Viral hemorrhagic fevers in India

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Viral hemorrhagic fevers (VHFs) are a group of etiologically diverse viral diseases unified by common underlying pathophysiology. VHFs describe a severe febrile syndrome with multisystem organ involvement. Characteristically the vascular system is damaged with attendant impairment of the body's ability to regulate itself leading to vascular instability and decreased integrity. Damage to the microvasculature, generally in accompaniment of reduced platelet function, results in its disruption and local hemorrhage. Bleeding is common and is generally a manifestation of the widespread vascular damage. Life threatening loss of blood volume is rare. [1,2]

Overview of Viral Hemorrhagic Fevers:

VHFs are caused by viruses belonging to four distinct virus families: Arenaviruses, Filoviruses, Bunyaviruses, and Flaviviruses (table1). All these families contain diverse enveloped RNA viruses, whose survival is dependent on an animal or insect host (natural reservoir) and are geographically restricted to the areas where their host species thrive. Human beings are not the natural reservoir for any of these agents, being infected only when they come in contact with any of the infected hosts. Nonetheless human to human transmission has been documented for some of the viruses like the Ebola, Marbug and the Crimean-Hemorrhagic fever, mostly attributable to direct contact with infected blood and body fluids. Outbreaks of hemorrhagic fevers occur sporadically and irregularly and cannot be predicted with certainty. As many of the VHF agents are highly infectious by aerosol, they have gained notoriety in the past decade from the enormous interest and fear generated by media. [1,2] Some of the viruses even have potential to be used as agents of biological terrorism as they are stable as respirable aerosols. The Centers for Disease Control and Prevention (CDC, Atlanta, USA) has classified most of the viruses causing HF like Ebola, Marburg, Lassa, Junin, as category A bioweapon agents. [2,3] This classification identifies agents associated with high mortality rates, ease of dissemination or person-to-person transmission, and potential for major public panic and social disruption, and that require special action for public health preparedness. However, The Working Group on Civilian Biodefense excluded the viruses causing dengue HF, Crimean-Congo HF (CCHF), and the agents of Hemorrhagic fever with renal syndrome (HFRS) as potential biological weapons.[3] Dengue virus was excluded from the list because it is not transmissible by small-particle aerosol,[4] whereas exclusion of CCHF and the agents of HFRS as tools of bioterrorism were based primarily on technical problems; most importantly, these agents do not readily grow to high concentrations in cell culture, which is necessary for weaponization of an infectious organism.[3]

Pathogenesis of HF is poorly understood and varies according to the viruses involved. The main common underlying pathophysiologic feature is that the vascular bed is attacked, with resultant microvascular damage and changes in vascular permeability. However, specific pathophysiologic findings can vary depending on the virus family and the species involved.

Direct damage to the vascular system or the target organs, inflammatory mediator induced injury and immune response are some of the mechanisms incriminated in the pathogenesis of the clinical syndrome.[5]

The various hemorrhagic fever syndromes caused by the various viruses are depicted in table 2. The spectrum of clinical involvement varies from mild to life-threatening illness, often dictated by the pathogen causing disease.[1,2,5,6] Clinical symptoms include abrupt onset fever with myalgias followed by malaise, prostration, headache, bodyaches, dizziness, photophobia, hyperesthesia, nausea, vomiting, chest or abdominal pain. Flushing of the face and head, conjunctival suffusion, periorbital edema and proteinuria commonly accompany the clinical picture. Bleeding into the skin and mucus membranes follows with hemorrhagic rashes and bleeding from body orifices especially the gastrointestinal, mucus membranes of the eye, nose and the mouth, and the genitourinary tract. Patients often manifest with combinations of these features. Blood pressure is often reduced and shock often supervenes in severe cases.[5,6] Pathogen specific manifestations may occur as well, like lung involvement in hantavirus pulmonary syndrome and DIC and renal involvement in HF with renal syndrome.[7] Bleeding is not frequent in Lassa Fever.[1,5,6] Hypotension, shock, diffuse bleeding and central nervous system manifestations (alteration in consciousness, coma and convulsions), which occur in severe cases, are considered poor prognostic factors. Laboratory abnormalities include leukopenia, thrombocytopenia, DIC and elevation of ALT/AST are common.

