

Dengue and Other Viral Hemorrhagic Fevers

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INTRODUCTION

Viral hemorrhagic fevers (VHFs) are caused by four distinct families of viruses (Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae). They are grouped together because they are all single-stranded RNA viruses with a lipid envelope.¹

They can cause illnesses ranging from mild fever to life-threatening diseases. The illness is characterized by damage to the walls of the blood vessels causing increased permeability and coagulopathy. The symptoms may vary from just fever in the mild form to hemodynamic instability, coagulopathies, and encephalopathy when severe.

The viruses are vector-borne which are arthropods and rodents making the diseases endemic in the geographic distribution of the host vectors. However, in recent times, these diseases are no longer confined to any particular regions due to international travel, tourism, and globalization.

EPIDEMIOLOGY

Viruses of the family Arenaviridae are rodent-borne and prevalent in Africa, America, Asia, and Europe. Humans are infected through rodent urine or droppings and sometimes through aerosolization of viral particles from rodent excreta. One of the members of this group, the Lassa virus spreads through direct contact with multimammate rats or those captured for human consumption. Lassa fever outbreak in West Africa had a case fatality rate of 50%.

Viruses belonging to the family Bunyaviridae are transmitted via arthropods and rodents. They are responsible for causing Crimean–Congo hemorrhagic fever, hantavirus infections, and Rift Valley fever. Exposure to blood or other bodily fluid can also cause transmission and the disease and all carry a high mortality.

Ebola virus disease (EVD) and Marburg hemorrhagic fever are caused by viruses belonging to the family Filoviridae. Initially, detected in bats in Africa, person-to-person transmission has made them endemic in humans. Fatality rates associated with both exceed 80%.

Dengue fever is caused by viruses from the family Flaviviridae and is transmitted by arthropods. It has become endemic across many continents. The spectrum of illness varies from mild fever to dengue shock syndrome (DSS) in the severe form.

We will confine our discussion to dengue fever, hantavirus infection, and Ebola virus (EBOV) infection in greater detail.²

DENGUE FEVER

Dengue fever is an acute febrile illness caused by dengue viruses, which exists as four serotypes, namely, DEN-1, DEN-2, DEN-3, and DEN-4. It is a single-stranded nonsegmented RNA virus and

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the principal vector is *Aedes aegypti*. According to World Health Organization (WHO),³ while a substantial proportion of the world's population is at risk, in India, the disease is prevalent in an endemic form and all four serotypes are known to be circulating, resulting in several outbreaks over the years.

Three phases are described in the clinical presentation: the febrile phase, a defervescence phase, and the spontaneous recovery phase. WHO dengue classification categorizes patients as having either dengue or severe dengue. The presence of plasma leakage resulting in shock, accumulation of serosal fluid to cause pulmonary edema, severe bleeding, and severe organ impairment are necessary to label the patients as having severe dengue.⁴ The same document also includes some warning signs which may herald the possibility of severe dengue.

PATHOGENESIS AND CLINICAL PRESENTATION

Transmission among human beings occurs by the mosquito, *Aedes aegypti*. The virus enters the host through an infected mosquito bite. The incubation period, i.e., time from infection to onset of illness ranges from 3 to 14 days, with an average of 4–7 days.

Dengue fever is characterized by a clinical picture⁵ which varies from asymptomatic illness to life-threatening conditions like DSS. The severe form of the illness is characterized by hypovolemic shock, coagulopathy, bleeding diathesis that can lead to multiorgan failure. However, the presenting signs and symptoms are not specific to dengue infection alone and are seen in other tropical fevers as well.

The main clinical features of dengue fever are high-grade fever accompanied by severe headache, joint pains, vomiting, and myalgia. It has been given the name “breakbone fever” because of severe myalgia and joint pains. Adults usually have a “flu-like syndrome” with gastrointestinal symptoms more commonly than respiratory symptoms. A majority of patients have facial flushing resulting from capillary dilatation. A maculopapular or morbilliform rash is seen after 3 – 7 days following the fever and only some

patients have bleeding diathesis in the form of epistaxis, gingival bleeding, petechial rash, or purpura. The end of febrile phase marks the beginning of the critical phase.

