Diagnosis and treatment of new world hantavirus infections

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Purpose of review

The purpose of this review is to summarize the current knowledge regarding the diagnosis and treatment of indigenous new world hantavirus infections.

Recent findings

Recent studies have defined the incubation period of new world hantavirus infections, provided additional evidence for person-to-person transmission of Andes virus, described a rapid method for the presumptive diagnosis of infection in the cardiopulmonary phase through a review of the peripheral smear, and suggested that intravenous ribavirin is probably not effective for the treatment of new world hantavirus infections when started in the cardiopulmonary phase.

Summary

Presumptive diagnosis may be made by a review of the peripheral blood smear after the onset of the cardiopulmonary phase. Critical care management includes the avoidance of fluid overload, pressors to maintain cardiac output, and the use of extracorporeal membrane oxygenation in the most severe cases, but treatment with intravenous ribavirin is probably not effective.

Keywords

extracorporeal membrane oxygenation, hantavirus cardiopulmonary syndrome, new world hantavirus infections, ribavirin

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Abbreviations

ANDV	Andes virus
ECMO	extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay
HCPS	hantavirus cardiopulmonary syndrome
HFRS	hemorrhagic fever with renal syndrome
PaO_2/FIO_2	arterial oxygen tension : fractional inspired oxygen
RT–PCR	reverse transcription–polymerase chain reaction
SIA	strip immunoblot assay
SNV	sin nombre virus

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Introduction

In contrast to old world hantaviruses, which cause hemorrhagic fever with renal syndrome (HFRS), new world hantaviruses cause a syndrome characterized by a febrile prodrome followed by a cardiopulmonary phase that may result in respiratory failure, cardiogenic shock and death. The latter syndrome is known both as hantavirus pulmonary syndrome and hantavirus cardiopulmonary syndrome (HCPS), but we prefer HCPS to emphasize that death almost invariably results from cardiogenic shock rather than from respiratory failure [1].

Virology

The number of hantavirus species is still debated, and species identification and classification is evolving. Approximately half of the approximately 20 known old and new world hantavirus species are known to cause human disease. New world hantaviruses that have been identified as etiological agents of HCPS include Andes virus (ANDV), Bayou virus, Black Creek Canal virus, Choclo virus, Juquitiba virus, Laguna Negra virus, and sin nombre virus (SNV) [2–11].

Hantavirus genomes are composed of single-stranded, negative sense RNA that is divided into an L, or large segment, an M, or middle, segment, and an S, or small segment [12]. The L segment encodes RNA-dependent RNA polymerase, and the M segment encodes the envelope glycoproteins, G1 and G2, which are also referred to as Gn and Gc, respectively. The S segment encodes the nucleocapsid protein N. The N protein is immunogenic in humans and is relatively conserved among hantavirus species. In contrast, antibodies against the G1 glycoprotein, which is also immunogenic in humans, are relatively specific for the viral species against which they are directed.

Epidemiology

Each hantavirus species is associated with a rodent reservoir. Hantavirus infection in the primary natural rodent reservoir is persistent and asymptomatic. The etiological agents of HCPS are carried by rodents of the subfamily *Sigmodontinae* within the family *Muridae*. Hantaviruses appear to have co-evolved with the rodent reservoir host species over many thousands of years [13].

Transmission

Airborne transmission from hantavirus-infected aerosols is thought to be the primary route of transmission from

the rodent reservoir to humans. Activities such as cleaning storage sheds or cabins that have been closed for the winter have been recognized as carrying a particularly high risk for the acquisition of new world hantaviruses, and relatively few cases involve direct contact with rodents or rodent bites [14,15]. Person-to-person transmission has been documented only for ANDV infection in Argentina and Chile [16,17,18••,19].

Incidence

HCPS occurs throughout much of north and south America. A milder variant of hantavirus pulmonary syndrome, which spares the heart, occurs in Panama. Although data on the incidence of HCPS are lacking or are infrequently updated in many countries, the US Centers for Disease Control and Prevention (CDC) and the Chilean Ministry of Health provide easily accessible incidence data for the United States and Chile, respectively, through web sites that are updated regularly. In the United States, 416 cases have been reported to 1 February 2006, with an overall case fatality ratio of 35%. The annual incidence has ranged from a low of eight cases in 2001 to a peak of 48 cases in 1993. In Chile, 477 cases have been reported to 17 April 2006, with an overall case fatality ratio of 37%. Between 2001 and 2005, the number of cases of HCPS in Chile ranged from a low of 56 cases in 2004 to a peak of 81 cases in 2001.