Table 1. Viral hemorrhagic fevers of humans

Virus Family Genus	Virus	Disease	Geographic distribution	Source
Arenaviridae				
Arenavirus	Lassa	Lassa fever	West Africa	Rodent
	Junin	Argentine HF	South America	Rodent
	Machupo	Bolivian HF	South America	Rodent
	Sabia	Brazilian HF	South America	Rodent
	Guanarito	Venezuelan HF	South America	Rodent
	Whitewater	Unnamed HF	North America	Rodent
	Arroyo			
Bunyaviridae				
Nairovirus	Crimean-Congo HF	Crimean-Congo HF	Africa, Central Asia, Eastern Europe, Middle East	Tick
Phlebovirus	Rift Valley fever	Rift Valley fever	Africa, Saudi Arabia, Yemen	Mosquito
Hantavirus	Agents of HFRS	HRFS	Asia, Balkans, Europe	Rodent
Filoviridae				
Ebolavirus	Ebola	Ebola HF	Africa	Unknown
Marburgvirus	Marburg	Marburg HF	Africa	Unknown
Flaviviridae				
Flavivirus	Dengue	Dengue HF	Asia, Africa, Pacific, Americas	Mosquito
	Yellow fever	Yellow fever	Africa, Tropical Americas	Mosquito
	Omsk HF	Omsk HF	Central Asia	Tick
	Kyasanur forest disease	Kyasanur forest disease	India	Tick

HF: hemorrhagic fever; HFRS: hemorrhagic fever with renal syndrome

Table 2. Common HF syndromes, incubation periods and case fatality ratios.

Syndrome	Age groups/Sex	Incubation period	Case fatality ratio
Crimean-Congo HF	All ages	3-12 d	15-30%
Dengue HF	All ages, predominant in children	2-7 d	<1%
HF with renal syndrome	Mainly adults, more in men	9-35 d	1-15%
Hantavirus pulmonary syndrome	Mainly adults, more in men	7-28	40-50%
Kyasanur Forest HF	All ages	Variable	5-10%
Lassa fever	All ages	5-16 d	15%
Marbug/Ebola HF	All ages	3-16 d	25-90%
Rift Valley fever	All ages	2-5 d	~50%
South American HF	All ages, more in men.	5-16 d	15%
Yellow fever	All ages	3-6 d	20%

Diagnosis is often suggested by history to travel to an endemic area within the incubation period.[1,5,6] Human to human transmission is however known in certain HF viruses and exposure history can mostly be traced to the initial contact. During the 2014 Ebola outbreak, one of the nurses caring for Ebola cases tested positive for Ebola virus depicting human to human transmission without a history of visit. [8]

Recognition of the syndromes is essential to order appropriate investigations for diagnosis and institute supportive therapy. Supportive therapy generally consists in fluids, vasopressors, replacement for clotting factors and platelets, treatment of superadded bacterial infections and other usual measures in the intensive care where these patients often require admission. Specific antiviral therapy is available for only some of the syndromes and strict infection control measures are indicated for containment of the infection.

Agents causing VHFs are distributed worldwide. In the Indian scenario, however, Dengue and Dengue hemorrhagic fever, and Kyasanur Forest Disease (KFD) infection are seen and are endemic (even hyperendemic). There is also an increasing recent interest in the Ebola virus as the current 2014 epidemic in the African subcontinent may soon spread beyond its boundaries and indeed some cases have already been reported from outside of the main affected region.

