StatPearls Hantavirus Pulmonary Syndrome (HPS)

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Dr. Christian A. García Sepúlveda
MSc. Mariana Alejandra Castro Mejía

Laboratorio de Genómica Viral y Humana
Facultad de Medicina
Universidad Autónoma de San Luis Potosí

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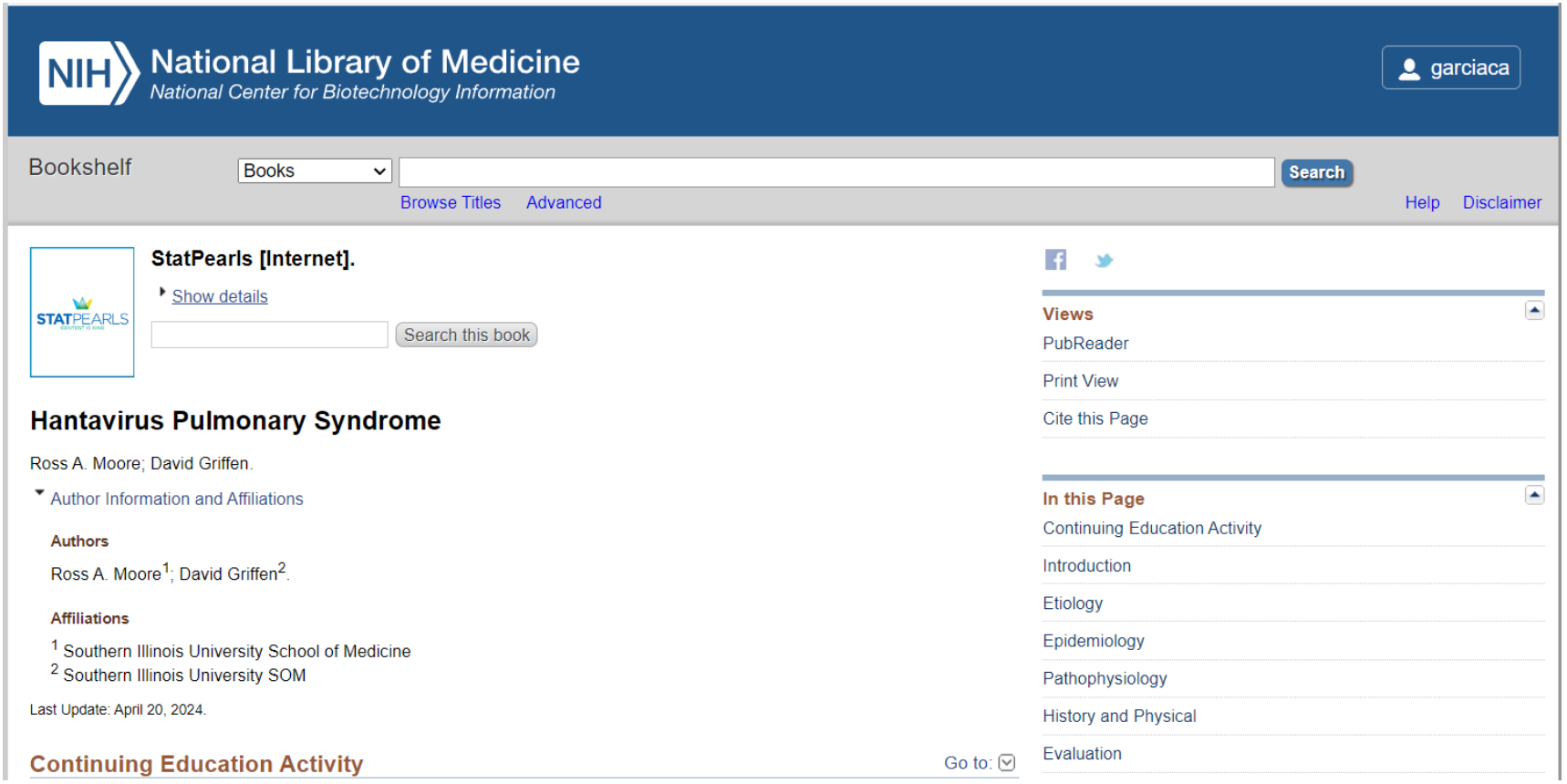

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Hantavirus Pulmonary Syndrome

Ross A. Moore; David Griffen.

Author Information and Affiliations

Authors

Ross A. Moore[1]; David Griffen[2].

Affiliations

[1] Southern Illinois University School of Medicine
[2] Southern Illinois University SOM

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Content

Comprehensive overview of HPS, including epidemiology, etiology, clinical manifestations, diagnostic approaches, and management strategies.

Latest research findings and pathophysiology of severe respiratory compromise.

Differences between HPS and hemorrhagic fever renal syndrome.

Practical preventive measures and public health interventions.

Evidence-based practices.

