transport with ability for pressor initiation and to a center with ECMO capability
Multidisciplinary Involvement in Treatment of HCPS

Call from outside provider via PALS with suspected Hanta Patient

ID Faculty → Critical Care Faculty

ICU charge nurse

PICU Faculty

Heme Pathology Faculty

ECMO team

CT Surgery Faculty

Depending on likelihood and severity of disease, all could be awaiting the arrival of the patient.
**Ribavirin**

- Given early in HFRS in China, 7-fold reduction in mortality risk
- Results in HCPS inconclusive
  - Does inhibit SNV *in vitro*
  - Pre-treatment reduced deer mice sero-conversion
- *in vitro* and *in vivo* inhibition ANDV
  - Provided protection in a lethal hamster model of HCPS
  - ? Beneficial for post-exposure prophylaxis

Jonsson, Clin Micro Rev, April 2010; Safronetz, Plos One, Aug 2011
Survival without ECMO
Ribavirin versus Placebo Recipients

Kaplan-Meier survival analysis by treatment arm (methylprednisolone vs placebo) and severity at entry by sequential organ failure score (SOFA)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Methylprednisolone</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
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<td>27</td>
<td>22</td>
<td>18</td>
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</table>
Immune serum

• Serum from survivors with neutralizing antibodies may combat the viremia present
• Hamster/rat/primate studies have shown passive protection from hantavirus challenge when given neutralizing Ab
• No controlled human trials
• Not available in the US

Safronetz, Plos One, Aug 2011
Management of HCPS

• Critical care management
• Monitor PaO$_2$/FiO$_2$, cardiac index, lactate
• Pressors rather than IV fluids
• If ECMO is available,
  – Early placement of vascular sheaths
  – Concurrent intubation and initiation of ECMO if medical management fails
• No role for ribavirin or methylprednisolone (ineffective in placebo-controlled trials)
Why ECMO for HCPS?

• Early experience showed short duration of critical condition
• Autopsy findings without tissue damage- circulating inflammatory mediators likely cause cardiopulmonary dysfunction
• Occurs in previously healthy patients
Criteria for ECMO

- ≤ 65 years of age
- No major organ system failure (cirrhosis, ESRD, neurologic dysfunction)
- HCPS by history, clinical judgment, smear
- CI<2.5 despite resuscitation or rapidly declining clinical status
- Hypotension
- Hypoxemia – PaO$_2$/FiO$_2$ <50 despite support
HCPS-ECMO Cannulation

• Femoral site-venoarterial
  venous- 27- 29 french
  arterial- 16-18 french

• Distal perfusion cannula – via posterior tibial artery

• Open vs. percutaneous- surgeon’s preference

• Right IJ 27 to 29 french for additional drainage
Extracorporeal Membrane Oxygenation (ECMO)
Typical ECMO Course

- Patient paralyzed and sedated
- Ventilator settings ~ SIMV 10/500cc/40%/10
- Hemodynamic improvement 12 hours
- Pulmonary improvement 48-72 hours
- Weaning from ECMO 4-5 days when pulmonary capillary leak resolves and cardiac function improves

Crowley, Crit Care Med, 1998
UNM Hanta Stats

• From 2000 to 5/16
  – Approximately 75 patients Hanta +, not all needed ECMO

• Several patients with HCPS died prior to or during transport to UNM
  – 2 within the last few months

  • From Four Corners area
    – One presented with GI complaints first day then represented next day in shock
    – Other one presented late
UNM ECMO Hanta Stats

- Total 59 patients: 04/15/1994 – 3/29/16
  - Survived ECMO 43/59 (73%)
  - Survived to hospital discharge 37/59 (63%)
- Age range 9 - 69
- Male 32, Female 27
- Duration of ECMO 5-276 hours (143)
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Atlanta, Georgia
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CDC Guideline for Prescribing Opioids for Chronic Pain (second call in a series of 4)

- Date: Wednesday, July 27, 2016
- Time: 2:00 – 3:00 pm (Eastern Time)

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