CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 15-2025: A 52-Year-Old Man with Fever, Nausea, and Respiratory Failure

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PRESENTATION OF CASE

Dr. Ignacio Lopez Saubidet: A 52-year-old man presented to the emergency department of Centro de Educación Médica e Investigaciones Clínicas (CEMIC) in Buenos Aires in early autumn with fever that had persisted for 1 week.

The patient had been in his usual state of good health until 7 days before the current presentation, when fever developed. He presented to the emergency department of CEMIC for evaluation. The temperature was 38.0°C, and testing of a nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was negative. Supportive care was recommended.

During the next 7 days, fever persisted and additional symptoms developed, including nausea, abdominal pain, and watery diarrhea. The patient had poor oral intake and became concerned about his ability to maintain adequate hydration. He returned to the emergency department for further evaluation. The temporal temperature was 36.3°C, the blood pressure 100/75 mm Hg, the pulse 91 beats per minute, the respiratory rate 22 breaths per minute, and the oxygen saturation 89% while he was breathing ambient air. The oxygen saturation increased to 93% after the administration of supplemental oxygen through a simple face mask at a rate of 2 liters per minute. The patient appeared to be confused but had no focal neurologic deficits.

Dr. Tomás Amerio: Portable chest radiography, performed in the emergency department, revealed diffuse ground-glass opacities in both lungs, predominantly in the lower lobes, with associated reticular opacities (Fig. 1). These findings were suggestive of volume overload or vascular redistribution; an underlying infection such as atypical pneumonia could not be ruled out.

Dr. Saubidet: The patient had worsening hypoxemia while he was receiving supplemental oxygen through a simple face mask. Supplemental oxygen was subsequently administered through a nonrebreather face mask at a rate of 15 liters per minute, but the oxygen saturation remained at 89%. He was admitted to the intensive care unit (ICU) of the hospital.

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CME

The patient's medical history was notable for cholelithiasis, for which cholecystectomy had been performed 2 years earlier. He was fully vaccinated against SARS-CoV-2 but not against influenza virus. He took no medications and had no known adverse drug reactions. The patient lived in Buenos Aires with his wife and son, had no pets, and worked in an office setting without occupational exposures. He reported no recreational drug use or high-risk sexual behaviors. His family history was notable for hypertension and diabetes. Approximately 1 month before the current presentation, he had undergone a dental root-canal procedure. The patient had recently visited a rural area in the region of Chascomús, located in the Buenos Aires Province of Argentina. While in Chascomús, he had camped outdoors in a tent. He reported no known insect bites, contact with rodents, or other exposures.

On admission to the ICU, the patient had persistent hypoxemia, with an oxygen saturation of 88%, and supplemental oxygen was administered through a high-flow nasal cannula. On examination, dry mucous membranes were noted. The oropharynx appeared to be congested, and there was evidence of poor dental hygiene, with decayed teeth. Crackles were heard at the base of both lungs. There was no murmur, jugular venous distention, or peripheral signs of embolic disease. The abdomen was soft, bowel sounds were present, and there was mild epigastric tenderness on palpation. No edema of the arms or legs was noted.

Laboratory studies revealed an elevated hematocrit (56.9%; reference range, 41 to 53), leukocytosis (16,500 white cells per microliter; reference range, 4500 to 11,000) with a predominance of neutrophils, and thrombocytopenia (54,000 platelets per microliter; reference range, 150,000 to 400,000). In addition, the blood urea nitrogen level was elevated (49 mg per deciliter [17.5 mmol per liter]; reference range, 8 to 25 mg per deciliter [2.9 to 8.9 mmol per liter]), with a normal creatinine level (1.23 mg per deciliter [109 μmol per liter]; reference range, 0.60 to 1.50 mg per deciliter [53 to 133 μmol per liter]); no previously obtained values were available. Additional laboratory test results are shown in Table 1.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission
Hemoglobin (g/dl)	13.5–17.5	19.7
Hematocrit (%)	41.0–53.0	56.9
White-cell count (per μl)	4500–11,000	16,500
Platelet count (per μl)	150,000–400,000	54,000
Sodium (mmol/liter)	135–145	133
Potassium (mmol/liter)	3.4–5.0	4.7
Chloride (mmol/liter)	98–108	95
Carbon dioxide (mmol/liter)	23–32	22
Urea nitrogen (mg/dl)	8–25	49
Creatinine (mg/dl)	0.60–1.50	1.23
Aspartate aminotransferase (U/liter)	10–40	56
Alanine aminotransferase (U/liter)	10–55	31
Alkaline phosphatase (U/liter)	15–115	49
Total bilirubin (mg/dl)	<1.2	0.4
Arterial blood gas measurements		
Partial pressure of arterial oxygen — mm Hg	80–100	42
Partial pressure of arterial carbon dioxide — mm Hg	35–45	70
Arterial pH	7.35–7.45	7.14

