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Hantavirus and the Andes Variant: A Brief Report

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INTRODUCTION

Hantaviruses are a zoonotic virus family with a nearly worldwide distribution. It is known to primarily cause two severe disease processes in humans, hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS), or also commonly referred to as hantavirus pulmonary syndrome (HPS), which can both have devastating consequences [1]. Though the two disease processes have particular clinical aspects, there is overlapping symptomology. The incidence of hantavirus infection varies greatly based on geography inside the United States and even more so as we expand our view to include other countries and the possibility of international travel. As of 2022, there have been 864 confirmed cases of Hantavirus in the United States [2]. Additionally, in one study which included 519 patients diagnosed with hantavirus, 99% were hospitalized, 84% of patients required admission to the Intensive Care Unit and 31% of those cases required mechanical ventilation [3]. A narrative review of the literature was conducted utilizing PubMed, Scopus, and Embase to identify contemporary clinical guidelines, epidemiological data, and critical care management strategies regarding hantavirus infection. This article will focus on what the emergency and first-contact clinician needs to know about hantavirus including epidemiological trends, clinical manifestations, diagnosis, critical care management, infection-control considerations and the unique challenges presented by the Andes (ANDV) strain.

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CLINICAL COURSE

As stated above, the two primary clinical courses of hantavirus strains include HCPS and HFRS. HFRS, or hemorrhagic fever with renal syndrome is a syndrome of increased endothelial permeability [1]. This endothelial permeability crisis includes the vasculature leading to and coagulation dysregulation, thrombocytopenia, acute kidney injury. After incubation for 2-6 weeks patients can begin to experience high fever, headache, nausea, arthralgias, and abdominal pain [1]. Hypotension is common in these patients as well due to the increased vascular permeability [1]. Given the coagulation and clotting pathway dysregulations, bleeding is common in these patients

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manifesting as petechiae, mucosal bleeding, epistaxis, menorrhagia, and gastrointestinal bleeding. However, it should be noted that fatal bleeding is rare [1]. Typical lab abnormalities can consist of proteinuria, hematuria, increased hemoglobin, and decreased plasma albumin owing to increased vascular permeability. Inflammatory markers can be elevated, and liver transaminases are also sometimes deranged. The most common cause of death in patients with HFRS is shock, renal insufficiency and multiorgan failure [1]. Cardiorespiratory failure can also occur in these patients, though it is more common in HCPS.

HCPS, or hantavirus cardiopulmonary syndrome is, as the name suggests, a syndrome primarily affecting the cardiac and pulmonary systems. It has 3 distinct phases, a prodromal phase, cardiopulmonary phase and a convalescent phase [4]. It begins with a febrile prodrome lasting 2-7 days including chills, headaches, myalgias, abdominal pain, vomiting, arthralgias and retro-ocular pain [1]. One noteworthy characteristic is the absence of nasal congestion, rhinorrhea, sore throat, or cough. The primary significant lab finding in this phase is thrombocytopenia, however, if there is no thrombocytopenia on first investigation then repeat labs within 24 hours is recommended as up to 95% of patients with HCPS develop thrombocytopenia [4]. Next the cardiopulmonary phase begins which manifests as a rapid decline of respiratory function, including cough, dyspnea, and hypoxia with cardiopulmonary failure developing within 24 hours of this phase onset [4]. Flash pulmonary edema is common in these patients due to the increased vascular permeability which can be seen on chest x-ray [4]. Additionally, the patient can develop acute congestive heart failure resulting in decreased ejection fraction, which can further exacerbate the pulmonary edema [4]. Similar to HFRS at this stage, lab abnormalities can be related to hemoconcentration and vascular leakage including increased hemoglobin, decreased albumin, LDH elevation and proteinuria [4]. The convalescent phase of this disease sees a ready correction of the ejection fraction and endothelial dysfunction, though exertional dyspnea has been noted to last for up to 2 years after infection [4].

While hantaviruses are primarily limited to zoonotic transmission by contact with contaminated rodent feces, urine, or saliva, the Andes strain (ANDV) represents a unique strain in that it can be transmitted from person-to-person through close contact with infected individuals [5]. Cases of the ANDV strain primary occur in South America, specifically Argentina and Chile. Travelers to endemic areas can become infected, leading to exportation to non-endemic areas [1, 3]. The M/V Hondius represents an ideal vessel for this disease to spread given the extended close contact, shared air ventilatory system, heavy watertight doors, numerous doorhandles, elevator buttons, stair and gangway rails, shared recreational equipment, public restroom fixtures, and shared kitchen items and this lent itself well to the infection seen in this population in recent news. While these are all potential risks for the increased transmission seen on the M/V Hondius, it remains unclear as to which factor contributed most to the spread of infection. There is an estimated incubation period of 7-49 days, with a median of 18days for the ANDV that can result in a variety of illness severity. The illness can present with non-specific symptoms such as fever, myalgia, and headache. However, more than half of patients with the ANDV have severe symptoms of HCPS [1, 5]. In 20-35% of reported cases, there is rapid onset of pulmonary edema that resulted in cardiogenic shock and death [5]. A study in Chile following 476 household contacts of 76 ANDV-confirmed index-cases displayed a ten times higher risk for sex partner and an increased risk for non-sex partners with close contact [5]. Notably, person-to-person transmission represents a small fraction of cases with occasional case clusters occurring [5]. In a previous study using data during the period 1993-2009 in the USA, the reported cases per year of HPS was an average of 30 [3]. In Argentina, there was a total of 1,243 confirmed cases of HPS between the years 1995-2019 [3].

