Hantavirus
Cardiopulmonary Syndrome

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Hantaviruses-History

• Korean War, 1951-54: 3000 cases “Korean Hemorrhagic Fever”
• Fever, shock, ARF, pulmonary edema
• 10% case-fatality ratio
• Tents “overrun with rodents”
• Virus isolated: 1978
• Hantaan River, Korea

Hantaviruses-History-2

• Europe/Scandinavia: “Nephropathia Epidemica”
• Gajdusek: “Related pathogens”- scoured old literature in multiple languages
• Puumala virus-1980
• Seoul virus-1982
• “Hemorrhagic Fever with Renal Syndrome”

Hantaviruses as of 1992-93

<table>
<thead>
<tr>
<th>Virus</th>
<th>Location</th>
<th>Disease</th>
<th>Host</th>
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</thead>
<tbody>
<tr>
<td>Hantaan</td>
<td>E. Asia</td>
<td>HFRS</td>
<td>Striped Field Mouse</td>
</tr>
<tr>
<td>Seoul</td>
<td>Worldwide</td>
<td>HFRS</td>
<td>Commensal Rats</td>
</tr>
<tr>
<td>Puumala</td>
<td>Europe</td>
<td>HFRS</td>
<td>Bank Vole</td>
</tr>
<tr>
<td>Dobrava</td>
<td>Europe</td>
<td>HFRS</td>
<td>yellow neck field vole</td>
</tr>
<tr>
<td>Prospect Hill</td>
<td>U.S.</td>
<td>none</td>
<td>Meadow Vole</td>
</tr>
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</table>

Hantavirus Cardiopulmonary Syndrome

• “Mystery Illness” –fulminant fever/ARDS
• Four Corners, USA (UT, CO, AZ, NM)
• Navajo Indians- very rural lifestyle
• Spared Pueblo Indians-- ? genetic influence
• 80% case-fatality ratio
• Cross reacted with HTN, PUU, SEO viruses (CDC)

Hantavirus Cardiopulmonary Syndrome (HCPS)

• Cardiopulmonary phase ranges from mild pulmonary disease to rapidly progressive respiratory failure with death from cardiogenic shock/arrhythmia.
• As such, hantavirus cardiopulmonary syndrome (HCPS) may be more accurate and descriptive than hantavirus pulmonary syndrome (HPS).
Deer Mouse (*Peromyscus maniculatus*)

Exposure Risk

Yes:
- Cleaning closed spaces
- Abandoned vehicles
- Food storage buildings

No:
- Gardening
- Jogging outdoors
- Weeding, removing brush

HANTAVIRUS GENOME AND ANTIGENS

(-) sense RNA

<table>
<thead>
<tr>
<th>Protein</th>
<th>Molecular Weight</th>
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<tbody>
<tr>
<td>L</td>
<td>240 kD</td>
</tr>
<tr>
<td>RDRP</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>125 kD</td>
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<tr>
<td>GPC</td>
<td></td>
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<tr>
<td>S</td>
<td>49 kD</td>
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<td>N Ag</td>
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</table>

Nucleocapsid
Envelope
RDRP
(RNA dependent RNA polymerase)

HCPS- Clinical Stages

- **INCUBATION** (8-30 d)
- **PRODROME** (1-6 d): Fever, chills, myalgias, headache, nausea, vomiting
- **CARDIOPULMONARY** (5-15d): Rapid decompensation, shortness of breath, dyspnea, cough
- **DIURESIS** (several days): Rapid recovery of PaO2/FIO2, diuresis
- **CONVALESCENCE**: Prolonged low energy state, dysphoria, decreased exercise tolerance, weight gain, abnormal PFTs
HCPS- When to suspect?
A toxic-looking patient from a rural area who presents with fever, chills, myalgias, and (often) nausea and vomiting, who has a low platelet count.

HCPS- What to ask?
• Recent camping, travel
• Exposures to cabins, other rural, rarely used buildings
• Sightings of rodents or droppings
• Housing- trailer, cabin
• Occupational exposures

HCPS- How to Dx?
• Low or falling platelet count
• Clinical progression
• WBC, H/H, immunoblasts L shift w/o toxic changes (smear)
• Specific antibody tests
  • Rapid- UNM/TriCore
  • Others- state health depts., CDC

Triage IF IN DOUBT
• 3º care
• Hanta experience
• ECMO capabilities
Many have died in transit

Differential Dx
• Appendicitis/acute abdomen
• Pyelo
• Pneumonia
• Rickettsial
• Plague
Localization of Virus

- Vascular endothelium (esp microvessels)
- Rarely in MΦ
- Some circulating mononuclear cells