Incubation period

The incubation period may be as short as a few days and may be up to 6 weeks or more [14,20,21]. In most cases the individual has had prolonged exposure to environmental sources and the exact incubation period is unknown. There have, however, been published reports from approximately 20 well-described cases in north and south America in which the period of exposure was limited to 2 days or less [14,20,21]. These included person-to-person transmission of ANDV after a day-long automobile trip [17], infection after rodent bites [14], and infection after brief trips to high-risk areas followed by the return to an urban area without risk of infection [21]. In these instances, the median incubation period was approximately 18 days, with a range of 11–32 days. The median of 18 days is probably close to the true median, but in light of the relatively small number of cases with short, well-defined exposures, the true range is probably wider than 11–32 days. For example, one case report had a well-documented incubation period of 46–51 days [22].

Clinical manifestations of hantavirus cardiopulmonary syndrome

The illness begins with a febrile prodrome with fever and myalgia that typically lasts 2–4 days but may be as long as a week to 10 days [23,24]. Headache, backache, abdominal pain, nausea and diarrhea are also commonly present. The latter may mimic an acute abdomen, and several patients have undergone exploratory laparotomy or laparoscopy during the prodromal phase. In Chile up to 25% of patients have a transient skin rash, and 10–20% have conjunctival suffusion.

The cardiopulmonary phase is heralded by the abrupt onset of cough and shortness of breath [1,25]. In mild cases, the patient can be supported with supplemental oxygen without mechanical ventilation. In severe cases, which represent at least 60% of hospitalized patients with HCPS, pulmonary edema and respiratory failure develop rapidly, usually over 12 h or less, and the patient requires intubation and mechanical ventilation. Chest radiographs are usually normal during the prodromal phase, but are uniformly abnormal at or shortly after the onset of the cardiopulmonary phase. The chest radiograph first shows bilateral interstitial edema, including Kerley B lines, indistinct hilar borders, and peribronchial cuffing [26]. In patients with severe disease, bilateral airspace disease develops, usually within hours of the onset of the cardiopulmonary phase.

Most of the patients with severe disease also develop cardiogenic shock, hemoconcentration, and lactic acidosis, often progressing to profound shock or arrhythmias, leading to pulseless electrical activity and death within minutes to a few hours after the onset of shock [1,25,27]. The average duration of the cardiopulmonary phase is 2–4 days, but may be longer in patients with severe disease who are maintained on extracorporeal membrane oxygenation (ECMO). In Chile, most patients have laboratory findings consistent with disseminated intravascular coagulation and mild renal insufficiency, with up to 25% of patients requiring hemofiltration or dialysis.

After 2–4 days the patient enters a diuretic phase, often with resolution of pulmonary edema over 12–24 h. The diuretic phase is often followed by a prolonged convalescent phase, with weakness, fatigue, impaired exercise tolerance and abnormal pulmonary function, including abnormal diffusion capacity.

Diagnosis

Although many patients with HCPS first seek medical attention during the febrile prodrome, the febrile prodrome is usually difficult to differentiate from other febrile illnesses based solely on the clinical presentation and on routine laboratory testing. Thrombocytopenia is the only laboratory abnormality in a routine, rapidly available laboratory test, and is typically, albeit not invariably, present during the prodrome. If a patient is thrombocytopenic and has had exposure to areas where pathogenic hantavirus rodent reservoirs are present, they should be observed closely and tested for hantavirus-specific IgG and IgM antibodies. In the case of a specific,

high-risk exposure such as a rodent bite from a known hantavirus reservoir, a laboratory accident, exposure to a rodent-infested enclosure, or household contact with a person with HCPS in Chile and Argentina, close observation and definitive testing for hantavirus IgG and IgM antibodies would be indicated in any febrile individual regardless of the platelet count.