Introduction

Hantavirus pulmonary syndrome (HPS) is a rare but severe disease characterized by pulmonary edema, hypoxia, and hypotension.

Hemorrhagic fever renal syndrome (HFRS)

- Acute kidney injury, thrombocytopenia, fever, and hypotension.
- Mainly in Asia, Eastern Russia, and parts of Europe.
- Caused by Hantaan, Dobrava, Seoul, and Puumala viruses.
- Mortality between 15% for HFRS.

Hantavirus Pulmonary Syndrome (HPS) or Cardipopulmonary Syndrome (HCPS).

- Fever, myalgias, and severe respiratory compromise.
- Mainly in North and South America.
- Caused by Sin Nombre virus in North America and Andes virus in South America.
- Patients often require mechanical ventilation.
- Despite appropriate care mortality is up to 40%.

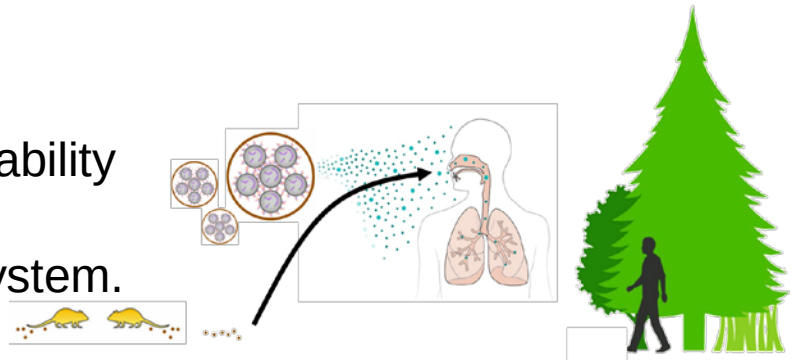
Nephropathia epidemica (NE)

- Mainly European.
- Mild form of HFRS with 0.1 to 0.5% mortality.

Introduction

Both HPS and HFRS

- affect the lungs and kidneys
- involve increased microvascular permeability
- consumptive platelet coagulopathy
- and hyperactivity of the host immune system.



All hantaviruses carried by rodents (and shrews and rarely bats) and spread to humans through inhalation of aerosolized urine, feces, or animal bites.

Reservoirs are asymptomatic carriers who shed virus lifelong.

Highest risk of infection in those who have close contact with animal hosts

Prevention is focused on decreasing human-rodent contact.

Taxonomy classifications were updated in ICTV Virus Taxonomy Profile: Hantaviridae 2024.

Etiology

Hantaviruses first discovered in 1950s in soldiers involved in the Korean War (Hantaan River).

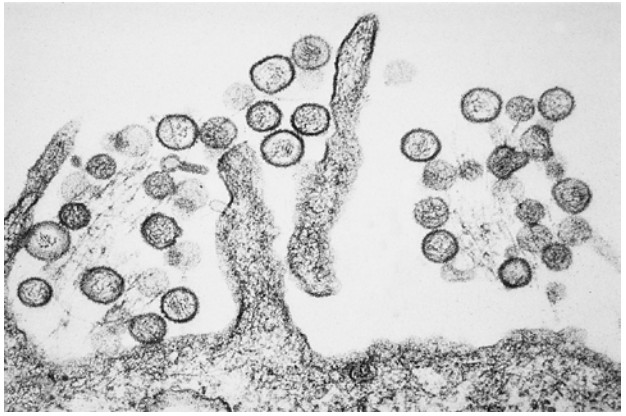
SNV emerged in 1993 in the Four Corners region, predominantly transmitted by the deer mouse (*Peromyscus maniculatus*) in the US.

ANDV predominate In South America, particularly virulent and the only strain known to cause human-to-human infection.

24 Hantavirus cause human disease, virus type varies by geographic location of reservoir.

Orthohantavirus are enveloped ssRNA(-).

Trisegmented genome:
Large segment (L) = RNA-dependent RNA polymerase
Medium segment (M) = glycoprotein precursor
Small segment (S) = nucleoprotein.



Virion size ranges from 70 to 160 nm.