A. Dengue Hemorrhagic Fever/Dengue Shock syndrome (DHF/DSS)

Dengue is caused by infection with one of four dengue virus serotypes viz, dengue 1-4 (DEN-1 to DEN-4) of the family Flaviviridae. Although all four serotypes are antigenically similar, they are different enough to elicit cross-protection for only a few months after infection by any one of them.[1,5,6] Infection with one serotype provides life-long immunity against reinfection by that same serotype, but not against the other serotypes. Secondary infection with another serotype or multiple infections with different serotypes leads to severe form of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue viruses are transmitted in the tropics, in an area roughly between 35 degrees north and 35 degrees south latitude, corresponding to the distribution of Aedes. aegypti, the principal mosquito vector[9] although A. albopictus, A. polynesiensis, and other species can transmit the virus in specific circumstances. Both A.aegypti and A.albopictus possess high vectorial competency for the dengue virus. [6] The close relationship of A. aegypti to humans is responsible for the intensification of dengue transmission in tropical cities, where growing populations live under crowded conditions.[10,11] Of the 4 serotypes, DEN2 is more virulent and unfortunately Aedes aegypti tends to be more susceptible to infection by DEN2 virus in Southeast Asian genotype (genotype iv and v), that's why DHF/DSS is more prevalent in this region. [12]

An estimated 50 million dengue infections occur worldwide annually and about 500 000 people with DHF require hospitalization each year. A very large proportion (approximately 90%) of them are children aged less than five years, and about 2.5% of those affected die. [6] The vast majority of dengue infections are asymptomatic but a proportion manifest as a non-specific febrile illness and even fewer progress to severe disease. Dengue viral infection results in a wide spectrum of disease; dengue fever, characterized by biphasic fever, myalgia, arthralgia, leukopenia and lymhadenopathy being one end of this spectrum while the other extreme encompasses severe syndromes like DHF and DSS representing an often fatal disease characterized by hemorrhages and shock syndrome. [1,5,6]

B.1 Transmission of the Dengue virus

For transmission to occur the female A. aegypti must bite an infected human during the viraemic phase of the illness that manifests two days before the onset of fever and lasts 4–5 days after its onset. Adult mosquitoes shelter indoors and bite during 1- to 2- hour intervals in the morning and late afternoon. After ingestion of the infected blood meal the virus replicates in the epithelial cell lining of the midgut of the host and escapes into haemocoele to infect the salivary glands and finally enters the saliva causing infection during probing. The genital track is also infected and the virus may enter the fully developed eggs at the time of oviposition. The extrinsic incubation period lasts from 8 to 12 days and the mosquito remains infected for the rest of its life. [13] The extrinsic incubation period is influenced in part by environmental conditions, especially ambient temperature and humidity. [1,6] A. aegypti is adapted to breed around human dwellings, where the insects oviposit in uncovered water storage containers as well as other containers holding water, such as vases, flower dishes, cans, automobile tyres, and other discarded objects. In tropical areas, transmission is maintained throughout the year and intensifies at the start of the rainy season. [1]

When the virus is introduced into susceptible populations, usually by viremic travelers, epidemic attack rates may reach 50% to 70%. Cross-protective immunity among the serotypes is limited; as such epidemic transmission recurs with the introduction of novel virus types. Also, as secondary infections predispose to DHF, the concurrent transmission of more than one viral serotype establishes favorable conditions for endemic DHF. Under these circumstances, virtually all DHF cases occur in individuals with secondary infections, primarily children with the relative risk being as high as 100. [1,6] Concomitant circulation of different serotypes in hyperendemic regions like India is ideal for a secondary infection by a different serotype.

