

7. CLINICAL MANIFESTATIONS AND TREATMENT OF HANTAVIRUS PULMONARY SYNDROME (61)

7.1 INCUBATION PERIOD

Few cases have had clearly defined exposures in time and place. The incubation period of other hantavirus diseases is typically one to four weeks, although HFRS from Hantaan virus has apparently had an incubation period up to six weeks. In an effort to determine the incubation period of HPS-causing viruses in the United States, eight cases were identified with well-defined and isolated exposures. These findings suggested an incubation period ranging from 9 to 35 days from the time of probable infection to onset of symptoms (J. Young, personal communication). For seven of the eight cases reviewed, the incubation period was within 9 to 24 days.

7.2 CLINICAL MANIFESTATIONS

Following aerosol exposure and deposition of the virus deep in the lung, infection is initiated. A viremic period ensues, with extensive pulmonary endothelial infection. The onset of symptoms coincides with the onset of the immune response, which may reduce virus shedding, suggesting that the disease process itself is immunopathologic.

The disease is divided into four phases: febrile, cardiopulmonary, diuretic, and convalescent phases (62). The febrile, or prodromal, phase typically lasts 3 to 5 days (range 1–12 days) and is indistinguishable from other viral prodromes (63). This phase is characterized by fever, myalgias, chills, asthenia, dizziness, headache, anorexia, nausea with or without vomiting, abdominal pain, and diarrhea. The abdominal pain may be sufficiently severe to mimic appendicitis or pyelonephritis. While conjunctival suffusion is rarely seen in HPS in North America, facial flushing is commonly seen in HPS cases in the Patagonian region of South America. Indications of upper respiratory tract disease, including sore throat, rhinorrhea, sinusitis, and ear pain, are usually absent. Physical examination may or may not reveal rales or find-

ings of pleural effusion. Cough, tachypnea, and exertional dyspnea are not reported at the onset of the prodrome, but appear later and herald the onset of pulmonary edema, the second phase.

The onset of hypotension and pulmonary edema may progress rapidly over the course of 4 to 24 hours. A respiratory rate of 24/min is a sensitive but not specific indicator of early pulmonary edema in HPS. Early pulmonary edema is imaged on the chest X-ray as Kerley B lines, peribronchial cuffing, and alveolar-interstitial fluid in the basal segments (64). At this point, hypoxemia becomes apparent, with an oxygen saturation of hemoglobin less than 95% at sea level and less than 90% at 2,000 m or more above sea level. Pulmonary edema is noncardiogenic in origin, as indicated by normal pulmonary capillary wedge pressures obtained through a Swan-Ganz catheter and normal heart size on the X-ray (65, 66). Markedly increased pulmonary capillary permeability results in high-protein pulmonary edema; severely ill patients may require up to 1 L/h of serum-resembling fluid to be removed from their airways by suction. Shock may be manifest as hypotension and is often accompanied by oliguria and delirium. Hypovolemia resulting from a shift in fluid from circulating blood to the lung interstitium and air spaces contributes to the fall in blood pressure. However, most patients also experience a serious depression of the myocardium (65). Seriously ill patients may have cardiac indices less than 2.2 L/min/m².

Spontaneous diuresis indicates the onset of the diuretic phase. This third phase of the disease is characterized by a rapid clearance of the pulmonary edema fluid, resolution of fever, and shock. Convalescence extends over the next two weeks to two months. Patients appear to recover fully, but formal studies of pulmonary function and other clinical parameters are needed.

In South America, some other clinical aspects have been described, including hemorrhagic complications (i.e., petechias, not observed in North America) and renal manifestations (46). As well, HPS has appeared in children, an uncommon finding in North America (40).

7.3 CLINICAL LABORATORY FINDINGS

Hematologic findings can be striking in HPS cases (62, 67). In SNV infection, the white blood cell count can be normal or elevated on admission (median 10,400 mm³; range 3,100–65,300 mm³) and usually increases, often to very high values (median of maximum values 26,000 mm³ with range 5,600–65,300 mm³). Similar values have been found with other viruses. There is an absolute neutrophilia and a relative lymphopenia. In addition to immature “band” forms, the blood almost always contains the more undifferentiated forms in the myeloid series, the myelocytes, and promyelocytes. Among the circulating lymphocytes are prominent mononuclear cells with deep blue cytoplasm by Giemsa stain and that measure greater than 18 μ in diameter. These immunoblasts are seen in few infections other than HPS and HFRS, and appear in the circulation coincident with the onset of pulmonary edema. Thrombocytopenia with a platelet count less than 150,000/mm³ is seen in almost every case and, in rare cases, may fall to 20,000/mm³. Thrombocytopenia is the first abnormality to appear in the peripheral blood, often two or three days before the onset of pulmonary edema, and may be used to screen undifferentiated fevers for HPS when the appropriate epidemiologic clues are elicited by history.