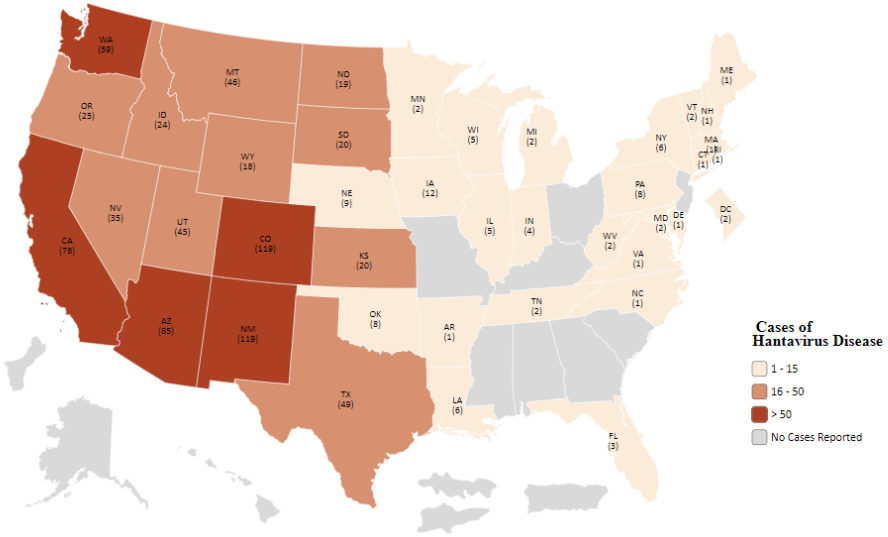
Epidemiology

HPS is the primary form of Hantavirus syndrome in North and South America.

In the US, most of the 697 cases (as of Jan 2017) were west of the Mississippi River.

7 states account for 70% of all US cases:

- New Mexico (109 cases)
- Colorado (104 cases)
- Arizona (77 cases)
- California (63 cases)
- Washington (47 cases)
- Texas (42 cases)
- Montana (41 cases).



50% of infections are due to domestic exposure.
10% due to workplace environment.
5% due to recreation activities.

American pathogenic orthohantaviruses

Sin Nombre Virus: Peromyscus maniculatus, Canada, United States.

New York Virus; Peromyscus leucopus, eastern United States.

Monongahela Virus: Peromyscus maniculatus nubiterrae, eastern United States.

Bayou Virus: Oryzomys palustris, southeastern United States.

Black Creek Canal Virus: Sigmodon hispidus, Florida, United States.

Laguna Negra: Calomys laucha, Paraguay, Bolivia.

Andes: Oligoryzomys longicaudatus, Argentina, Chile, Uruguay.

Oran: Oligoryzomys longicaudatus; northern Argentina.

Choclo: Oligoryzomys fulvescens, Panama.

Rio Mamore: Neacomys spinosus, Peru.

Lechiguanas: Oligoryzomys flavescens, Argentina.

Pathophysiology

Inhalation of hantavirus result in viral deposition in alveoli or terminal bronchioles.

Hantaviruses infect endothelial, epithelial, dendritic, & lymphocyte cells.

Viremia follows alveolar macrophage infection leading to infection of the pulmonary capillary endothelium.

Endotheilal infection induces interferon-alpha (IFN-α), prodromal manifestations.

Replication in vascular endothelium does not have direct cytopathic effects.

Endothelial injury due to immune response.

Infected endothelial cells activate CD8+ T cells and macrophages.

Activated macrophages and immunoblasts migrate to lung interstitium.

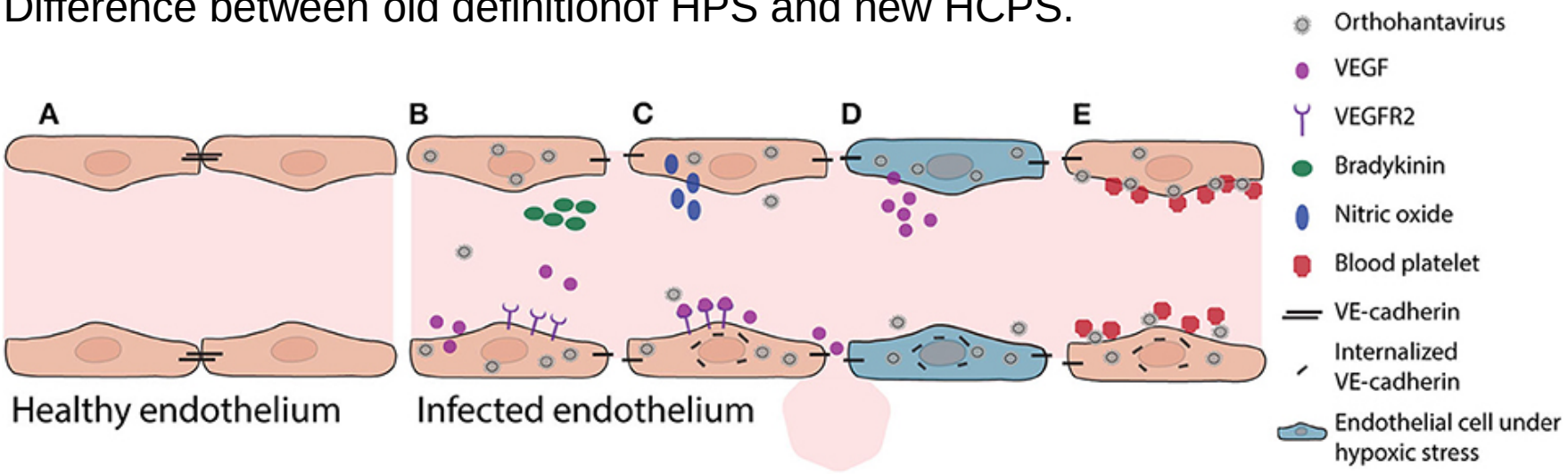
Beta-3 integrins which regulate platelet activation and vascular permeability mediate hantaviruses' cell entry.