B.2 Pathogenesis of DHF

After an infectious mosquito bite, the virus replicates in local lymph nodes and within 2 to 3 days disseminates through the blood to various tissues. It circulates in the blood for about 5 days in infected monocyte-macrophages mainly and to a lesser degree in B and T cells. It also replicates in skin and reactive spleen lymphoid cells. [14] Self-limited dengue fever is the usual clinical outcome of infection and most infections are subclinical, but an immunopathologic response in some patients, produces the syndrome of DHF. Even as DHF can occur in patients with a first attack of dengue fever, its greater frequency in cases with secondary infection [1,6] implicates the role of immune system, both innate as well as adaptive, in its causation. Enhancement of immune activation leads to exaggerated cytokine response resulting in changes in vascular permeability. In addition, viral products such as NS1 may play a role in regulating complement activation and vascular permeability. [15,16] A number of cytokines have been implicated but the relative importance of these is unknown and in fact the pattern of the cytokine response may be related to the cross-recognition of dengue specific T cells. TNF-alpha has been found to be high in animal models of DHF. The main features of DHF are increased vascular permeability without morphological damage to the capillary endothelium, thrombocytopenia, altered number and functions of leucocytes, altered haemostasis and liver damage. [1,5,6] Macrophage/monocyte infection is central to the pathogenesis of DHF/ DSS. Extensive plasma leakage occurs in various serous cavities of the body including the pleura, pericardium and peritoneal cavities. Associated hemorrhages and diffuse leakage in patients with severe DHF may result in profound shock, the DSS.[5,6] The hemorrhagic diathesis is complex and not well understood, reflecting a combination of cytokine action and vascular injury, viral antibodies binding to platelets or cross-reacting with plasminogen and other clotting factors, reduced platelet function and survival, and a mild consumptive coagulopathy. Paralleling the pathogenetic role of secondary enhancing antibodies in DHF, memory cellular responses to heterologous antigens also may contribute to immunopathology. [17] The rise of levels of serum neutralizing antibodies is correlated with the clearance of viremia, but immunity is associated with both humoral and cellular immune responses. Cross-protective immunity from infection with one dengue viral serotype is brief as infection with a second type during the same transmission season is not uncommon. However, illness after infection with two serotypes (i.e., a third bout of dengue) occurs infrequently, and illness after three infections, virtually never occurs. Higher levels of viral load in DHF patients in comparison with DF patients have also been demonstrated in many studies. [18,19]

B.3 Clinical features

Typical cases of DHF are characterized by high fever, haemorrhagic phenomena, hepatomegaly, and often circulatory disturbance and shock. The clinical course typically begins sudden rise in temperature accompanied by facial flush and other symptoms resembling dengue fever, such as anorexia, vomiting, severe frontal headache, retro-orbital pain, nausea, vomiting and skin eruptions Apart from this severe muscle and bone pain and arthralgia (break bone fever) is almost always the rule. Sore throat and pharyngeal hyperemia may be observed. [1,5,6] A bi-phasic fever pattern may be observed and temperature may be as high as 40^0 C. [6]

Moderate to marked thrombocytopenia with concurrent haemoconcentration/rising haematocrit are distinctive laboratory findings. The major pathophysiological changes that determine the severity of DHF and differentiate it from DF and other viral haemorrhagic fevers are abnormal haemostasis and leakage of plasma selectively in pleural and abdominal cavities. The critical phase of DHF, i.e. the period of plasma leakage, begins around the transition from the febrile to the afebrile phase. Evidence of plasma leakage, pleural effusion and ascites may, however, not be detectable by physical examination in the early phase of plasma leakage or mild cases of DHF, and a rising haematocrit, e.g. 10% to 15% above baseline, is the earliest evidence. [6] Criteria for the diagnosis of DHF/DSS are given in Table 3. Significant loss of plasma can lead to hypovolemic shock. In mild cases of DHF, all signs and symptoms abate after the fever subsides. In moderate to severe cases, the patient's condition deteriorates a few days after the onset of fever. Persistent vomiting, abdominal pain, refusal of oral intake, lethargy or restlessness or irritability, postural hypotension and oliguria are warning signs of a deteriorating patient. Near the end of the febrile phase, by the time or shortly after the temperature drops or between 3–7 days after the fever onset, there are signs of circulatory failure. Without treatment, the patient may die within 12 to 24 hours. Encephalopathy may occur in association with multiorgan failure, metabolic and electrolyte disturbances. Patients with prolonged or uncorrected shock have a poor prognosis and high mortality. The severity of DHF is classified into four grades (grade 1-4) that has been found clinically and epidemiologically useful in DHF epidemics. (Table 4)