Elevated creatinine and blood urea nitrogen reflect the degree of shock and hypovolemia. Proteinuria may be seen and microscopic hematuria is found in most cases. Patients infected by Bayou, Black Creek Canal, and Andes viruses may have more prominent renal failure, even requiring hemodialysis (17, 45, 68, and Lázaro, personal communication). Elevated hepatic enzymes are seen in all cases, but rarely attain a level greater than five times the upper normal limit, and hyperbilirubinemia is not seen. The multiorgan failure common in sepsis or posttraumatic adult respiratory distress syndrome (ARDS) rarely occurs in HPS. Specific pathology of these organ systems has not yet been described with any of the HPS viruses, but experience and surveillance definitions are limited.

In contrast to HFRS, the coagulopathy of HPS is usually subclinical. Almost all patients have evidence of coagulopathy but with elevated partial thromboplastin times. Circulating D-dimers are not common, and fibrinogen levels falling below 200 mg/dl are rare.

7.4 EARLY CASE RECOGNITION

Clinicians should consider HPS in patients with fever and myalgias, particularly of the larger muscle groups, including shoulders, thighs, and lower back. The addition of such gastrointestinal complaints as nausea, vom-

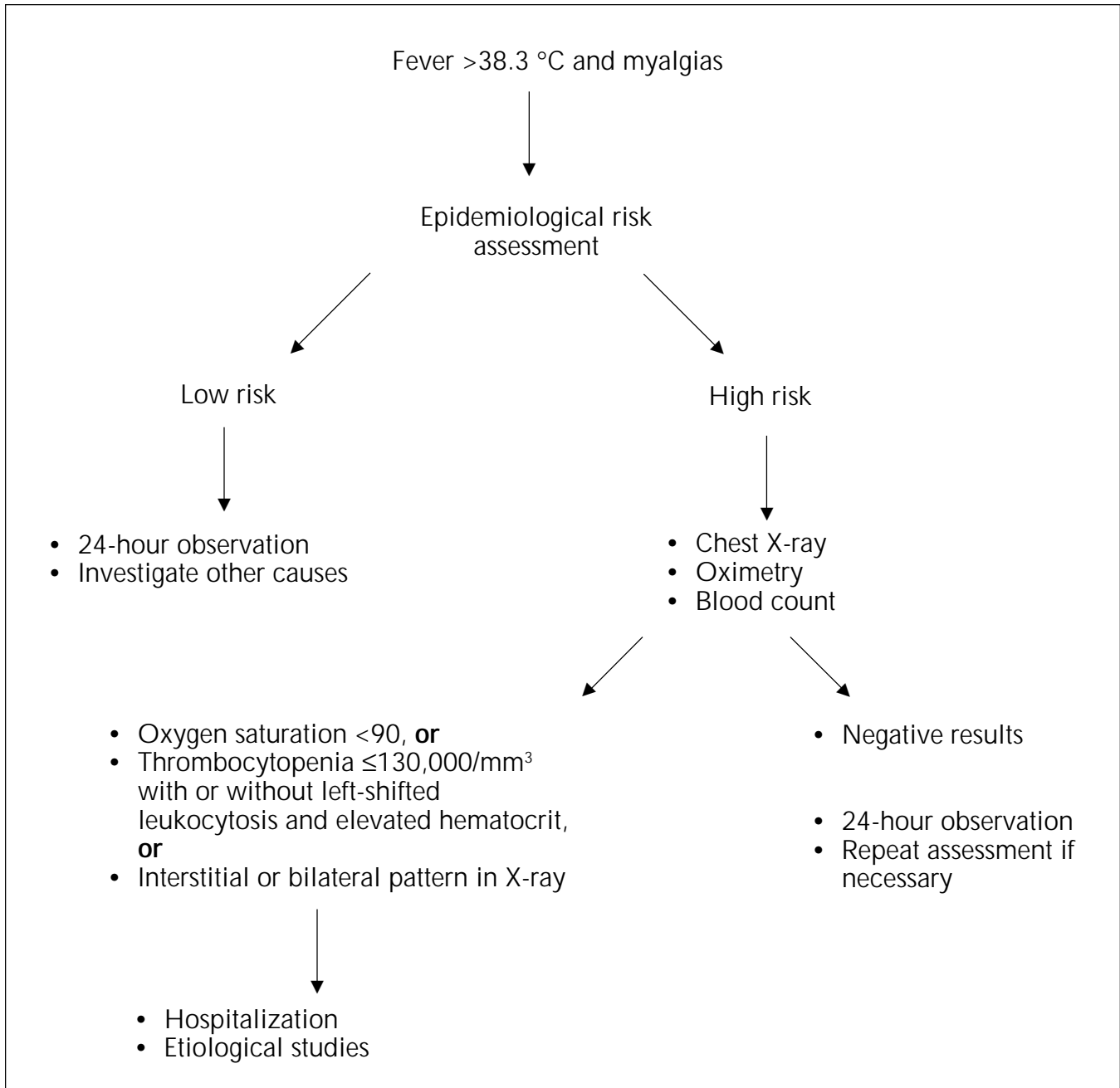
iting, and abdominal pain should raise the index of suspicion and prompt the clinician to inquire about potential rodent exposures. Tachypnea is an important sign, and hypotension may be present. The absence of certain signs and symptoms can help to distinguish HPS from other acute viral syndromes: rash, conjunctivitis, sinusitis, otitis, rhinorrhea, exudative pharyngitis, and arthritis are notably rare in HPS (63). Initial laboratory workup in suspected cases should include pulse oximetry, chest radiograph, and a complete blood count. The likelihood of HPS is high in those with a compatible clinical history plus an oxygen saturation measurement of less than 90%, interstitial infiltrates or other indications of pulmonary edema on chest X-ray, and thrombocytopenia, particularly if the last is accompanied by left-shifted leukocytosis and an elevated hematocrit.