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used are for adults at Centro de Educación Médica e Investigaciones Clínicas and may not be appropriate for all patients.

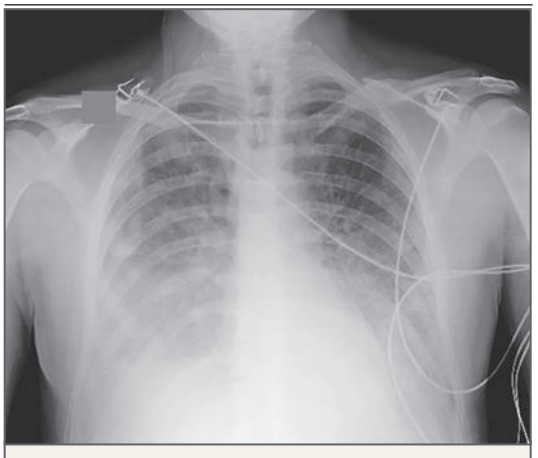

Figure 1. Chest Radiograph.

Portable chest radiography was performed in the emergency department. An anteroposterior radiograph shows diffuse ground-glass opacities in both lungs, predominantly in the lower lobes, with associated reticular opacities.

Blood and sputum were obtained for culture. Testing for common respiratory pathogens, including SARS-CoV-2 and influenza virus types A and B, was negative, as was urinary antigen testing for *Streptococcus pneumoniae*. Serologic testing for human immunodeficiency virus (HIV), dengue virus, and leptospira was also performed.

Dr. Amerio: Computed tomography of the chest, performed without the administration of intravenous contrast material, showed interlobular septal thickening in both lungs, predominantly in the lower lobes, along with peribronchovascular thickening (Fig. 2A). Patchy ground-glass opacities and some areas of consolidation were present in both lungs, along with mosaic attenuation and increased vascular diameters, predominantly in the lower lobes (Fig. 2B). In the right upper lobe, nodular opacities with adjacent ground-glass changes were observed, a finding consistent with the halo sign (Fig. 2C), which was suggestive of an invasive fungal infection.[1] In the right middle lobe and left lower lobe, parenchymal bands were identified, a finding consistent with atelectasis. Additional findings included ground-glass opacities in the posterior aspects of the lower lobes, which were most likely indicative of dependent atelectasis, and thickening of the fissures. Overall, the findings were consistent with pulmonary edema; the possibility of a superimposed infection could not be ruled out.

Dr. Saubidet: Empirical antimicrobial therapy with ceftriaxone, vancomycin, clarithromycin, and oseltamivir was initiated. The patient continued to receive supplemental oxygen through a high-flow nasal cannula at a rate of 50 liters per minute, with a fraction of inspired oxygen of 100%. However, the partial pressure of arterial oxygen was 42 mm Hg (reference range, 80 to 100), with a partial pressure of arterial carbon dioxide of 70 mm Hg (reference range, 35 to 45) and an arterial pH of 7.14 (reference range, 7.35 to 7.45). The trachea was intubated, and mechanical ventilation was initiated.