In some case unusual neurological, hepatic, renal and other isolated organ Involvement can occur which have been categorized as the 'Expanded dengue syndrome" [6]

B.4 Laboratory diagnosis

The diagnosis can be achieved by the following methods

1. Isolation of the virus in cell cultures

2. Identification of viral nucleic acid

3. Identification of viral antigen

4. Detection of virus specific antibodies

5. Analysis of hematological parameters

Viral isolation is used for early, definitive and serotype specific identification of dengue infections during the acute phase of the disease. Live virus or virus components (RNA or antigens) can be detected in serum, plasma, whole blood and infected tissues from 0–7 days following the onset of symptoms. Suckling mice (intra cranial inoculation) have been used as a laboratory host to amplify virus. Also mammalian cell cultures and mosquito cell cultures are used for viral isolation. Although isolation of virus is the most sensitive and specific diagnostic modality it is not routinely performed. Dengue viral RNA can be detected using a nucleic acid amplification test (NAAT) on tissues, whole blood or sera taken from patients in the acute phase of the disease. RT-PCR gives high level of sensitivity and specificity. NS1-antigen based assays provide simplified way of diagnosing dengue. Enzyme linked Immunosorbent Assays that target non-structural protein 1 (NS1) have shown that high concentrations of this antigen can be detected in patients with primary and secondary dengue infections up to 9 days after the onset of illness. The acquired immune response to dengue virus infection consists of the production of immunoglobulins (IgM, IgG and IgA) that are mainly specific for the virus envelope (E) protein. Detection of theses antibodies affords easy method of diagnosis of dengue infection. The use of rapid IgM based dengue diagnostic tests, in the form of lateral flow immunochromatographic strips, are quick and easy for use as point of care or bedside tests. [1] Routine haematological parameters like hematocrit, leukocyte counts and platelet counts aid the diagnosis and severity of DHF. [1,6]

Table 3. Diagnostic Criteria for Dengue Hemorrhagic Fever (DHS) and Dengue Shock Syndrome (DSS)

Dengue Hemorrhagic Fever	
Presence of all of the following:	
Fever (Acute onset of 2-7 days)	
Haemorrhagic manifestations	Evidenced by positive tourniquet test, petechiae, ecchymoses or purpura, or bleeding from mucosa, gastrointestinal tract, injection sites, or other locations.
Thrombocytopenia	Platelet count of ≤100 000 cells/mm^3
Dengue Shock Syndrome (DSS)	
Criteria for DHS (As above) and signs of shock	Tachycardia, cool extremities, delayed capillary refill, weak pulse, lethargy or restlessness (a sign of reduced brain perfusion).
	Pulse pressure ≤20 mmHg with increased diastolic pressure, e.g. 100/80 mmHg.
	Hypotension by age, defined as systolic pressure <80 mmHg for those aged <5 years or 80 to 90 mmHg for older children and adults.

The first two clinical criteria, plus thrombocytopenia and haemoconcentration or a rising haematocrit, are sufficient to establish a clinical diagnosis of DHF. The presence of liver enlargement in addition to the first two clinical criteria is suggestive of DHF before the onset of plasma leakage. In cases with shock, a high haematocrit and marked thrombocytopenia support the diagnosis of DSS. A low ESR (<10 mm/ first hour) during shock differentiates DSS from septic shock.(6).

Table 4. Grading of severity of DHF

Grade	Clinical features	Lab features
I	Fever and haemorrhagic manifestation (positive tourniquet test) and evidence of plasma leakage	Thrombocytopenia <100 000 cells/mm³; HCT rise ≥20%
II	As in Grade I plus spontaneous bleeding	Thrombocytopenia <100 000 cells/mm³; HCT rise ≥20%
III	As in Grade I or II plus circulatory failure (weak pulse, narrow pulse pressure (≤20 mmHg), hypotension, restlessness).	Thrombocytopenia <100 000 cells/mm³; HCT rise ≥20%
IV	As in Grade III plus profound shock with undetectable BP and pulse	Thrombocytopenia <100 000 cells/mm³; HCT rise ≥20%