At the onset of pulmonary edema, almost every case displays thrombocytopenia, left-shifted myeloid series, and immunoblasts. This hematologic diagnostic triad is sufficiently sensitive and specific to use to initiate transfer to intensive care and treatment (see Section 7.6). Prior to the onset of the signs and symptoms of either shock or pulmonary edema, the diagnostic triad is not present on the peripheral blood smear. Therefore, to raise the suspicion of impending HPS, the clinician must use the combination of three factors: epidemiologic clues to potential exposure, the reported findings of fever and myalgias, and thrombocytopenia. Although fully developed HPS is a characteristic disease, no combination of symptoms is sufficiently sensitive or specific to distinguish its early stages from a host of other pulmonary infections (63); this requires the clinician to retain a level of suspicion until HPS is ruled out. When sufficient evidence for HPS has accumulated, the patient should be transported immediately to a unit skilled in intensive cardiopulmonary care, as rapid transport can be lifesaving. However, the decision to move the patient must be weighed against the rapid onset of hypoxemia and the local capabilities for medical evaluation. In all areas with previously known or suspected cases of HPS, active clinical investigation to definitively diagnose HPS should be performed in all persons with unexplained febrile syndrome and epidemiologic risk factors (see Figure 2).

7.5 DIFFERENTIAL DIAGNOSIS

The differential diagnosis is extensive prior to the serologic identification of hantavirus infection. Most commonly encountered are bilateral pneumonia with sepsis, adult respiratory distress syndrome complicating systemic infections, trauma and other life-threatening conditions, and sepsis syndrome complicated by either disseminated

FIGURE 2. Hantavirus pulmonary syndrome algorithm.



intravascular coagulation (DIC) or alcohol toxicity. A variety of enzootic infections encountered in rural areas of North America may be confused initially with HPS, particularly when thrombocytopenia is present. These include plague, tularemia, Rocky Mountain spotted fever or murine typhus, granulocytic or monocytic ehrlichiosis, leptospirosis, relapsing fever due to *Borrelia hermsii*, and acute parvovirus infection. In Latin America, other diagnostic possibilities would include dengue fever, dengue hemorrhagic fever, and arenavirus infections

(Junin, Machupo, Sabia, and Guanarito viruses). When abdominal or back pain is severe, possible diagnoses of pyelonephritis, appendicitis, abdominal abscess, or gynecological infection should be considered.

