Hantavirus Pulmonary Syndrome

Hantaviruses are a genus of virus that infects rodents worldwide. Each species of hantavirus has a different severity and presentation associated with infection. Most hantaviruses affect the kidneys (hemorrhagic fever with renal syndrome), but in 1993 there was an outbreak of pulmonary hantavirus infection for the first time in the U.S. Now known as Hantavirus Pulmonary Syndrome (HPS),and cause by the Sin Nombre virus, it is the most commonly found hantavirus in the U.S. and Arizona.[1, 2]

A. Agent:

Hantaviruses are in the family Bunyaviridae, and are comprised of negative-sensed, single-stranded RNA, which are enveloped. There are 25 antigenically distinct species of hantaviruses, each infecting a unique primary rodent host. The type most commonly seen in North America is known as Sin Nombre virus.[1, 2]

B. Clinical Description:

Hantavirus Pulmonary Syndrome (HPS) is a febrile illness characterized by bilateral interstitial pulmonary infiltrates and respiratory compromise usually requiring supplemental oxygen. The typical prodrome consists of a fever higher than 101°F, chills, myalgia, headache, and gastrointestinal symptoms. Laboratory findings usually include hemoconcentration, left shift in white blood cell count, neutrophilic leukocytosis, thrombocytopenia, and circulating immunoblasts. This initial period of illness is followed by significant respiratory distress and hypotension. There is potential for rapid progression towards severe respiratory failure and shock. The case fatality rate can be as high as 30–35%. When cases do survive recovery can be rapid, but it may take months to regain complete normal functioning. There have been rare occasions of patients never fully recovering complete lung function. The most severe cases may have renal or hemorrhagic manifestations, but this is not common.[1, 2, 3] While progression to cardiopulmonary symptoms consistent with HPS occurs in most patients, some patients with confirmed infection may show signs of only the prodrome (Hantavirus infection, non-Hantavirus pulmonary syndrome).

- Differential Diagnosis:
  Presents similarly to acute respiratory disease syndrome (ARDS).

C. Reservoirs:

Infected rodents act as reservoirs. In the U.S. the deer mouse (*Peromyscus maniculatus*) is the most common host for Sin Nombre virus, but other hantaviruses can be found in other hosts. Each virus has a unique primary rodent host. The New York hantavirus, the host of which is the white-footed mouse, is associated with HPS cases in the northeastern US. The Black Creek hantavirus, hosted by the cotton rat, is found in the southeastern US. These reservoirs are necessary for human infections to occur. Mild winters and summer rainfall may allow for a dramatic increase in rodent populations. This, in turn, leads to rodent overcrowding and a greater likelihood of interactions with humans.[1, 2, 4]

D. Mode of Transmission:
Transmission occurs when rodent urine, feces, or saliva becomes aerosolized and is inhaled. This most frequently occurs when disturbing a rodent habitat and through releasing particles of dried urine, feces, and saliva up into the air. The classic example is cleaning out a shed in the springtime in which rodent hosts were overwintering. The likelihood of transmission is increased by the use of brooms or vacuum cleaners. Direct contact with rodent urine, feces or nests may also lead to infection. Other mammal species, including domestic dogs and cats, can become infected but don't seem to spread the disease to humans.[1, 2, 4]

E. Incubation Period:
Thought to be 2 weeks, but has shown a range from anywhere between a few days and 6 weeks.[1, 2, 3]

F. Period of Communicability:
Person to person transmission of hantavirus has been documented, but is exceedingly rare. Communicability between people is not a major concern. [1, 5]

G. Susceptibility and Resistance:
Immunity is presumed following clearance of an infection. There have been no documented second cases of hantavirus infection, but the duration and efficacy of post-exposure immunity is unknown. There have likewise been no documented cases of asymptomatic infections, and therefore, all virologically naïve people are assumed to be susceptible to infection. There is no vaccine available.[1]

H. Treatment:
There is no specific treatment, cure, or vaccine for hantavirus infections. However, it has been documented that early clinical intervention in an intensive care unit leads to better outcomes in HPS patients. Patients should receive intervention for their respiratory distress while in the ICU, this may include intubation and supplemental oxygen. Patients are more likely to be receptive to oxygen therapy earlier on in their illness, making early diagnosis imperative. Ribavirin IV has shown some benefit in patients.[1, 2, 6]