HCT= Hematocrit

B.5 Treatment

Treatment is largely supportive and consists in fluid resuscitation, management of hypotension by vasopressors/cardiotonic drugs and management of the haemorrhagic complications by appropriate blood and blood product (platelet concentrates, fresh frozen plasma or cryoprecipitate) transfusions. Isotonic crystalloid solutions should be used throughout the critical period except in the very young infants <6 months of age in whom 0.45% sodium chloride may be used. Hyper-oncotic colloid solutions (osmolarity of >300 mOsm/l) such as dextran 40 or starch solutions may be used in patients with massive plasma leakage, and those not responding to the minimum volume of crystalloid. [6] There is anecdotal evidence for efficacy of IV anti-D globulin in management of dengue hemorrhagic fever. Fatalities are rare but do occur especially in cases of fulminant hepatitis and or renal failure.

B.6 Prevention:

Vector control is important and must be instituted by public health authorities. A recombinant, live, attenuated, tetravalent dengue vaccine for dengue has recently been demonstrated to be effective and safe after 25 months of active surveillance in 10 countries among different populations (including a variety of ages and ethnic backgrounds) over different seasons with different circulating serotypes and levels of endemicity. [20]

C. Kyasanur Forest Disease

The report of an outbreak of monkey deaths and hemorrhagic fever with jaundice in 1957 in the Kyasanur Forest of Mysore, India triggered an investigation of what was suspected to be the much-feared introduction of yellow fever to Asia. The isolated virus was in fact a novel member of the antigenic complex of tick-borne flaviviruses that was transmitted between various ixodid ticks and forest rodents, insectivores, and monkeys. Haemaphysalis spp. ticks are the vectors for the disease. That epidemic and subsequent sporadic cases and outbreaks occurred during the dry season among peasants clearing forests for pasture, and the endemic area gradually spread and enlarged in connection with those activities. [21-23]

Transmission to humans may occur after a tick bite or contact with an infected animal, most importantly a sick or recently dead monkey. No person-to-person transmission has been described. Large animals such as goats, cows, and sheep may become infected with KFD but play a limited role in the transmission of the disease. These animals provide the blood meals for ticks and it is possible for infected animals with viremia to infect other ticks, but transmission of KFD virus to humans from these larger animals is extremely rare. Furthermore, there is no evidence of disease transmission via the unpasteurized milk of any of these animals.

C.1 Clinical features:

The incubation period is 3 to 8 days and the onset of illness is abrupt. Fever, headache, chills, vomiting, myalgia, photophobia, and conjunctival suffusion are the common manifestation of the disease. Facial and conjunctival hyperemia, hepatosplenomegaly, lymphadenopathy, and petechiae are found on examination. Diffuse hemorrhages in the skin and the mucus membranes like nose, gums, and gastrointestinal tract develop, with hemorrhagic pulmonary edema in 40% of cases and renal failure developing in severe cases. Patients may experience abnormally low blood pressure, and low platelet, red blood cell, and white blood cell counts. . After 1-2 weeks of symptoms, some patients recover without complication. However, the illness is biphasic for a subset of patients (10-20%) who experience a second wave of symptoms at the beginning of the third week. These are characterized by fever with neurologic symptoms like severe headache, mental disturbances, tremors, and vision deficits which are observed in 15-50% of cases. Patients have detectable viremias up to 12 days after the onset of illness. Between 5% and 10% of cases are fatal, and iridokeratitis has been reported in survivors.

C.2 Geographic distribution

KFD is unique to 5 districts (Shimoga, Chikkamagalore, Uttara Kannada, Dakshina Kannada, and Udupi) of Karnataka State and occurs as seasonal outbreaks during January–June. [22, 24] However, in November 2012, samples from humans and monkeys tested positive for KFDV in the southernmost parts of the state that is in neighborhood of states like Tamil Nadu and Kerala, indicating the possibility of wider distribution of KFDV. Additionally, a virus very similar to KFD virus (Alkhurma hemorrhagic fever virus) has been described in Saudi Arabia.