Pathophysiology

Capillary endothelial permeability greatly increases after the secretion of tumor necrosis factor-alpha (TNF-α), IFN-γ, and nitric oxide, which results in pulmonary edema.

Soluble mediators such as TNF-α, IFN-γ, and nitric oxide are suggested as etiologies of myocardial depression in this infection, resulting in cardiogenic shock.

Difference between old definitionof HPS and new HCPS.



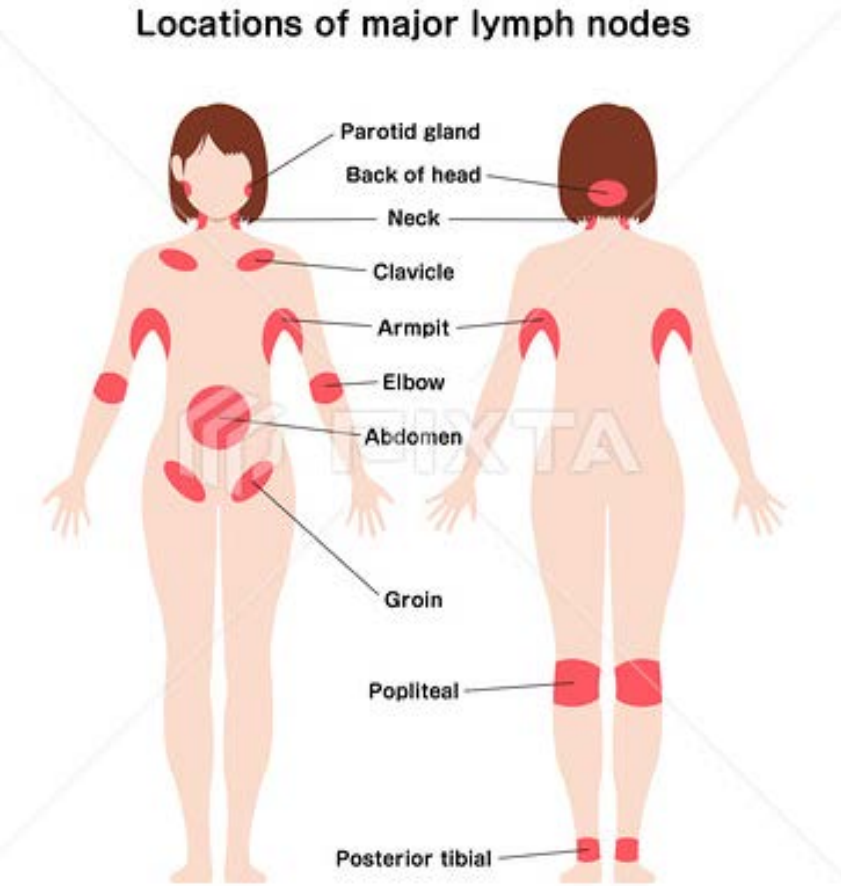
Noack D, et al. Front Cell Infect Microbiol. 2020 Aug 4;10:399.