Owing to persistent abdominal pain and severe hypoxemia, point-of-care ultrasonography of the heart, chest, and abdomen was performed. No visceromegaly was noted in the abdomen. Pleuropulmonary findings included a severe diffuse alveolar–interstitial syndrome with bibasilar consolidations and mild bilateral pleural effusions. Focused cardiac ultrasonography showed normal biventricular function.

A diagnostic test was performed.

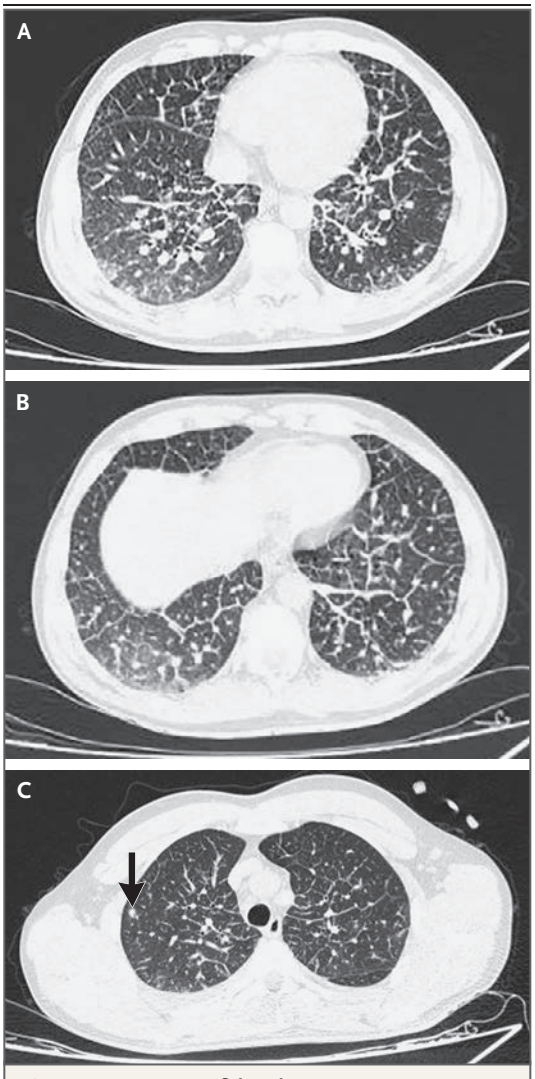

Figure 2. CT Images of the Chest.

CT of the chest without the administration of intravenous contrast material was performed on admission to the intensive care unit. Interlobular septal thickening is present in both lungs, predominantly in the lower lobes, along with peribronchovascular thickening (Panel A). Patchy ground-glass opacities and areas of consolidation are present in both lungs, along with mosaic attenuation and increased vascular diameters in the lower lobes (Panel B). A pulmonary nodule surrounded by a rim of ground-glass opacity is present, a finding consistent with the halo sign (Panel C, arrow).

DIFFERENTIAL DIAGNOSIS

Dr. Martín Hunter: I participated in the care of this patient and am aware of the final diagnosis. This previously healthy and presumably immunocompetent 52-year-old man presented to CEMIC in Buenos Aires with fever that had persisted for 1 week. His illness evolved into hypoxemic respiratory failure, with multifocal pulmonary opacities seen on chest radiography and marked hemoconcentration noted on initial laboratory testing. His clinical presentation posed several diagnostic challenges, which will serve as the basis for my discussion and differential diagnosis.

COMMUNITY-ACQUIRED PNEUMONIA

The patient's syndrome could be compatible with community-acquired pneumonia. In an immunocompetent adult presenting with a severe case of community-acquired pneumonia, the most likely causes include bacterial pathogens (e.g., *S. pneumoniae*, *Haemophilus influenzae*, *Legionella pneumoniae*, and *Mycoplasma pneumoniae*), as well as respiratory viruses (e.g., influenza virus, SARS-CoV-2, and respiratory syncytial virus). This patient had two negative tests for SARS-CoV-2. His urinary antigen test for *S. pneumoniae* was negative, which made pneumococcal pneumonia unlikely, and the absence of productive cough and of focal lobar consolidation on imaging further reduced the likelihood of typical bacterial pneumonia.