RISK STRATIFICATION & ISOLATION

Risk stratification of exposure is represented well by the CDC and is outlined as follows. High risk exposures include those on the M/V Hondius cruise ship starting on April 1st 2026 until the time of disembarkment, or those who had close contact with those on the ship or those who were on the ship at the time previously mentioned [6]. Other high risk exposures include washing dishes, touching soiled clothing, sharing a bathroom, sexual contact, sharing a toothbrush, sharing a vape/cigarette, sitting near an exposed individual on an airplane, or within 6 feet of an symptomatic exposed individual for 15 minutes or more [6]. Standard risk includes those who sat on an airplane with a symptomatic individual further than 2 seats away [6].

Isolation procedure for exposures can vary based on exposure risk. Health departments should provide contacts with a way to contact the health department at any time at any sign of symptoms. The incubation and recommended monitoring period is 42-45 days after the last known exposure and during this period high risk exposed individuals should monitor their symptoms and take their temperature at least once per day [6]. They should also isolate away from others during this time, preferably in a place with a private bathroom. If proper isolation cannot be attained, other precautions must be undertaken. Wearing a well-fitting mask, maintaining distance, refraining from sharing items, refraining from kissing/hugging, and deferring all appointments until such time that they are cleared by a health care provider [6]. They may spend time outdoors provided

they are not near other individuals during this time [6]. Those in the standard risk group have no such travel restrictions or recommended activity modification, but should monitor their symptoms closely [6].

CLINICAL DIAGNOSIS & MANAGEMENT

Hantavirus has a wide array of presentations, but no current curative treatment. At present, the standard of care for hantavirus infection is supportive care including conditions such as respiratory failure, heart failure, and cardiogenic shock [4, 7]. Therefore, if there is reasonable concern for a hantavirus infection, pending hemodynamic stability, obtain a robust history, serology, and RT-PCR. A robust history can elicit important information regarding travel history or exposure to close contacts who recently traveled to endemic areas of the ANDV strain. It can also help determine the current severity of illness, as patients can rapidly deteriorate, with most deaths related to HCPS occurring within 24 hours of hospital admission(1,8). Serology tests are available and is the diagnostic method of choice but can have variable sensitivity and specificity due to cross-reactivity [8]. It should be noted that the CDC indicates that laboratory testing may not be widely available and can be sent to the state Public Health Laboratory [6]. Chest imaging may be utilized when there is adequate suspicion for HCPS. However, chest radiographs are usually normal during the prodromal phase of infection and patients can rapidly develop pleural effusions and mixed interstitial and alveolar patterns during the cardiopulmonary phase [1].

In the event of worsening respiratory function, high flow nasal cannula or non-invasive mechanical ventilation may be employed, but close monitoring should not prevent the use of intubation and invasive mechanical ventilation (IMV) [8]. If intubation is required, standard ventilatory protocol for acute respiratory distress syndrome should be followed [8]. If there is concern for hemodynamic instability, transfer to an ECMO-capable ICU immediately for advanced respiratory care and access to Extracorporeal Membrane Oxygenation (ECMO) should occur as soon as possible [4, 7]. Because there is a high mortality risk within the first 24 hours, ECMO is commonly utilized as a short-term hemodynamic support as the patient surpasses this critical phase [8]. There is some evidence that supports ECMO usage without IMV due to a theorized reduction in adrenergic drive secondary to IMV resulting in worsening cardiac failure and cardiogenic shock [4]. The important objective to note is that ECMO availability/capability should be present at the admitting hospital. If unavailable, transfer to the nearest hospital that has ECMO capabilities is recommended. Lauren Dvorscak et al. displayed successful triaging of hantavirus positive patients utilizing rapid blood smear tests [9]. The blood smear had five criteria: hemoconcentration, thrombocytopenia, left shift in the granulocytic lineage to include increased circulating myelocytes, lack of significant toxic changes in the myeloid series, and increased immunoblasts [9]. The findings showed sensitivity of 89% and specificity of 93% with a positive predictive value of 86% and a negative predictive value of 96% [9]. This could be a useful diagnostic tool if the patient's clinical condition is rapidly worsening and is unable to wait for serology results. However, it is important to keep in mind this was a single hospital system study the Arizona, Colorado, Utah, and New Mexico region, which has an average of four new cases of HCPS per year [9]. More studies should be performed to obtain a more accurate representation of its diagnostic capabilities as these predictive values can change depending on the local prevalence of infection. Another study by López et al. Showed that high volume hemofiltration could be used early in the course of severe HCPS [10]. However, out of the five patients that were included in the study, two of them deteriorated and required VA ECMO support [10]. Due to lack of substantial evidence, usage of high-volume hemofiltration prior to VA ECMO should be performed at a hospital with ECMO capabilities [10].