Pathophysiology

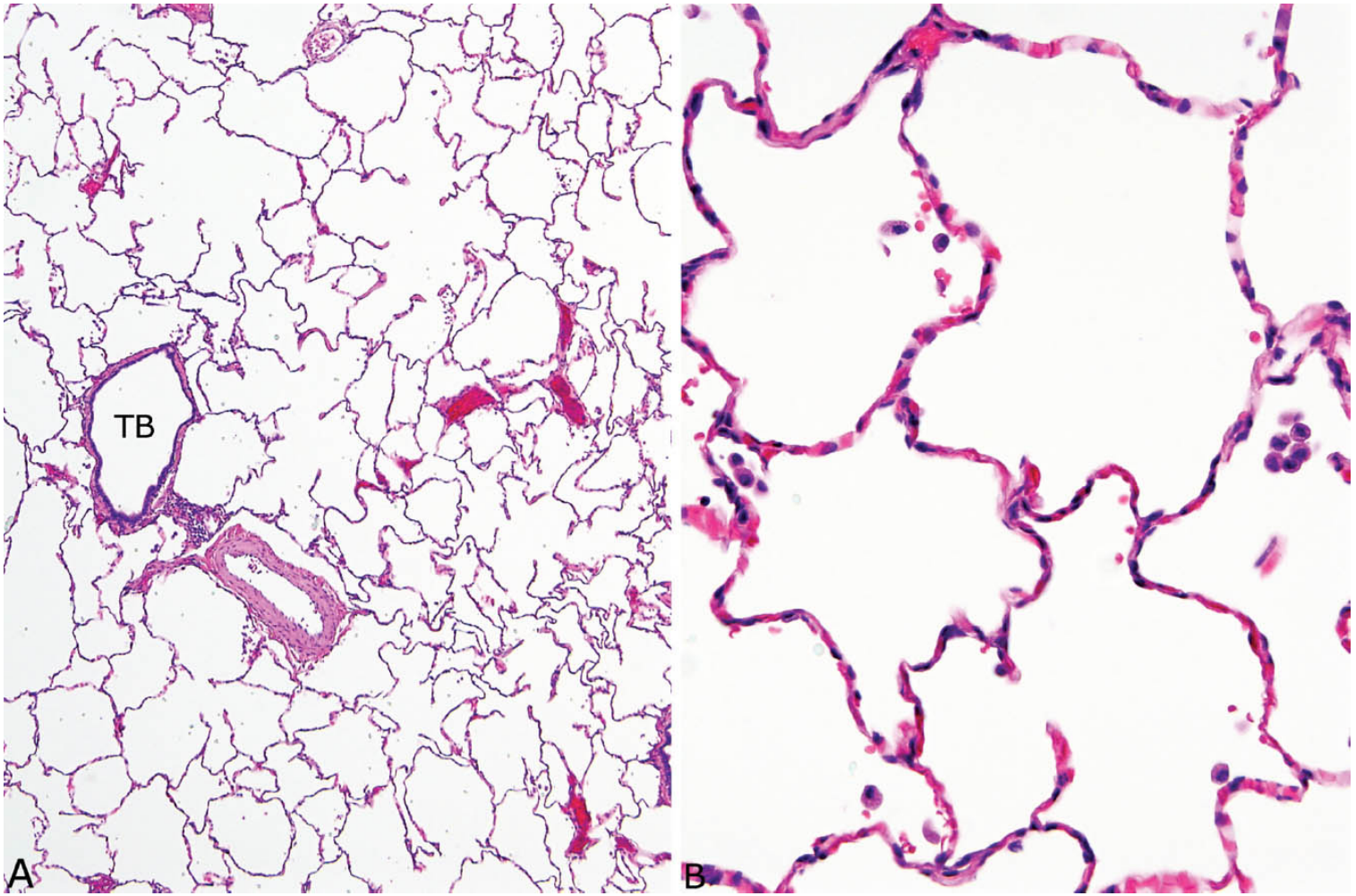
Immature dendritic cells transport virus through lymphatic tissue to regional lymph nodes which support further viral replication.

Unlike other hemorrhagic fever viruses that inhibit dendritic cell maturation, Hantaviruses induce their maturation eliciting a profound T-cell response.

After endothelial infection immunoblasts may be seen in the peripheral blood smear.