MYELOPROLIFERATIVE DISORDER

The patient had an elevated hematocrit, leukocytosis, and epigastric abdominal tenderness that might have suggested splenomegaly. These findings initially pointed toward an underlying myeloproliferative disorder, such as polycythemia vera. In this context, an invasive fungal infection, such as pulmonary aspergillosis, could have been responsible for the pulmonary findings. Further supporting this possibility was the presence of the halo sign, a feature that is often associated with invasive fungal infections. However, the presence of thrombocytopenia and the absence of visceromegaly on bedside abdominal ultrasonography ultimately made the diagnosis of a myeloproliferative disorder unlikely, which reduced the likelihood of opportunistic infections that would typically be seen in immunocompromised hosts.

PULMONARY–RENAL SYNDROME

Possible noninfectious causes of this patient's presentation included pulmonary–renal syndrome, which may manifest with diffuse alveolar hemorrhage and lead to hypoxemic respiratory failure.[2] Diffuse alveolar hemorrhage can result from coagulopathy, the use of anticoagulant therapy, or pulmonary capillaritis, which can occur in the context of an autoimmune disorder such as anti–glomerular basement membrane disease (Goodpasture's syndrome) or antineutrophil cytoplasmic antibody–associated vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, or microscopic polyangiitis). Systemic lupus erythematosus can also manifest with concurrent pulmonary hemorrhage and acute kidney injury. In this patient, the absence of hematuria, red-cell casts, and other overt signs of systemic autoimmune disease made these diagnoses unlikely.

HANTAVIRUS CARDIOPULMONARY SYNDROME

The patient had hemoconcentration and bilateral pulmonary opacities, features suggestive of capillary leak syndrome, which is characterized by marked endothelial permeability with subsequent hemoconcentration and hemodynamic instability. Capillary leak syndrome can be caused by severe sepsis, toxic shock, envenomation, anaphylaxis, and viral infections.[3] Given the patient's acute disease course, infectious diseases were prioritized in the initial evaluation.

The profound acute hypoxemic respiratory failure due to noncardiogenic pulmonary edema, as well as the hemoconcentration, were suggestive of hantavirus cardiopulmonary syndrome. The patient had recently traveled to the Chascomús region of Argentina, where hantavirus is hyperendemic. Infection with hantavirus serovariants that are found in this region has been associated with the development of hantavirus cardiopulmonary syndrome, which is characterized by a febrile illness followed by capillary leak syndrome that leads to respiratory failure and hemoconcentration.

Given the rapid progression of pulmonary edema, the absence of left ventricular dysfunction on echocardiography, and the severe hemodynamic instability, a multidisciplinary discussion was held with the ICU team. On the basis of the patient's clinical presentation and the absence of an alternative unifying diagnosis, a joint decision was made to pursue serologic and molecular testing for hantavirus.

DR. MARTÍN HUNTER'S DIAGNOSIS

Hantavirus cardiopulmonary syndrome.

HOSPITAL COURSE AND CRITICAL CARE MANAGEMENT

Dr. Hunter: The patient's condition deteriorated rapidly. Worsening hypoxemia led to endotracheal intubation and mechanical ventilation within the first hospital day. Refractory shock developed, and high-dose combination vasopressor therapy with norepinephrine and vasopressin was administered.

Shortly after the patient's arrival in the ICU, anuric acute kidney injury also developed. Management in the ICU included the placement of a central venous catheter, a radial arterial catheter, and a dialysis catheter for the initiation of continuous renal-replacement therapy.

The patient had features that satisfied the Berlin criteria for acute respiratory distress syndrome: the presence of bilateral pulmonary opacities, an acute disease course, the presence of severe hypoxemia with a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of less than 100, and the absence of left ventricular dysfunction. Mechanical ventilation was administered according to a lung-protective strategy, with the use of low tidal volumes (<6 ml per kilogram of predicted body weight) and high positive end-expiratory pressure (14 cm of water). Continuous sedation with midazolam and fentanyl was implemented to optimize gas exchange, as was neuromuscular blockade with rocuronium.