Disease Management

I. Clinical Case Definition:[7, 8]

Hantavirus Pulmonary Syndrome (HPS)
Hantavirus Pulmonary Syndrome (HPS) is an acute febrile illness (i.e., temperature greater than 101.0 F [greater than 38.3 C]) with a prodrome consisting of fever, chills, myalgia, headache, and gastrointestinal symptoms, and one or more of the following clinical features:
• Bilateral diffuse interstitial edema, or
• Clinical diagnosis of acute respiratory distress syndrome (ARDS), or
• Radiographic evidence of noncardiogenic pulmonary edema, or
• An unexplained respiratory illness resulting in death, and includes an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable cause, or
• Healthcare record with a diagnosis of hantavirus pulmonary syndrome, or
• Death certificate lists hantavirus pulmonary syndrome as a cause of death or a significant condition contributing to death

Hantavirus infection, non-Hantavirus pulmonary syndrome (non-HPS)
Non-HPS Hantavirus infection is a febrile illness with non-specific viral symptoms including fever, chills, myalgia, headache, and gastrointestinal symptoms, but no cardio-pulmonary symptoms. Typical clinical laboratory findings include hemoconcentration, left shift in the white blood cell count, neutrophilic leukocytosis, thrombocytopenia, and circulating immunoblasts.

J. Laboratory Criteria for Diagnosis:

- Detection of hantavirus-specific immunoglobulin M or rising titers of hantavirus-specific immunoglobulin G, OR
- Detection of hantavirus-specific ribonucleic acid (RNA) sequence by polymerase chain reaction in clinical specimens, OR
- Detection of hantavirus antigen by immunohistochemistry in lung biopsy or autopsy tissues.

Case Classification[7, 8]	
Confirmed	● Hantavirus Pulmonary Syndrome: A clinically compatible case of HPS that is laboratory confirmed ● Hantavirus infection, non-HPS: A clinically compatible case of Non-HPS Hantavirus infection that is laboratory confirmed.

K. Classification of Import Status:[8]
A case is considered imported if the person became infected outside of the United States. This should be considered when the opportunity for exposure and epidemiological evidence are more suggestive of infection elsewhere. A case may also be imported from one state into another, or one local jurisdiction into another. All opportunities for exposure and epidemiological evidence should be documented for assessment of import status.

L. Laboratory Testing:
Collect both a serology and culture to be sent to the Arizona State Public Health Lab for testing.

TEST	SPECIMEN	METHOD	NOTES
Serological Assay	Serum or blood sample, acute and convalescent phase serum	Detection of hanta-virus specific IgM or rising titers of IgG	ASPHL
Immunohistochemical (IHC)	Tissue sample	Detection of antigen	CDC - Often used when serum samples and frozen tissues are unavailable for testing
PCR	Fresh frozen lung tissue, blood clots, or nucleated blood cells	Detection of hantavirus specific RNA sequence	CDC

M. Assessing Laboratory Results:

Serological assay: Tests based on specific viral antigens from Sin Nombre Virus (SNV) have since been developed and are now widely used for the routine diagnosis of HPS. CDC uses an enzyme-linked immunosorbent assay (ELISA) to detect IgM antibodies to SNV and to diagnose acute infections with other hantaviruses. This assay is also available in some state health laboratories, including ASPHL.

Immunohistochemistry: IHC testing of formalin-fixed tissues with specific monoclonal and polyclonal antibodies can be used to detect hantavirus antigens and has proven to be a sensitive method for

laboratory confirmation of hantavirus infections. IHC has an important role in the diagnosis of HPS in patients from whom serum samples and frozen tissues are unavailable for diagnostic testing and in the retrospective assessment of disease prevalence in a defined geographic region.

Reverse transcriptase-PCR: RT-PCR can be used to detect hantavirus RNA in fresh frozen lung tissue, blood clots, or nucleated blood cells. However, RT-PCR is very prone to cross-contamination and should be considered an experimental technique. Differences in viruses in the United States complicate the use and sensitivity of RT-PCR for the routine diagnosis of hantavirus infections.

N. Outbreak Definition:

A hantavirus outbreak is defined as any amount of confirmed hantavirus cases which outnumber the usual amount in a specific time and geographic location. As a general rule of thumb, having two cases in the same county with a common source of exposure and within the same season could be considered an outbreak.

Investigation Guidelines

O. Time Frame:

A report must be submitted within five working days of receiving a positive test result.

P. Forms:

- ADHS Hantavirus Disease Investigation Form: http://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/disease-investigation-resources/hanta.pdf

Q. Investigation Steps:

- **Confirm Diagnosis**
  i. Before contacting the patient or family, determine what information is available from medical records, laboratory reports, etc.
  ii. Obtain information that supports clinical findings in the case definition and information on the onset date and order of the symptoms, including:
    - Hospitalization, outcome/status, symptom severity and duration.
  iii. Obtain information on any laboratory tests that were performed, along with results or date results are expected.
    - If laboratory tests have not been run to test for hantavirus, coordinate testing to confirm the case.
    - Testing should be coordinated with ADHS.
  iv. Make a note of the laboratory (location and contact information) performing any tests and the expected turn-around time for testing.
  v. For hospitalization, obtain medical records, including admission notes, progress notes, laboratory report(s), and discharge summary.