Histopahtology

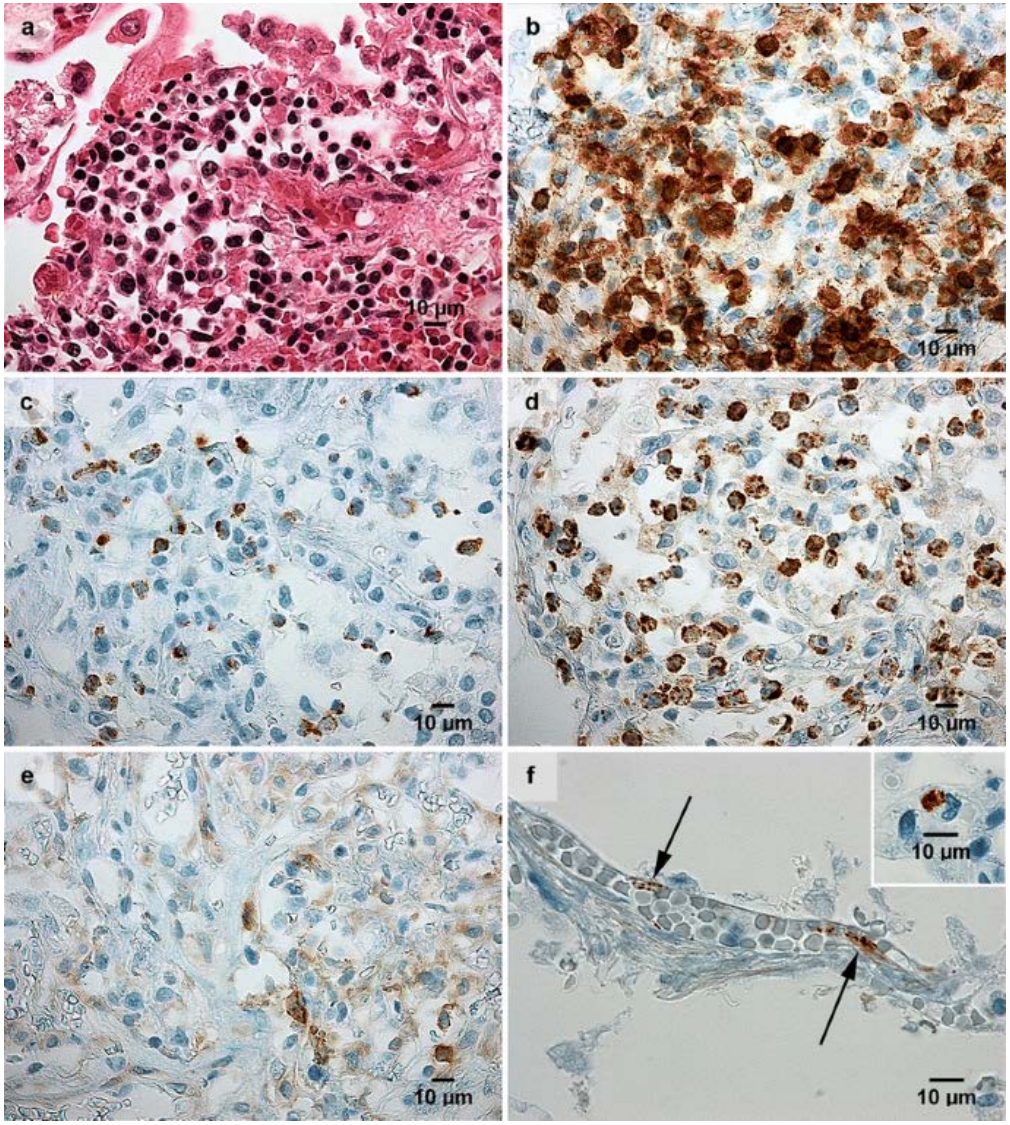


Normal lung histology as seen in HE stain

J Rasmuson, *et al*. Eur J Clin Microbiol Infect Dis . 2011 May;30(5):685-90.

Histopahtology

Edema with alveolar fibrinous exudate and mononuclear cell infiltrates.



CD8+ T lymphocytes

Granzyme B Containing lymphocytes

Lymphocytes bearing T cell restricted antigen-1, TIA-1

CD4+ helper T lymphocytes are rare

Viral antigen detected in capillary vascular endothelium and mononuclear cells.

J Rasmuson, *et al*. Eur J Clin Microbiol Infect Dis . 2011 May;30(5):685-90.

Patient history and physical examination

History of contact with rodents or their feces, urine or rodent bite in last 7 to 40 days:

- Farmers, forestry occupations, and cleaners of rodent-infested shacks.

Prodromal phase often influenza-like illness (ILI) and nonsuggestive.

- Headache
- Myalgia
- Vomiting
- Abdominal pain.

3 to 6 days after prodromal phase rapid (in 48 hrs) respiratory compromise

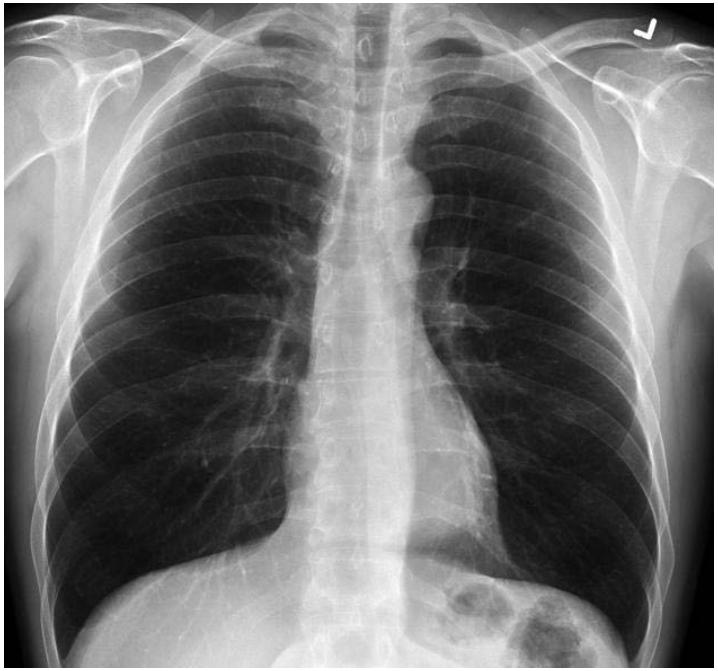
- Dyspnea
- Pulmonary edema
- Hypotension, and
- Cardiogenic or non-cardiogenic shock.
- Cardiovascular collapse
- Metabolic acidosis due to severe infection.
- Mortality rate between 40% to 70%.
- Other signs such as decreased urine output, petechiae, and hemorrhage.

Radiographic findings

Chest x-ray shows Bilateral, diffuse interstitial pulmonary edema on initial radiograph in 1/3 of patients.

All patients will have interstitial lung edema 48 hours after admission.

2/3 of pts develop bibasilar opacities or perihilar opacities with pleural effusions.



Normal chest x-ray

Hantavirus Pulmonary Syndrome

Laboratory findings

Thrombocytopenia on admission, predicts disease progression.