This critical phase is characterized by weak pulse, delayed capillary refill, narrowing of pulse pressure, tachycardia, oliguria, and hypotension. Patients may also have abdominal pain and may present with easy bruising, or bleeding from venepuncture site.

In most patients, this critical phase is followed by a rapid convalescence phase. The convalescence phase can be complicated by encephalopathy, bradycardia, premature ventricular ectopics, and, rarely, myocarditis and encephalitis.

Recognizing the clinical warning signs which indicate the onset of severe illness remains the cornerstone in preventing fatality. Invasive monitoring and, if required, prompt corrective action might be warranted in these patients.

LABORATORY INVESTIGATIONS

The initial changes in laboratory findings include leukopenia and thrombocytopenia, which occurs in the febrile phase. The most commonly used diagnostic tests include a nucleic acid demonstration by polymerase chain reaction (PCR), serological testing of viral antigens like NS1 or IgM antibody detection.

MANAGEMENT

The requirement for hospital admission should be made based on case to case basis depending on the warning signs. Age and comorbidities, like in any other condition add to the risk of the development of severe dengue. No specific treatment is currently available for dengue. Fluid management and fever control form the cornerstone of treatment in febrile phase. Fluids can be taken orally in mild disease or given intravenously in critically ill patients.

In patients with warning signs and clinical features of severe dengue, intravenous fluid therapy should be initiated to replace the fluid lost by sequestration due to plasma leakage. An increase in hematocrit indicates that hemoconcentration indicates the requirement for more fluids. The recommended intravenous fluids are crystalloid solutions (lactate Ringer solution) or normal saline solution.

Although thrombocytopenia is present in dengue, the cause of bleeding in dengue can be multifactorial. The platelet count is neither predictive nor does it correlate with the severity. The most common site of bleeding is the gastrointestinal tract, and silent hemorrhage should be suspected if the hematocrit falls. Blood and blood products may be needed for actively bleeding patients with close monitoring of coagulation parameters. According to guidelines, prophylactic platelet transfusion is indicated at level of $<10,000/\text{mm}^3$ even in absence of bleeding manifestations.

Hepatic and kidney dysfunction, thrombocytopenia, and DSS are associated with a higher risk of mortality. Since these complications occur in young patients in the productive age group, it has a significant public health impact. Dengue has been given public health importance and mortality and morbidity targets have been defined as per the WHO's Global Strategy for Dengue Prevention and Control. Vector control and future vaccine development are among the five technical elements in the strategy. Many vaccines are under evaluation and have received approval from regulatory authorities. The first dengue vaccine (Dengvaxia, CYD-TDV) was registered in Mexico in 2015. WHO recommends vaccines in geographic areas having a high burden of the disease.

Survivors of dengue infection can have three outcomes. First, a durable protection against the particular DENV strain. Second, some protection against different dengue serotype, and third, any infection from a different dengue serotype may result in severe disease. This is due to a phenomenon known as antibody-dependent enhancement. As per this phenomena, subsequent infections are manifested in the more severe form when the infecting serotype is different from the previous one.⁶

HANTAVIRUS INFECTION

Hantaviruses are spherical-shaped single-stranded enveloped RNA viruses belonging to the family Bunyaviridae. The genome comprises three negative-sense, single-stranded RNAs. The three segments, *S* (small), *M* (medium), and *L* (large), encode the nucleoprotein (*N*), envelope glycoproteins (Gn and Gc) respectively, and the *L* is itself a viral RNA-dependent RNA polymerase.⁷

Hantavirus is a zoonotic infection and the vectors implicated are rodents, field mice, voles, and rats. Infected rodents shed the virions in their urine, feces, and saliva. Humans are accidentally infected when they inhale the virions from aerosolized urine, feces, and saliva. Infections from direct contact are also reported from rodent bites. Human-to-human transmission has not been reported except in Andes virus, a recently discovered agent that causes hantavirus pulmonary syndrome in Argentina.

The term hantavirus originates from the prototype hantavirus, Hantaan virus which causes hemorrhagic fever with renal syndrome (HFRS) in Asia. Epidemics of HFRS were described as early as 900 AD. The western world was exposed to it in the Korean wars in 1950s when the United Nations force had an outbreak of over 3000 cases. The virus responsible for HFRS was identified in 1978. Another outbreak was reported in 1993 in South West America (the four corner epidemic) which was found to be due to a novel hantavirus, the Sin Nombre virus.⁸

Although some hantavirus infections are asymptomatic (e.g., the Prospect Hill virus) three disease syndromes have been frequently described.