- **Conduct Case Investigation**
  Epidemiological investigation report should be submitted in MEDSIS by filling out the full DSO and Travel Table.
  i. Interview case to determine source, risk factors and transmission settings.
  ii. Collect information as specified on the Communicable Disease Report. Also collect the following information:

- Demographic data (birth date, county, sex, race/ethnicity), dates of exposure, reason for infection (e.g. animal contact, cleaning an outdoor or unattached area, etc.), occupation.
- Resident of your county? If not, determine if case is an international import or an out-of-state import.
- Type of domicile (e.g. rural, urban, well protected from pests and rodents, not protected from pests, barns, shed, garage type, etc.)
- Travel history:
  - Dates of exit from and reentry to Arizona
  - Locations (include dates of locations traveled)

iii. Focus on an incubation period of 2 weeks, but remember the range can be anywhere from a few days to six weeks.

iv. File relevant reports with the state. Note the state investigation ID number for cases previously reported. Highly suspect sources not previously reported should be investigated as a case and reported.

v. Collect information on the following:
- Any visits to a doctor's office, clinic, or hospital (exact date and time).
- Any outdoor events, work conditions, or hobbies that would bring cases into contact with infected rodents.
- Case finding and defining transmission setting.

▪ **Conduct Contact Investigation**

i. Susceptible contacts are anyone who came into contact with the same exposure source as the first patient.

ii. Follow-up symptomatic contacts as suspect cases.

▪ **Initiate Control and Prevention Measures**

Any suspicious cases should be reported to the appropriate health authority. Hantavirus is essentially non-contagious. Therefore, efforts should focus on recognizing symptoms, treating those exposed, and sterilizing the exposure source and location, when possible. Additional preventative measures and non-pharmaceutical interventions include:

- Prevent rodents' access into houses, garages, basements, shed, outhouses, etc.
- Keep food in rodent proof containers to avoid creating incentives for rodents to access the house.
- When an area is known to have been contaminated with rodents, wipe down or spray until very wet with bleach (1:10 bleach solution) or other strong disinfectants. Do not dust, sweep or vacuum the area, as this can cause aerosolization of infected rodent waste products.
- Minimize exposure to wild rodents.
- Test rodents bred in laboratory colonies as precaution against asymptomatic infections. This helps prevent potential laboratory exposure.
- Suggest calling an exterminator to the area in which the case was infected.

▪ **Isolation and Restrictions**

Hantavirus is essentially non-contagious, treatment isolation is not required.

▪ **Case Management**

Not applicable.