Given the refractory shock and the diagnostic uncertainty, a pulmonary-artery catheter was placed to guide tailored therapy. The initial hemodynamic measurements were as follows: a right atrial pressure of 7 mm Hg; systolic, diastolic, and mean pulmonary-artery pressures of 30, 20, and 23 mm Hg, respectively; a pulmonary-artery wedge pressure of 11 mm Hg with a cardiac output of 4.7 liters per minute; and a cardiac index of 2.6 liters per minute per square meter of body-surface area, measured by means of thermodilution. The systemic vascular resistance calculation of 1405 $dyn \cdot sec \cdot cm^{-5}$ supported the diagnosis of hypovolemic shock. The patient received aggressive fluid resuscitation with lactated Ringer's solution, and the hemodynamic measurements improved.

Because the patient had severe acute respiratory distress syndrome and refractory hypoxemia, the possibility of treatment with extracorporeal membrane oxygenation was discussed. However, his oxygenation improved in the subsequent days with the use of mechanical ventilation and sedation, and extracorporeal membrane oxygenation was not needed.

DIAGNOSTIC TESTING

Dr. Maria V. Leone: In the first few hospital days, several test results were reported. Cultures of blood and sputum showed no growth. Serologic tests for HIV, dengue virus, and leptospira were also negative. However, serologic and molecular tests for hantavirus were positive.

Initial testing was positive for hantavirus-specific IgM but was negative for hantavirus-specific IgG. Hantavirus-specific nucleic acid amplification testing (NAAT) was positive. On follow-up testing, performed on samples obtained 6 days after the initial set, IgG was detected. These findings confirmed the diagnosis of hantavirus infection manifesting as hantavirus cardiopulmonary syndrome.

The use of an enzyme-linked immunosorbent assay (ELISA) for the detection of hantavirus-specific IgM or IgG seroconversion remains the cornerstone of the diagnosis of hantavirus infection (Fig. 3). In Argentina, ELISA is commonly used and has a sensitivity of 96.6% and a specificity of 90.6%.[4] The sensitivity approaches 100% during the cardiopulmonary phase or the late prodromal phase, but it may be lower during the early prodromal phase, when the absence of antibodies does not rule out the disease.[4] The