Presumptive diagnosis during the cardiopulmonary phase

In contrast to the difficulty in differentiating the febrile prodrome from other febrile illnesses, a presumptive diagnosis may be established during the cardiopulmonary phase based on the presence of pulmonary edema and a review of the peripheral smear. Typical peripheral smear findings in the cardiopulmonary phase of HCPS include thrombocytopenia, myelocytosis, a lack of significant toxic granulation in neutrophils, hemoconcentration and more than 10% lymphocytes with immunoblastic morphological features. In a blinded comparison of blood smears obtained from patients with HCPS after the onset of pulmonary edema and blood smears from patients referred for evaluation for HCPS who were found to be seronegative, the presence of four of the five findings listed above had a sensitivity of 96% and a specificity of 99% [28]. The presumptive diagnosis is also supported by a characteristic hemodynamic pattern, with a normal or low cardiac index and elevated systemic vascular resistance. Hyponatremia and transaminase elevations are common but less specific findings.

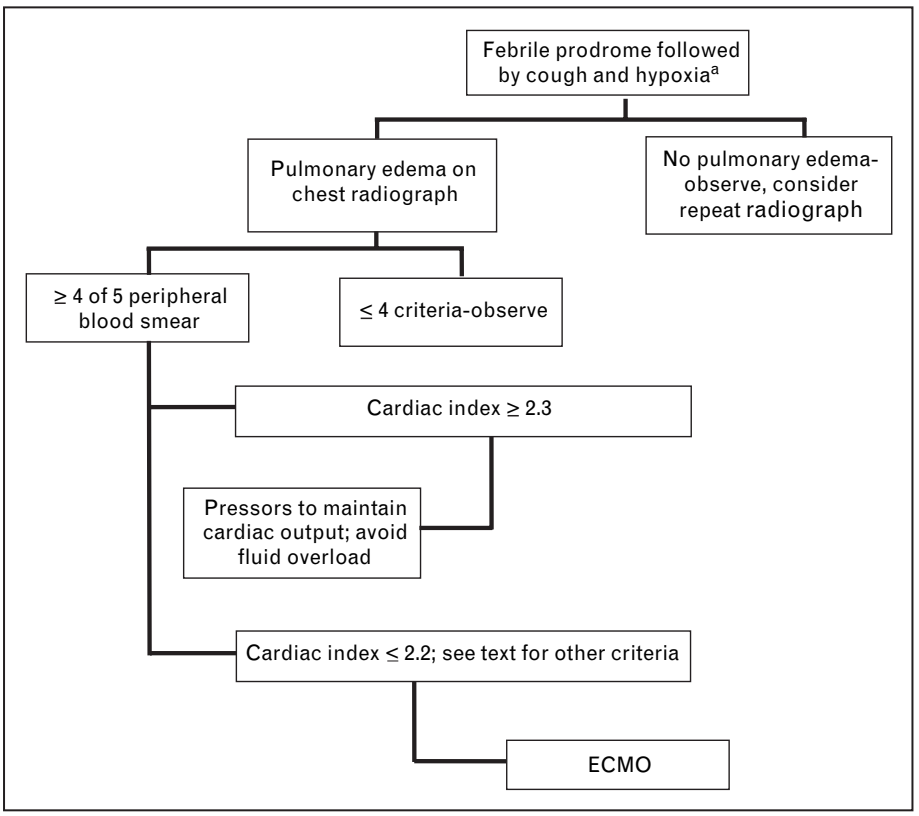
Once the cardiopulmonary phase begins, progression to cardiogenic shock and death may occur within hours. Although testing for specific antihantavirus IgG and IgM antibodies is available within 8–24 h at our centers, significant treatment decisions, often including the decision whether or not to initiate ECMO, must often be made before the results of antibody testing are available (Fig. 1). As such, we make an effort to make a presumptive diagnosis based on the presence of pulmonary edema and a review of the peripheral smear as soon as the patient is admitted.

Serological tests

The definitive diagnosis of HCPS is usually based on serological testing for hantavirus-specific IgG and IgM antibodies, which are absent before the onset of symptoms, and typically appear at the onset or early in the course of the febrile prodrome. Acute infection may be differentiated from past infection by the presence of

Figure 1 Flow diagram for the management of patients suspected of having hantavirus cardiopulmonary syndrome in the cardiopulmonary stage pending IgG and IgM antihantavirus antibody results

ECMO, extracorporeal membrane oxygenation. [a]Potential exposure at any time during the 6 weeks before the onset of symptoms includes living or visiting any area, usually rural, where a rodent reservoir of a pathogenic hantavirus may be present or close contact with a person with hantavirus cardiopulmonary syndrome who could have acquired Andes virus infection.



specific antihantavirus IgM antibody, IgG or IgM antibodies against the G1 glycoprotein or by a fourfold rise in the titers of specific antihantavirus IgG antibody.