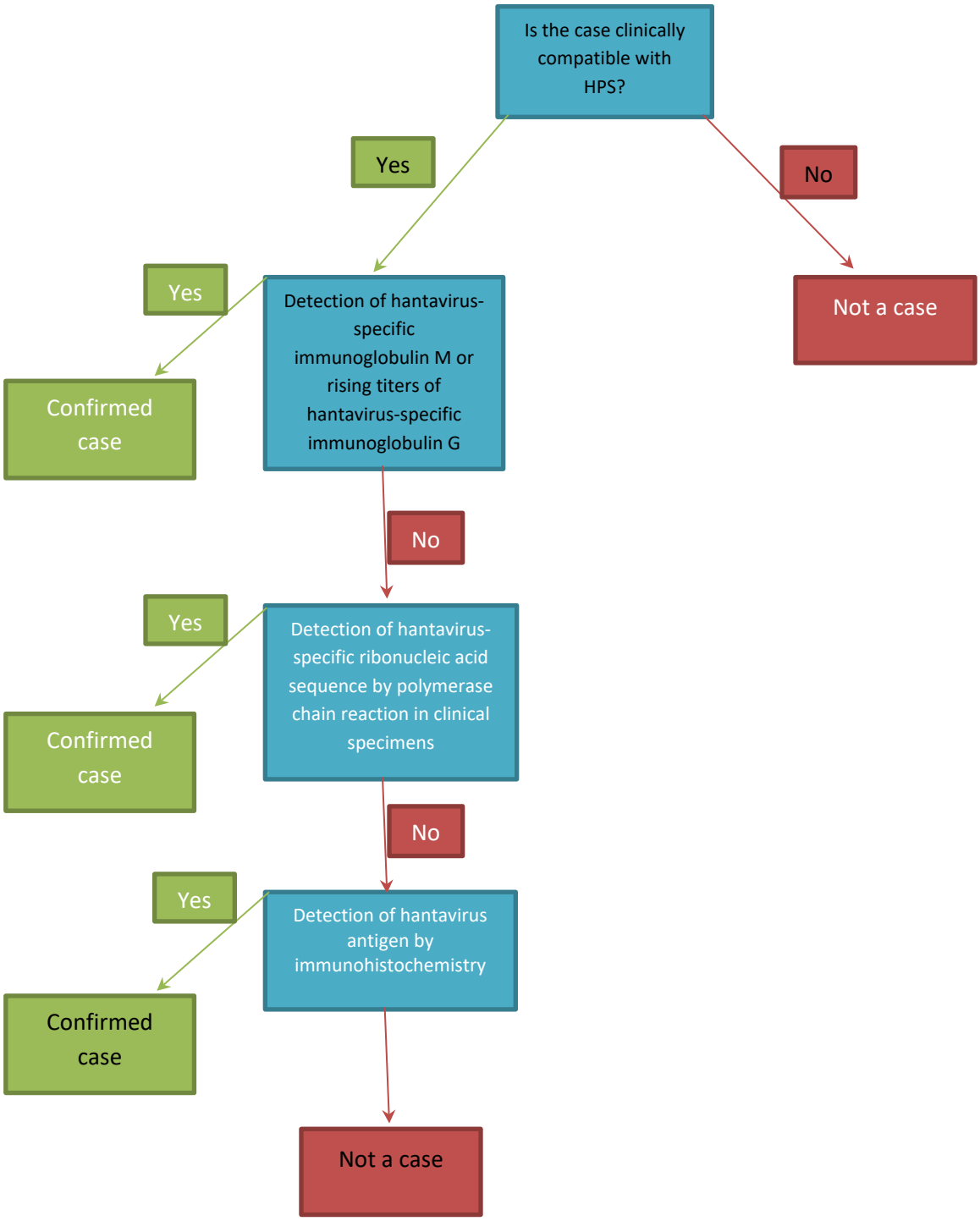
▪ **Contact Management, including Susceptible Contacts**

All potentially exposed individuals should be assessed by a clinician. If symptomatic, they should be considered a potential case until proven otherwise.

- **Notifications**
  i. Report all cases by telephone to ADHS within 5 working days of positive lab results.
  ii. Encourage the consideration of a HPS diagnosis in those fitting the clinical case definition and make clinicians and public health officials aware of differential diagnoses. Emphasize the need to report all suspected cases immediately to increase positive patient outcomes.
  iii. As appropriate, notify the case, contacts, and other individuals or groups.
  iv. Submit each hantavirus infection case to ADHS, as specified in Article 2, Table 4, the information required under R9-6-206(D).[9]

R. Outbreak Guidelines:
Notify program manager/ADHS immediately!
Regular hours: 602-364-4562
After hours: 480-303-1919

Hantavirus Pulmonary Syndrome Algorithm



References

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2. American Academy of Pediatrics. 2021 Red Book: Report of the Committee on Infectious Disease, 32nd Edition. Illinois, Academy of Pediatrics, 2021.

3. Centers for Disease Control and Prevention. Hantavirus: Signs & Symptoms. https://www.cdc.gov/hantavirus/hps/symptoms.html

4. Centers for Disease Control and Prevention. Hantavirus: Transmission. https://www.cdc.gov/hantavirus/hps/transmission.html

5. Centers for Disease Control and Prevention. Hantavirus: Hantavirus Pulmonary Syndrome (HPS). https://www.cdc.gov/hantavirus/hps/index.html

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7. Centers for Disease Control and Prevention. Hantavirus: Hantavirus Pulmonary Syndrome (HPS) Case Definition. https://www.cdc.gov/hantavirus/health-care-workers/hps-case-definition.html

8. Arizona Department of Health Services. In: Case Definitions for Reportable Communicable Morbidities: 2021. 2021 [cited 2022Feb24]; Available from: https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/disease-investigation-resources/casedefinitions/case-definitions.pdf

9. Arizona Regulations/Statutes Related to Infectious Disease. http://www.azsos.gov/public services/Title_09/9-06.pdf

For additional information and/or questions concerning isolate submission, and laboratory supplies:

- Arizona Department of Health Services (ADHS) State Public Health Laboratory (ASPHL), located at 250 N 17th Avenue, Phoenix, AZ 85007, Ph: 602-542-1188, Fax: 602-542-0760. http://www.azdhs.gov/lab/documents/microbiology/lab-guide.pdf