7.6 LABORATORY DIAGNOSIS

The most practical approach for the laboratory diagnosis of hantavirus infection in humans is the detection

of IgM antibodies in acute serum samples using an ELISA IgM capture assay. Virtually all confirmed HPS patients have demonstrable IgM in the first or second serum sample taken after hospitalization. And while ELISA tests to detect IgG antibodies may also be used to confirm diagnosis, two serum samples taken two to three weeks apart are required to demonstrate rising titers of IgG antibodies. Results of testing can be obtained within a few hours after the specimen is received in the laboratory. Less commonly used serological tests, such as immunofluorescent assay and particle agglutination, can also be applied to hantaviral diagnosis (69).

Initial detection of HPS-related hantaviruses was accomplished using heterologous hantaviral antigen (70). A more sensitive Sin Nombre recombinant nucleocapsid antigen was developed in response to the outbreak in 1993 in the United States; it is now widely used throughout the Americas in ELISA tests for the detection of New World hantavirus infections. More recently, other recombinant antigens have been developed, such as Andes virus nucleocapsid. Due to the cross-reactive nature of these antigens, they cannot discriminate among closely related hantavirus species.

In fatal cases, fresh frozen tissue, fixed tissue, and blood can be used to confirm the diagnosis by RT-PCR, immunohistochemistry, or ELISA methods, respectively. Collection of blood clots from initial samples of all suspect cases is also recommended for subsequent RT-PCR on selected seropositive individuals. RT-PCR is a molecular diagnostic technique targeting specific regions of the virus genome and is available only at selected research laboratories. RT-PCR is not recommended for routine diagnosis, but is valuable in defining the virus genotype, searching for new viruses, and performing certain epidemiological studies. Immunohistochemistry is particularly well suited to retrospective diagnosis. Viral inclusions have rarely been observed in pulmonary capillary endothelial cells by electron microscopy.

Some Old World hantaviruses have occasionally been isolated from patient serum or whole blood drawn within three to nine days of onset of illness. However, propagation of hantaviruses is difficult and this is not a recommended diagnostic procedure (71).

7.7 PATHOGENESIS

The pathogenesis of HPS is related to a profound abnormality in vascular permeability. The capillary leak syndrome is virtually confined to the lungs, and chest radiograph series typically chronicle the rapid onset of diffuse, bilateral interstitial, and later alveolar, pulmonary edema (64). There is also evidence for myocardial failure as an important component of the shock syndrome observed (65).

At postmortem the lungs are massively edematous, but microscopic studies find little necrosis. There are scant to moderate hyaline membranes, intact pneumocytes, and scarce neutrophils (67). However, there is interstitial infiltration by T lymphocytes and activated macrophages (72). These findings differ from those of typical adult respiratory distress syndrome and many pneumonias. Hantaviral antigens are detected primarily in endothelial cells, and those in the lung are heavily involved. Lesser amounts of antigen are found in scattered endothelial cells throughout the body, as well as occasional involvement of macrophages, myocytes, and many other cell types.

In contrast to such diseases as South American hemorrhagic fevers, circulating antibodies appear early in the clinical course of HPS and often correspond to clinical decline rather than improvement (73, 74). Thus, the impaired vascular permeability is thought to be immunologically mediated, probably strongly influenced by the infiltrating T cells in the lungs.

7.8 TREATMENT

There is no known effective antiviral therapy for HPS, although the drug ribavirin has shown a treatment effect in reducing HFRS mortality (75). Open-label ribavirin treatment had no obvious effect in a limited number of HPS patients, and a placebo-controlled clinical trial is currently under way in the United States. In the absence of a proven pharmacological treatment and in light of the rapid progression of HPS, effective clinical management depends heavily on careful fluid management, hemodynamic monitoring, and ventilatory support. Therapeutic responses to shock in patients with HPS must be guided by an understanding of the underlying pathophysiology of this disorder, that is, profound pulmonary capillary leak in the presence of primary myocardial pump dysfunction.

Experimental therapies have been used to treat severely ill patients with HPS. These include extracorporeal membrane oxygenation (ECMO) and nitrous oxide inhalation. Experience is very limited in the use of these experimental measures to treat HPS patients, and they have generally been used only as a last resort form of therapy. There are no clinical data on the effectiveness of administering immune plasma to treat HPS patients. While this therapy has been effective for Argentine hemorrhagic fever (AHF), the differences in immune response and pathophysiology between AHF and HPS suggest it is unlikely to be effective in HPS.