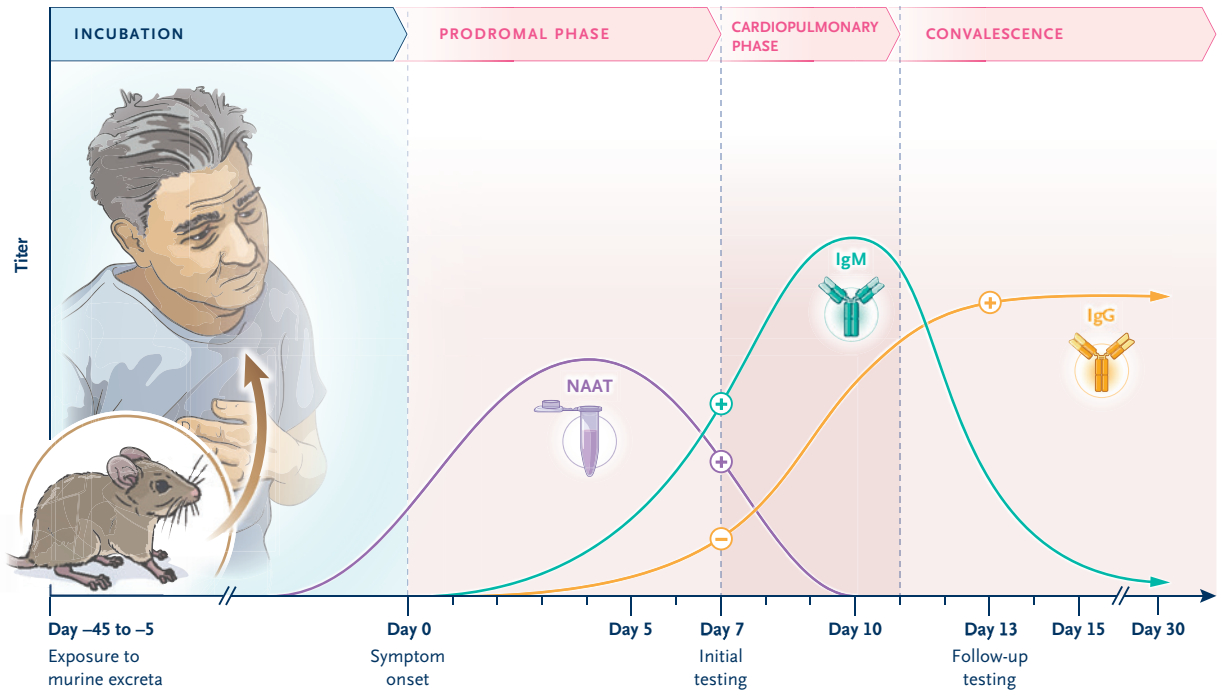

Figure 3. Diagnostic Testing for Hantavirus Infection.

The kinetics of diagnostic testing for human hantavirus infection are shown relative to symptom onset. IgM levels become detectable 1 to 3 days after symptom onset, peak at approximately day 10, and decline by approximately day 30. IgG levels start to rise 3 to 5 days after symptom onset, and elevation continues for a prolonged period. Viral RNA can be detected on nucleic acid amplification testing (NAAT) before and up to approximately 10 days after symptom onset. Results of serologic and molecular testing performed in this case are also shown. The patient initially had detectable IgM and positive NAAT, and IgG was later detected. These findings confirmed the diagnosis of hantavirus infection manifesting as hantavirus cardiopulmonary syndrome. Hantavirus cardiopulmonary syndrome progresses through four phases, which can vary in length; typical durations are shown.

presence of IgM is indicative of recent infection. IgM levels can be detected 1 to 3 days after symptom onset and remain detectable for up to 30 days, although persistence for several months has been reported. IgG levels can be detected later and persist for prolonged periods. The absence of IgG during the cardiopulmonary phase may indicate a poor prognosis.[5]

NAAT enables the detection of the viral genome in serum, clotted blood, or tissue samples. Amplification products can be sequenced for phylogenetic analysis in order to identify specific viral genotypes. This method can detect the virus earlier than serologic testing, particularly during the prodromal phase of disease; it is useful up to 10 days after symptom onset.[5]

INFECTIOUS DISEASE MANAGEMENT

Dr. Leone: Hantavirus infection is a consideration in patients presenting with fever of unknown cause, especially those with clinically significant epidemiologic risk factors, such as exposure to wild rodents or environments contaminated by their excreta within 6 weeks before symptom onset. In areas where the disease is endemic, including rural parts of the Buenos Aires Province of Argentina such as the Chascomús region, hantavirus infection should be suspected in any patient presenting with a nonspecific febrile syndrome, particularly when interstitial opacities are seen on chest imaging and when laboratory findings include thrombocytopenia, hemoconcentra-

tion, leukocytosis with neutrophilia, and lymphocytosis.

BIOLOGIC AND EPIDEMIOLOGIC FEATURES OF HANTAVIRUS INFECTION

Hantaviruses are RNA viruses of the bunyaviridae family that are distributed worldwide, with more than 20 genotypes identified in the Americas. These viruses are hosted by rodents of the muridae family, which harbor chronic asymptomatic infections and excrete the virus through urine, saliva, and feces, contaminating their environment.

In Argentina, 8 hantavirus genotypes have been linked to hantavirus cardiopulmonary syndrome, including Andes virus, Lechiguanas virus, Laguna Negra virus, and Orán virus. Andes virus is unique in its potential for human-to-human transmission, which has been observed predominantly in the Patagonia region, where outbreaks associated with mortality as high as 40% have occurred.[6] Argentina has the highest reported annual case numbers in South America, and there are distinct epidemiologic patterns across regions. The northwestern regions have the highest incidence and the lowest mortality, whereas the central and southern regions have a lower incidence and a higher mortality.