Serological assays for hantavirus infections include enzyme-linked immunosorbent assay (ELISA), Western blot, strip immunoblot assay (SIA), indirect immunofluorescence assay, complement fixation, hemagglutinin inhibition and neutralization tests [29–32]. The ELISA, which was developed by the CDC, uses a recombinantly expressed N antigen. The CDC ELISA is available in many state health departments in the United States, and the SIA is available through the TriCore Reference Laboratory in Albuquerque. Reference laboratories in south America generally use ELISA for screening, but some use the SIA.

Although molecular epidemiology research is based primarily on sequencing viral complementary DNA, either analysis of antibody responses to the G1 antigen (by SIA or Western blot) or cross-neutralization studies may be used to differentiate antibody responses to different hantaviruses. Therefore, for example, an analysis of antibody responses to G1 antigen or cross-neutralization studies could easily differentiate the antibody response to SNV from the antibody response to Hantaan virus, Puumala virus, Seoul virus, Choclo virus or ANDV, but neither the antibody response to G1 nor cross-neutralization studies would be helpful in differentiating antibodies to SNV infection acquired in different regions of the United States or Canada. For the latter, the sequencing of viral cDNA is necessary.

Polymerase chain reaction

In patients with SNV and ANDV infection, it is generally possible to detect viral RNA by nested reverse transcription–polymerase chain reaction (RT–PCR) in peripheral blood mononuclear cells and in serum during both the febrile prodrome and early in the course of the cardiopulmonary phase. Furthermore, in a prospective study of household contacts of index patients with HCPS in Chile, we found that ANDV RNA can be detected in peripheral blood cells by RT–PCR for up to 2 weeks before the onset of symptoms or the development of antihantavirus antibodies (M. Ferres, unpublished data). RT–PCR may also be used to detect hantavirus RNA in frozen or fixed tissues obtained at autopsy from individuals who die during the cardiopulmonary phase of HCPS.

Virus culture

The isolation of pathogenic hantaviruses such as SNV and ANDV from humans is rarely attempted, partly because virus culture must be performed in a BSL-3 laboratory. To date, there is only a report of a human hantavirus isolate (ANDV) in the Americas [33].

Immunohistochemistry

Immunohistochemistry, employing antibodies to the viral N antigen, has been used for the detection of hantavirus antigens in tissues obtained at necropsy [34,35]. In individuals who die during the cardiopulmonary phase, viral antigen can easily be detected in tissue, particularly in the cytoplasm of vascular endothelial cells in the lung and kidney. This technique has been used to confirm the diagnosis when serum or peripheral blood cells are not available, including tissue from autopsies performed 10 years or more before the recognition of HCPS in 1993.

Treatment

The initial signs of the cardiopulmonary phase may be cough and pulmonary edema on chest X-ray. HCPS abruptly transitions from the prodrome phase to the cardiopulmonary phase with the development of pulmonary edema, and severe cases may progress to shock and death within hours. Whenever possible, transport to a tertiary care facility or to a facility for other support such as ECMO is recommended as quickly as possible, ideally before the onset of shock. Intensive care unit support includes avoiding fluid overload, ventilatory support when necessary, and the early use of pressors to maintain cardiac output [1,25,27]. Ventilatory support continues during the period of capillary leak and the recovery of cardiac function. When they are available, centers that are able to provide ECMO should be given preference over centers that do not.

Extracorporeal membrane oxygenation

If ECMO is available, the patient should be evaluated by critical care and the ECMO team, including cardiothoracic or vascular surgery, as soon as a presumptive diagnosis is established. If advanced shock is not present, the cardiac index and other parameters should be monitored closely to determine whether ECMO should be initiated. The use of ECMO is reserved for patients with advanced HCPS who would not be expected to survive without ECMO. ECMO must be initiated quickly once advanced shock or respiratory failure develops.