Antiviral therapy with a drug such as ribavirin may be more effective if given to patients identified very early in the prodromal stage. Such patients might be close contacts of a confirmed HPS case (about 10% of hantavirus cases occur in clusters, regardless of the issue of possible

interhuman transmission of Andes virus) or persons with very high risk exposure. Protocols should be developed to permit controlled studies of early, expectant antiviral treatment initiated prior to laboratory testing. Argentina has such a protocol that may be requested as a template.¹ For every new procedure or therapeutic measure it is strongly recommended that controlled studies be performed.

7.8.1 Initial Treatment of Hantavirus Pulmonary Syndrome in the Emergency Room and During Transport

Initial treatment during the observation period should be directed to symptomatic and supportive measures, such as the control of fever and pain with paracetamol (avoiding the use of aspirin), antiemetics, and bed rest. The observation period could be managed at a primary care center. However, if there is a high suspicion of HPS according to the proposed HPS algorithm (Figure 2), patients should be immediately transferred to an emergency room (ER).

Treatment in the ER should focus on maintenance of blood pressure and oxygenation while transfer to an intensive care unit (ICU) is organized. When patients present with shock to the ER, the case fatality rate exceeds 80%. In contrast, the case fatality rate is 10% in the absence of shock at this time, indicating the importance of cardiogenic shock as a cause of death. While some patients may have fluid requirements of 1 to 2 L due to vomiting and diarrhea, it must be kept in mind that excessive fluid resuscitation will exacerbate the pulmonary edema without commensurate improvement in cardiac output. Early use of inotropic agents (see Section 7.8.2) may be necessary, depending on the ability to monitor response to therapy. Due to the rapid onset of pulmonary edema, hypoxemia may deteriorate rapidly over several hours, and continuous monitoring of oxygenation by pulse oximetry is preferred.

7.8.2 Treatment in the Intensive Care Unit

Close monitoring of oxygenation is extremely important so that timely intubation and mechanical ventilation can be provided when required (when PAO_2/FIO_2 falls below 150). Oxygen delivery is usually maintained until the cardiac index falls below 2.2 L/min/m². Mechanical ventilation is required for about two-thirds of patients and typically lasts for five to seven days. Be-

cause patients with this viral infection can deteriorate so rapidly, a Swan-Ganz catheter should be inserted as soon as is clinically warranted. Intravenous crystalloid fluid is used to maintain as low a wedge pressure (8–12 mmHg) as is compatible with satisfactory cardiac indices (cardiac index >2.2 L/min/m²). Inotropic agents, such as dobutamine, dopamine, and norepinephrine, are begun earlier in the resuscitation of these patients than in the usual patient, rather than continued fluid boluses. The use of loop diuretics such as furosemide is discouraged, since salt and water will be removed from circulating blood before being removed from the alveolar and interstitial compartments in the lung, thus exacerbating hypotension. Red blood cells are usually not required to maintain oxygen delivery unless hemoglobin concentration falls below 8.5–10 g/dl. Thrombocytopenia has not required support with platelet transfusion. So far there is no evidence that pharmacological doses of corticosteroid offer any benefit in the treatment of HPS. Cardiac arrhythmias, particularly any episodes of electromechanical dissociation, portend a poor outcome and should be aggressively treated. Renal failure and need for hemodialysis is rare among Sin Nombre virus infections but was reported for two HPS cases due to Andes virus in southern Argentina and Chile. Extracorporeal membrane oxygenation (an experimental procedure) should be considered when available if the serum lactate level exceeds 4 mmol/l and cardiac index <2.2 L/min/m².

Due to the extensive differential diagnosis, all patients should be treated for more common events, such as sepsis. A broad-spectrum antibiotic such as intravenous ceftriaxone or ampicillin-sulbactam, as well as doxycycline used to treat rickettsioses, ehrlichioses, plague, and tularemia, should be administered until either HPS is confirmed or another diagnosis is made.

7.8.3 Case Management in a Rural Setting

In rural settings without access to intensive care facilities, treatment of cases should focus on maintenance of blood pressure and oxygenation. In addition, broad-spectrum antibiotics such as suggested in Section 7.8.2 should be administered until either HPS is confirmed or another diagnosis is made. Intravenous crystalloid fluid should be used carefully so as not to exacerbate pulmonary edema. It is recommended that fluid balance be maintained, with replacement fluid administered according to the amount lost. In case of shock, it would be necessary to use such inotropic agents as dobutamine or dopamine, even in the absence of cardiac monitoring. Oxygen delivery should also be initiated early on, and a nonbreathing mask could be used to ensure 100% oxygen concentration.

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