Mori et al 1999

Non-ARDS
ARDS

HCPS lung
HCPS kidney

Mori et al 1999

Presumptive Diagnosis by scanning the Peripheral Blood Smear: A Blinded Study

<table>
<thead>
<tr>
<th>Group (N)</th>
<th>Mild HCPS (21)</th>
<th>Severe HCPS (25)</th>
<th>ARDS/sepsis (37)</th>
<th>Bacterial Pneumonia (29)</th>
<th>Fl. syndrome (62)</th>
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</thead>
<tbody>
<tr>
<td>% mortality</td>
<td>0</td>
<td>68</td>
<td>43</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Platelet range</td>
<td>31-154</td>
<td>21-147</td>
<td>17-344</td>
<td>33-781</td>
<td>11-443</td>
</tr>
<tr>
<td>% platelets &lt; 150K</td>
<td>95</td>
<td>100</td>
<td>62</td>
<td>7</td>
<td>15</td>
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<tr>
<td>% myelocytes present</td>
<td>95</td>
<td>100</td>
<td>54</td>
<td>45</td>
<td>21</td>
</tr>
<tr>
<td>% immuno blasts present</td>
<td>95</td>
<td>100</td>
<td>41</td>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td>% correct diagnosis</td>
<td>90</td>
<td>100</td>
<td>97*</td>
<td>100*</td>
<td>97*</td>
</tr>
</tbody>
</table>

*correct diagnosis = not hantavirus.

Koster et al 2001

Clinical and Laboratory Progression in HCPS

<table>
<thead>
<tr>
<th>Fever</th>
<th>Pulmonary edema</th>
<th>Shock</th>
<th>Diuresis</th>
<th>Immuno blasts</th>
<th>Platelets</th>
<th>HCT</th>
<th>AST</th>
<th>LDH</th>
<th>PTT</th>
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3-6 d  7-10 d

Clinical SIA- TriCore

<table>
<thead>
<tr>
<th>Strip ID</th>
<th>IgG</th>
<th>IgM</th>
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<tbody>
<tr>
<td>C.B.</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SNV-N</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>SOD/G1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>1+</td>
<td>+</td>
<td>-</td>
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**Pathophysiology**

**T cell Responses in HCPS - Evidence for Role in Shock**

- Appearance of circulating, activated CD8+ and CD4+ cells is coincident with the onset of shock and pulmonary edema
- The same cells are in the pulmonary interstitium
- At least some are antiviral CTL

**T cell Responses in HCPS - are T cells the mediators?**

- Initial enthusiasm has died down as studies differed in whether abundant T cell responsive is maladaptive or adaptive
- A great deal rides upon 1 outlier case in Kilpatrick et al
- Other models have come forth, e.g. VEGF/viral interaction → ↑vascular permeability

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**HCPS mortality: US**

- Prior to 1993: 43/78 (55%)
- To January 11, 1999: 87/205 (42%)
- To Dec 15, 2010: 190/529 (36%)
- University Hospital: 13/38 (34%)
- ECMO (2006): 23/35 (66%)
- Last 21 ECMO cases: 18/21 (85%)

**Hemodynamics at Clinical Nadir of Eight Patients with HCPS (HPS) with Shock vs. Normal Ranges**

H. Levy et al, unpublished data

<table>
<thead>
<tr>
<th>Metric</th>
<th>HCPS (Mean +/- SEM)</th>
<th>Normal Ranges</th>
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<tbody>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.1 ± 0.33</td>
<td>2.5 - 4.2</td>
</tr>
<tr>
<td>Systemic vasc. resist. index (dyne.sec.cm⁻⁵/m²)</td>
<td>2114 ± 258</td>
<td>1,700 - 2,500</td>
</tr>
<tr>
<td>Stroke volume index (mL/beat/m²)</td>
<td>17.9 ± 3.5</td>
<td>33 - 47</td>
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ECMO

ICU management: Therapy

- Monitor oxygenation and maintain mean blood pressure > 70 mmHg
- Monitor wedge pressure and continuous cardiac output
- Avoid fluid overload
- Use vasopressors early
  - Dobutamine, dopamine, (nor)epinephrine
- High PEEP & FiO2

from H. Levy

ICU management: Warning signs

- Requirement for mechanical ventilation
- Inappropriate bradycardia and arrhythmias
- Low or falling cardiac index
- Oliguria reflecting poor perfusion
  - Creatinine > 3 mg/dL
- Serum lactate > 4 mmol/L

from H. Levy

Future Directions: HTS

Summary

- H(C)PS a rare but serious infection
- Stereotypical presentation
- Stereotypical epidemiology
- No specific Rx
- ECMO likely saves lives when available
- Best course: awareness/prevention