- HFRS, most of these cases come from old rodents (as in the Middle East).
- *Hantavirus Cardiopulmonary Syndrome* (HCPS), mostly seen in the western hemisphere.
- *Neuropathia epidemica* (NE). Generally a mild form of HFRS common in Western Europe and caused by Puumala virus.

Syndrome overlaps and milder presentation have also been reported. The syndromes share a common pathophysiology, namely, increased vascular permeability leading to hypotension, thrombocytopenia, and leucocytosis.

HEMORRHAGIC FEVER WITH RENAL SYNDROME

The clinical course of HFRS can be divided into five distinct phases: febrile, hypotensive, oliguric, polyuric, and convalescent.

The incubation period ranges from 2 to 4 weeks after which the febrile phase begins. This is characterized by high fever, chills, headache, backache, abdominal pains, nausea, and vomiting. This phase lasts for 3 – 7 days. Conjunctival hemorrhages and petechial may occur. This is followed by the hypotensive phase lasting for few hours to 2 days and presents as septic shock needing high fluid and vasopressors. One-third of the HFRS related deaths occur in this phase. Hemorrhagic manifestations may occur in any part of the body and may include fatal intracranial hemorrhages. Blood

investigations show thrombocytopenia and leucocytosis. Patients surviving this enter into a phase of oliguria and proteinuria with abnormal urinary sediment. The biochemical findings are typical of acute kidney injury (AKI) and some patients require hemodialysis.

Renal function and urine output improve in the polyuric phase, which may last for days to weeks. Clinical recovery is usually complete and improvement of laboratory parameters occurs in the convalescent phase.

HANTAVIRUS CARDIOPULMONARY SYNDROME

HCPS is more lethal with mortality rates of 30 – 50%. It has three phases, namely, prodromal, cardiopulmonary, and convalescent.

The prodromal phase is similar to HFRS. Gastrointestinal symptoms may predominate. However, they dramatically deteriorate and have a progressive cough, shortness of breath, and tachycardia. This cardiopulmonary phase can have hypotension, noncardiogenic pulmonary edema, and respiratory failure often requiring mechanical ventilation. Cardiogenic shock and massive hemoconcentration may complicate the clinical picture and this phase has a high mortality. Survivors enter a convalescent phase characterized by weakness and fatigue but recovery is usually without any sequela.

NE is considered a benign disease. The initial presentation is similar to HFRS. It is characterized by interstitial nephritis which causes AKI. Neurological features may include encephalopathy and there may be presence of meningeal irritation. It is usually followed by complete recovery.

There is growing evidence that many patients have overlapping features of both syndromes, namely, HFRS and HCPS.

The current CDC definition for a suspected case of HPS is twofold.

- Fever (temperature $\geq 38.3^{\circ}\text{C}$) with ARDS or bilateral interstitial pulmonary infiltrates developing with one week of hospitalization and hypoxia requiring supplemental oxygen.
- Unexplained respiratory illness resulting in death, with an autopsy examination demonstrating noncardiogenic pulmonary edema with no identifiable or specific cause of death.
- Excluding criteria include as follows:
 - Predisposing underlying medical condition (cancer, AIDS, and steroid therapy)
 - The possibility of an acute illness that provides a likely explanation for the respiratory compromise.

In addition to the compatible clinical syndrome, confirmed cases must have positive serology, positive PCR, or positive immunohistochemical assay results for hantavirus. It is suspected that many cases go undiagnosed because of the failure to consider HPS in the differential diagnosis of severe community-acquired pneumonia.

DIAGNOSIS AND TREATMENT

Early signs of the disease are nonspecific, but symptoms like high fever, headache, abdominal and back pains and presence of leucocytosis, thrombocytopenia, and renal failure and hematuria should alert the physician to at least rule out the possibility of hantavirus infection especially in the presence of an interstitial pneumonia.