Circulating immunoblasts, atypical lymphocytes, and elevated hematocrit.

Peripheral blood smear may have myelocytes, metamyelocytes, and promyelocytes.

Hypocapnia & hyponatremia may be present.

Slightly prolonged activated partial thromboplastin time.

Hipoproteinemia, mildly elevated low-density lipoprotein level, and microscopic hematuria.

Diagnostic standard is RT-qPCR for specific viral species

Diagnosis can be made by immunofluorescent or immunoblot assay.

An IgM ELISA is the preferred diagnostic strategy when quantitative RT-PCR is not available.

Medical management (treatment)

Symptoms drive patients to seek medical attention but often result in discharge.

Respiratory failure can be severe, 40% require mechanical ventilation.

Extracorporeal membrane oxygenation, Univ of New Mexico with 70% success rate.

In spite of ICU around 1/3 of patients will die in the first 48 hours after admission.

50% will not need mechanical ventilation if managed with fluids and close monitoring.

Ribavirin proposed as a treatment option.

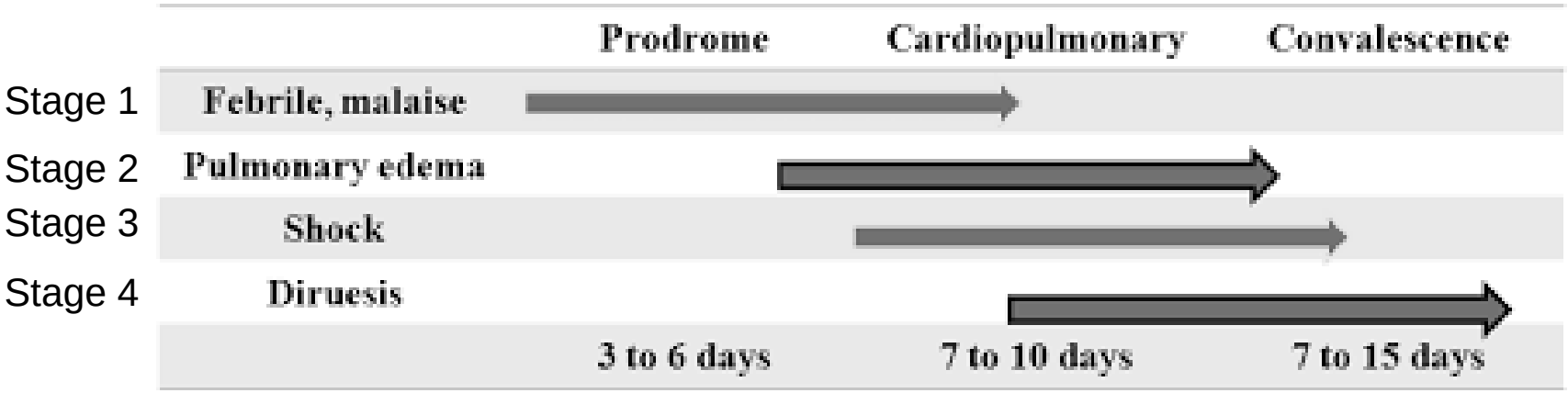
Maintain normal-high filling pressures on cardiac output & minimize lung edema.

Inotropic agents (dobutamine) encouraged early.

Death associated with disseminated intravascular coagulation (hemorrhage and drastic leukocytosis).

Clincal improvement in first days indicative of extubation within the first week.

Clinical staging



By the time a patient requires hospitalization he is in stage 2.

Stage 2: Cough and vomiting.
Orthostatic hypotension.
Tachycardia & tachypnea .
Thrombocytopenia.

Stage 3: Mechanical ventilation (Hipoxemia).

Stage 4: Convalescence with mild residual acute kidney damage (hematuria).

Differential diagnosis

Acute Respiratory Distress Syndrome

- Usually a consequence of pneumonia, sepsis, brochoaspiration or severe trauma.

Mycobacterial Pneumonia

Influenza Pneumonia

Viral Hemorrhagic Fevers

Leptosipirosis

Murine typhus, spotted fever and other rickettsiosis

Lymes disease (Borreliosis)

Babesiosis and Human granulocytic anaplasmosis

Crimiean-Congo Haemorrhagic Fever

See presentation on COVID-19 misdiagnosis (2024 COVID Misdiagnoses).

Pertinent Studies and Ongoing Trials

Fresh frozen plasma from patients who have recovered from HPS has been used with good effect (eg, results from a study showed a decrease in mortality from 32% to 14%).

Saavedra F, et al. Immunology. 2021.
Ye C, Emerg Infect Dis. 2004 Mar;10(3):478-82.

Animal studies are being conducted that use recombinant antibodies to Hantavirus.

Afzal S, Front Microbiol. 2023 Oct 12;14:1233433.

Hantavax has been used in Asia since the 1990s; this is believed to effectively decrease the incidence of new cases.