CLINICAL FEATURES AND DISEASE COURSE

Hantavirus infections may manifest as one of two specific syndromes: hemorrhagic fever with renal syndrome, which results from infection with genotypes that are prevalent predominantly in Europe and Asia (sometimes referred to as Old World hantaviruses), and hantavirus cardiopulmonary syndrome, which results from infection with genotypes that are prevalent across South America and North America (sometimes referred to as New World hantaviruses) (Fig. 4).[7] Although some patients who become infected with hantavirus in the Americas present with a nonspecific febrile syndrome, the most severe infections lead to hantavirus cardiopulmonary syndrome, which progresses through four distinct phases.

The incubation period lasts for 5 to 45 days, during which the patient is asymptomatic. The prodromal phase typically lasts for 3 to 7 days but can last up to 12 days and is characterized by fever, fatigue, arthralgia, and myalgia. Gastrointestinal symptoms such as nausea, vomiting, and abdominal pain develop in one third of cases and can mimic surgical emergencies such as appendicitis, diverticulitis, or cholecystitis. The cardiopulmonary phase is marked by the abrupt onset of hypoxemia, pulmonary edema, and distributive shock. This phase usually lasts for 2 to 4 days, and the risk of death is highest within 24 to 48 hours after hospital admission. Those who survive the infection enter the fourth and last phase, convalescence, in which they may have rapid improvement in respiratory and hemodynamic function, but with polyuria and fatigue persisting for weeks.

Hantavirus cardiopulmonary syndrome is the result of an interplay between a direct viral infection and a dysregulated immune response that culminates in a profound capillary leak syndrome.[8] This process not only leads to respiratory failure due to pulmonary edema but also precipitates systemic circulatory collapse. A deeper understanding of these mechanisms is essential, as it may inform the development of targeted therapies aimed at modulating the immune response and preserving endothelial integrity in affected patients.

Management of hantavirus cardiopulmonary syndrome is primarily supportive, focusing on oxygenation, hemodynamic stabilization, and fluid management to address capillary leak syndrome. Early recognition and intensive care are critical to improving outcomes.

FOLLOW-UP

Dr. Saubidet: Because the patient had profound hypoxemia and refractory shock on admission, he remained in the ICU for 40 days. Over the course of his hospitalization, his hemodynamic and respiratory function gradually improved. A percutaneous tracheostomy was performed to facilitate prolonged mechanical ventilation. Once his condition was clinically stable, he was transferred to a specialized rehabilitation center for respiratory and neuromuscular recovery. Before discharge, the patient had complete renal recovery, with return of his baseline renal function and return of robust urine output. Several weeks after completing rehabilita-