Serological tests include IgM and IgG antibodies against a panel of common hantavirus antigens with an enzyme-linked immunosorbent assay. PCR can be done on RNA extracted from

body fluids and frozen tissue specimens using hantavirus-specific primers. Immunohistochemical assays for viral antigens can be done on formalin-fixed specimen using monoclonal or polyclonal antibodies. This test is not commercially available. The confirmation of hantavirus is done in specialized laboratories by nucleic acid tests, reverse transcriptional-polymerase chain reaction (RT-PCR), and genotyping.

Treatment is primarily supportive and includes maintaining fluid and electrolyte balance, circulating volume, or renal replacement therapy for patients with severe renal insufficiency. Patients with respiratory failure might need ventilator support.

Ribavirin has shown beneficial effects in HFRS like reducing the severity of renal insufficiency but a similar benefit could not be seen in HCPS patients. However, an open-label trial followed by a placebo-controlled, double-blind trial failed to demonstrate its benefit.⁹ As of now, Ribavirin cannot be recommended for routine therapy of HPS.

The preventive measures mainly consist of rodent control and avoiding physical contact in areas likely to be infested with rodents. As of now, there are no approved vaccines for hantavirus infection.

EBOLA VIRUS DISEASE

EVD is caused by EBOV. The EBOV belongs to the family *Filoviridae*, the other genera in the family being *Marburgvirus* and *Cuevavirus*. These are all encapsulated single-stranded RNA viruses. The outbreaks occur when humans are infected by probable zoonotic transmission. This is followed by human-to-human transmission via direct contact or by fomites.

The disease is characterized by fever, gastrointestinal signs, and multiple organ dysfunction syndrome. The incubation period is usually shorter with higher viral load, the normal range being from 2 to 21 days. The EBOV has a predilection for dendritic cells and macrophages, partially explaining their most frequent point of entry in primates that is the mucosa. For viral replication, the EBOV using its glycoprotein outer capsule attaches to the cell membranes. After cell entry, viral RNA and its associated proteins are released into the cell's cytoplasm. The L protein translates EBOV's negative-sense RNA into positive-sense messenger RNA from which EBOV's replicates and then spreads through the lymphatics or blood.¹⁰

Later in the disease, multiple organs may get involved due to a massive release of cytokines (Interleukin I and II, tumor necrosis factor- α , etc.) called the cytokine storm. This is characterized by profound third space loss leading to hypotension and shock. In most patients, death occurs due to hypovolemic shock or, more commonly, multisystem organ failure. The WHO and the CDC criteria¹¹ for the diagnosis of EVD are high fever of sudden onset and three of the following: headache, vomiting, loss of appetite, diarrhea, lethargy, stomach pain, aching muscles or joints, dysphagia, dyspnea, or hiccupping.

The diagnosis is made on the basis of CDC criteria. The confirmation is by RT-PCR that detects the viral RNA or rapid diagnostic tests based on immunoassays to detect EBOV antigens. However, the associated hazards mean that only a few laboratories in the world can safely perform them. These tests are performed in a biosafety level-4 facility. Portable devices that can detect the EBOV in less than 3 hours with a high degree of specificity and sensitivity are being introduced for a quick point of care diagnosis.

The treatment is largely supportive and includes oral and intravenous fluid resuscitation. It is essential to address renal impairment. Blood parameters including hematocrit values,

electrolytes, arterial blood gas, lactate, and blood glucose need continuous monitoring. A higher viral exposure and a shorter incubation period increase the likelihood of death.

Recently a vaccine, the EBOV-targeted vaccine has been approved by European and US regulatory agencies.¹² Randomized clinical trial for specific therapy have shown survival benefits from vaccines which are monoclonal antibody based and target the membrane glycoprotein of the virus. A wealth of clinical experience has been gained from the Western African outbreak (2013–2016) and the ongoing Ebola outbreak in the Democratic Republic of the Congo.

As of now, the only ways to control the pandemic are early diagnosis to quickly isolate the patients, tracing contacts of individual patients, isolation of patients, and strict adherence to infection control procedures.

SALIENT POINTS

- The VHF's dealt here are all caused by single-stranded RNA viruses making them amenable to handwashing as a means of prevention.
- The clinical syndrome produced by each one of them starts as nonspecific fever, but may rapidly progress to hypovolemic shock and multisystem organ failure.
- Treatment is mainly supportive and the vaccines against them are in the process of development.

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