Liu R, et al. Front Microbiol. 2020.
Zhang H, NPJ Vaccines. 2024 Feb 10;9(1):28.
Paulsen GC, J Infect Dis. 2024 Jan 12;229(1):30-38.
Liu R, Virus Res. 2023 Sep;334:199149.
Stass R, Nat Microbiol. 2023 Jul;8(7):1293-1303.

Hantavirus vaccines

Summary of hantavirus vaccines used in humans and non-human primates

Hantavirus	Vaccine format	Immunogen(s)	State of development	Country
HTNV	Inactivated virus	Whole particle	Human mass vaccination	South Korea
HTNV, PUUV	Inactivated virus	Whole particle	Clinical studies	South Korea
HTNV, SEOV	Inactivated virus	Whole particle	Human mass vaccination	China
HTNV	Recombinant vaccinia virus	G_N, G_C, N	Clinical studies (not pursued)	US
HTNV, PUUV	DNA vaccine	G_N, G_C	Clinical studies	US
ANDV, HTNV, PUUV, SEOV	DNA vaccine	G_N, G_C	Pre-clinical studies (Rhesus, Cynomolgus)	US

Boudreau E, *et al.* Abstracts of the VIII International Conference on HFRS HPS and Hantavirus, Athens, Greece. 2010:83.
Hammerbeck CD, *et al.* London: Academic Press/Elsevier; 2009. pp. 379–412.
Schmaljohn C. Vaccine. 2009;27:61–64.
Zhang YZ, *et al*, Emerg Infect Dis. 2010;16:1195–1203.

CME activity

HPS is a rare but serious condition marked by pulmonary edema, hypoxia, & hypotension.

HPS is caused by Orthohantavirus genus, Hantaviridae family.

HPS presents with fevers, myalgia, and severe respiratory compromise, with 40% mortality.

The most common etiology is SNV in North America and the ANDV in South America.

Respiratory failure can be avoided with judicious volume management.

Mechanical ventilation is common shortly upon disease onset.

Care is supportive, prevention is the key.

Public health measures should reduce human-rodent contact.

StatePearls Quiz

Quiz: Hantavirus Pulmonary Syndrome (Id:1728773)

Question 1 of 2

A 25-year-old man presents with 2 days of fatigue, fever, and myalgia. He recently traveled to New Mexico, where he ate the local food, drank water from a stream, and reported mice in his hotel room. Vital signs are heart rate 100 bpm, blood pressure 100/70 mm Hg, respiratory rate 24 breaths/min, and temperature 101 °F (38.3 °C). Laboratory results are white blood cell count 12,000/µL, platelets 90,000/µL, and serum sodium 129 mEq/L.

A chest radiograph shows bilateral interstitial infiltrates. Serology testing is positive for IgM antibodies against an organism endemic to the region. What is the organism?

- A. Legionella
- B. *Borrelia burgdorferi*
- C. Mycoplasma
- D. Hantavirus

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Question 2 of 2

A 41-year-old healthy man presents to the emergency department in Colorado after camping in the woods in an abandoned house for 2 weeks. He complains of cough, vomiting, and dark urine. Vitals include a heart rate of 119 bpm, respiratory rate 22 breaths/min, blood pressure 119/68 mm Hg, which drops to 95/47 mm Hg upon standing, temperature 37.9 °C (100.2 °F), and oxygen saturation 94% on room air. Laboratory studies are grossly normal except for thrombocytopenia and a few metamyelocytes. Chest x-ray findings demonstrate bilateral basilar infiltrates. Despite initiating a sepsis protocol, including intravenous fluids, broad-spectrum antibiotics, and the placement of oxygen, the patient's condition continues to decline. He is presumed to have an infection transmitted by a rodent vector, and serology confirms the diagnosis. Given the likely diagnosis, which of the following is most associated with impending death in this patient's condition?

- A. Polyuria with urine output of 4 liters per day
- B. Oliguria with urine output of 200 mLs per day
- C. Disseminated intravascular coagulation
- D. Hyponatremia with hypomagnesemia

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Christian A. García-Sepúlveda — Laboratorio de Genómica Viral & Humana, Facultad de Medicina UASLP
Sandra E. Guerra-Palomares — Laboratorio de Genómica Viral & Humana,Facultad de Medicina UASLP
Juan Carlos Cuevas Tello — Grupo de Bioinformática, Facultad de Ingeniería UASLP
Ignacio Amezcua Osorio — Comité Estatal para el Fomento y Protección Pecuaria de San Luis Potosí (CEFPP)
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Fernando Díaz-Barriga Martínez — Centro Colaborador OMS/OPS CIAAS, Facultad de Medicina UASLP
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Dulce Ma. Hernández Piña — Lab manager, LGVH UASLP
J. Manuel Mendoza Méndez — Hantavirus americanos en roedores silvestres, LGVH UASLP
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