The criteria for the initiation of ECMO in HCPS patients have evolved since we started using ECMO for these patients at the University of New Mexico in 1994. Our inclusion criteria at this time for the use of ECMO in a patient with known HCPS are if they have a cardiac index of less than 2.3 l/min per square meter, or an arterial oxygen tension : fractional inspired oxygen (PaO_2/FIO_2) ratio of less than 50, and are unresponsive to conventional (non-ECMO) support. Patients with HCPS can rapidly deteriorate from being stable to cardiac arrest and death in just a few hours. Therefore, if the patient is in severe cardiopulmonary failure and deteriorates despite aggressive escalation of ventilator

and vasoactive support, we will initiate ECMO even if they have not yet met the criteria listed above. As circulatory support is essential, veno-arterial ECMO is always used in HCPS patients, even if the patient presents primarily with respiratory failure. Our cardiothoracic surgery team performs the cannulation, cannulating the femoral artery and vein, and also placing a small cannula down the femoral artery to ensure good leg perfusion. Our ECMO exclusion criteria are: patients older than 70 years, with severe pre-existing disease, or with neurological impairment.

At the University of New Mexico, we have treated 35 patients with HCPS with ECMO, with 23 surviving, neurologically intact, to discharge (66% survival). Of the last 21 treated with ECMO, 18 have survived to discharge (85% survival). Five of the 12 patients who died had prolonged cardiac arrest (greater than 10 min) before ECMO. The mean time from admission to our intensive care unit and the initiation of ECMO was 10 h, and the mean time from intubation to ECMO was 4 h. We believe the key factors in our improved outcome are the rapid diagnosis of HCPS by clinical presentation and blood smear criteria, aggressive critical care resuscitation, and the rapid implementation of ECMO if critical care resuscitation is unsuccessful and the patient meets ECMO criteria. Our ECMO team is present and ready to cannulate an HCPS patient on arrival from transport from an outside hospital, and will often wait for hours to ensure the patient is stable before leaving the bedside.

At the Clinica Alemana in Santiago, Chile, two adult patients with HCPS have been treated with veno-arterial ECMO and both survived [36•]. Both patients had cardiac indices of less than 2.0 l/min per square meter, PaO_2/FIO_2 ratios of less than 100, and serum lactate levels greater than 10 mmol/l before ECMO. Three patients with severe HCPS survived without ECMO. They had cardiac indices equal to or greater than 2.3 l/min per square meter, PaO_2/FIO_2 ratios greater than 100, and lactate levels less than 10 mmol/l.

Antiviral therapy

There is no approved antiviral therapy for HCPS, and no antiviral therapy has been shown to be effective. Although intravenous ribavirin reduced the severity of HFRS [37], a controlled trial of intravenous ribavirin for the treatment of HCPS in the United States and Canada did not suggest any benefit [38]. The HCPS trial was terminated before reaching full accrual, but there was no trend suggesting benefit in the ribavirin arm. Furthermore, a futility analysis based on the initial results predicted the need for a sample size that would have required enrollment of all HCPS patients in north America over several decades. In contrast to the ribavirin trial in HFRS, when ribavirin was often initiated several days before the onset of the renal phase, all subjects in the US/Canada ribavirin trial were enrolled after the onset of the cardiopulmonary phase. The authors of the trial felt that the pace of the cardiopulmonary phase in HCPS was probably too rapid for ribavirin to have any effect.

Research protocols that are in progress or in development are based on the assumption that patients with HCPS are unlikely to present for treatment before the onset of the cardiopulmonary phase, that treatment can be initiated on the basis of a presumptive diagnosis and cannot be delayed until the results of serological testing are available, and that the intervention must have a rapid therapeutic effect. In light of evidence that the cardiopulmonary phase may be largely immune-mediated, there is an ongoing, controlled trial of methylprednisolone therapy for HCPS in the cardiopulmonary phase being conducted in Chile. In addition, it is known that SNV and ANDV neutralizing antibody titers, respectively, are significantly lower in samples obtained on the day of hospital admission from patients who subsequently progress to severe HCPS or death compared with titers in patients with mild disease. As such, there is interest in the development of treatment protocols to evaluate the efficacy of treatment with high-titer hantavirus neutralizing antibodies.

Conclusion

Indigenous new world hantavirus infections occur throughout the Americas and include viruses such as SNV and ANDV, with a case fatality ratio that may approach 40%, and person-to-person transmission may occur with ANDV. The median incubation period in cases with brief, well documented exposures is 18 days. Presumptive diagnosis may be made by a review of the peripheral blood smear after the onset of the cardiopulmonary phase. Critical care management includes the avoidance of fluid overload, pressors to maintain cardiac output, and the use of ECMO in the most severe cases. Although treatment with intravenous ribavirin was effective in HFRS, the treatment of HCPS after the onset of the cardiopulmonary phase with intravenous ribavirin is probably not effective.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 496).

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