In summary, when met with a patient who has clinical signs of hantavirus infection, it is important to obtain a robust travel and exposure history, serology, and RT-PCR. Chest radiographs can be utilized to help determine when the patient transitions to the cardiopulmonary phase. Blood smear may be considered if the patient needs rapid triage due to decompensation. It is important to monitor their condition, as rapid decompensation can occur within 24 hours of admission. In such event, oxygen supplementation with high flow nasal cannula, non-invasive mechanical ventilation, or intubation following ARDS ventilatory protocol should be employed with transfer to an ECMO-capable ICU. ECMO should be utilized as soon as possible once the patient shows signs of respiratory failure and hemodynamic instability to ensure survival during the critical phase.

Presently, there is no available vaccine for hantavirus in Europe, Latin America, or USA. There are inactivated vaccine available in China and Korea, but they failed to show effectiveness for the local strain in Korea [11]. There are currently promising vaccines in development for hantavirus [11].

There are currently no pharmaceutical interventions that have proven to be more effective than placebo. Ribavirin is one of the more studied antiviral therapies for hantavirus, and the studies did not show differences between the ribavirin group and the control group or any differences in mortality [8]. There are promising therapies in development, but none are available to change the current gold standard of supportive management.

Long-term follow up of these patients who have survived their hantavirus infection has shown evidence of a few persistent clinical symptoms. While not within the scope of this manuscript, long-term complications are one of the most important outcomes in clinical medicine. Some of these include persistent fatigue, exercise intolerance, neurocognitive symptoms, reduced quality of life, and psychological disturbance owing to an extended ICU stay. These patients with long-term problems may present themselves to the Emergency Department or their primary care physician and they require clinical recognition and appropriate management including psychiatric, neurological, and pulmonology referral as well as education on maintenance of physical activity.

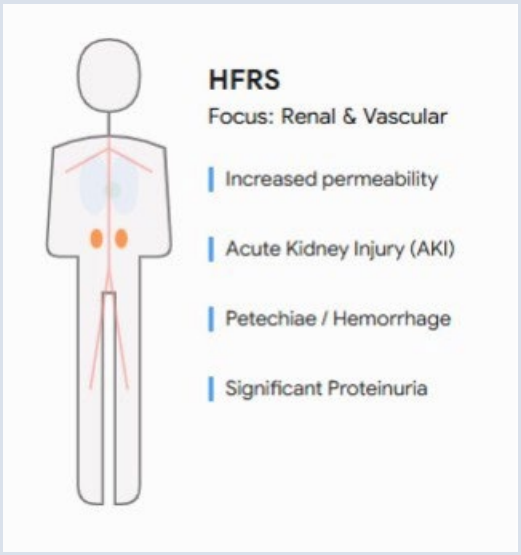

FIGURE 1 - Cartoon rendering providing overview of the clinical symptoms of HFRS.

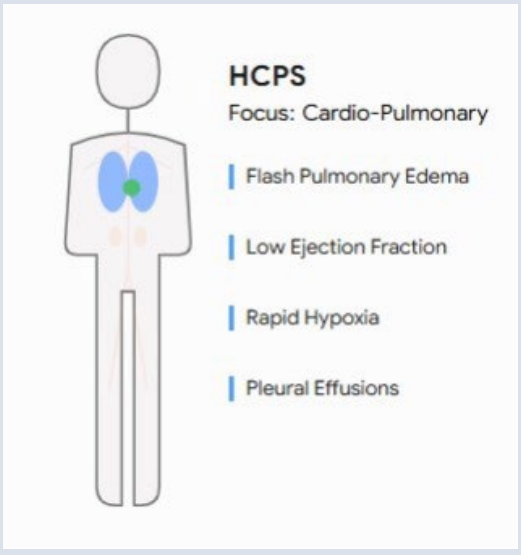

FIGURE 2 - Cartoon rendering providing overview of clinical symptoms of HCPS.

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Author contributions

All authors contributed equally and validated the final version of record.

Declarations

Conflicts Of Interests

The Authors declare that there is no conflict of interest.

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Registration

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Ethical approval for this study was not required.

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