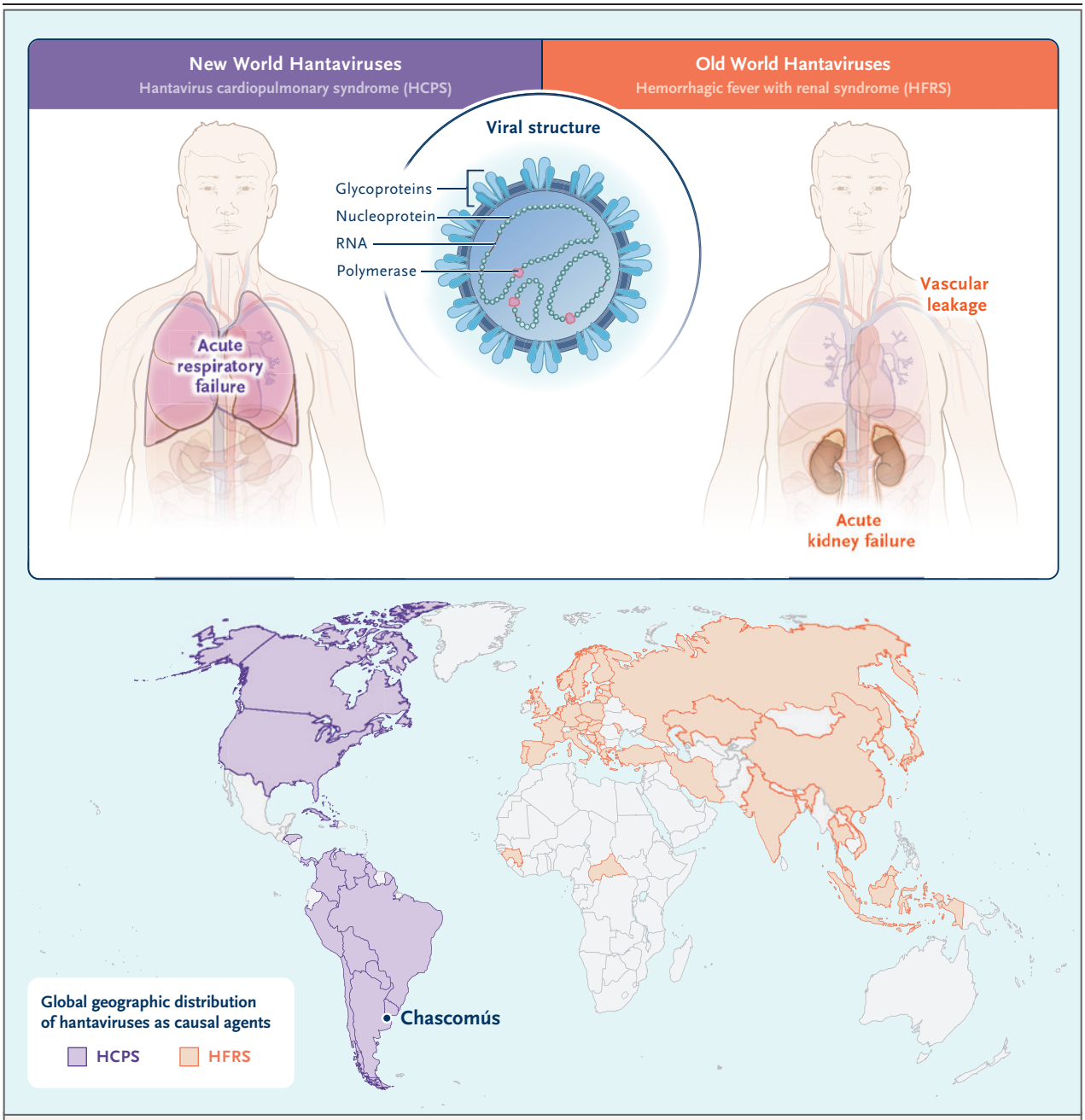

Figure 4. Global Geographic Distribution and Clinical Manifestations of Hantavirus Infection.

The global distribution of hantavirus infection is shown according to clinical manifestations. Infection with genotypes that are prevalent predominantly in Europe and Asia (Old World hantaviruses) manifests as hemorrhagic fever with renal syndrome. Infection with genotypes that are prevalent across South America and North America (New World hantaviruses) manifests as hantavirus cardiopulmonary syndrome. In this case, hantavirus exposure most likely occurred in the region of Chascomús, located in the Buenos Aires Province of Argentina. The map data are from Kim et al.[7]

tion, the patient had made a full recovery and was able to visit the ICU where he had received his care.

As part of the follow-up, discussions were initiated regarding potential infection-control measures at the rural property in Buenos Aires Province where the patient had most likely been exposed to hantavirus. Education on rodent control, environmental decontamination, and personal protective measures was emphasized to reduce the risk of recurrent or additional exposures. Collaboration with local public health authorities was recommended to assess and mitigate ongoing risks in the region.

FINAL DIAGNOSIS

Hantavirus cardiopulmonary syndrome.

This case was presented as part of the Case Records of the Massachusetts General Hospital–NEJM International Case Series.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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