C.3 Risk factors:

People with recreational or occupational exposure to rural or outdoor settings are potentially at risk for infection by contact with the infected ticks. Such people include hunters, herders, forest workers, farmers within the Karnataka State. Seasonality is another important risk factor as more cases are reported during the dry season, from November through June. [25]

C.4 Treatment:

There is no virus specific treatment for KFD. However early hospitalization and supportive therapy is important. Supportive therapy includes the intravenous fluid therapy and infusion of blood or blood products as dictated by the patient's clinical condition and laboratory abnormalities.

C.5 Prevention:

Since 1990, vaccination campaigns using formalin-inactivated tissue-culture vaccine have been conducted in the districts to which KFD is endemic. Earlier studies showed vaccine efficacy of 79.3% with 1 dose and 93.5% with 2 doses. [26] The vaccination program identifies villages reporting KFD activity (laboratory-confirmed cases in monkeys and/or humans, or infected ticks), and all villages within 5 km of the affected location are targeted for vaccination. Two doses at 1-month interval are administered to persons 7–65 years of age. Because of the short-lived nature of the immunity conferred, booster doses are administered at 6–9-month intervals consecutively for 5 years after the last reported KFD activity in the area. If KFD activity is reported where vaccination has been administered during pre-transmission seasons, additional vaccination campaigns are conducted. [26]

1. Other viral hemorrhagic fevers in India:

Although there are 12 viruses that are capable of causing hemorrhagic fevers, only 2 are consistently seen in India.

Chikungunya fever is another commonly encountered flavi-viral fever however it is not classified as a regular cause of HF. "Chikungunya virus," is an alphavirus of the family Togaviridae. Infection is transmitted by the bite of infected Aedes albopictus mosquitoes.

The disease reemerged in India after 32 years in October 2005 as an outbreak.[27] The incubation period varies from 3 to 12 days. Onset is abrupt with high grade fever and is characterized by severe arthralgias, myalgias, and skin rash. Swollen tender joints and arthritis are commonly encountered.[27] In some patients, a biphasic pattern of fever has been observed. A febrile episode (4 to 6 days) is followed by an afebrile period with recurrence of high grade fever later. Fever now can last for a few days. It can be clinically differentiated from dengue as classic dengue fever does manifest with arthritis. In a majority of the patients, the joint pains resolve in 1 to 3 weeks. However, the arthritis can persist in some patients for months to years.[28,29]

Reverse transcription polymerase chain reaction (RT PCR) has been found to be useful but serological tests for immunoglobulin M and immunoglobulin G antibodies against Chikungunya virus are more frequently used.[27] Viral culture is the gold standard but not routinely done and is used mainly as a research tool.

Chikungunya is a self-limiting disease, responding readily to supportive treatment.[27] Adequate fluid intake must be ensured. Paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDS) may be used for symptom relief. Aspirin should be avoided due to its effect on platelets.[27] Paracetamol can be safely taken up to 4 grams in 24 hours. Fever usually resolves in 3 to 4 days. Severe manifestations like meningoencephalitis, fulminant hepatitis, and bleeding manifestations can be life-threatening and should be actively looked for.[28] Treatment is symptomatic.

Crimean Congo hemorrhagic fever (CCHF) is a severe form of hemorrhagic fever with a very high mortality rate. It is endemic in Africa, Asia, Eastern Europe and the Middle East. An outbreak was recorded recently in parts of Gujarat, claiming four lives. It is a zoonotic viral disease and is caused by Nairovirus (family Bunyaviridae). Hyalomma tick is the vector responsible for transmission. The disease is asymptomatic in infected animals but highly fatal in humans including unsuspecting health care workers.[30] Small animals like hare etc, act as amplifying hosts and maintain the virus in nature.

The typical course of infection has four distinct phases.

The incubation period (3-7 days) is influenced by the route of infection, viral load, source of infection-blood or tissue from livestock.[30]

The Prehemorrhagic phase (4-5 days) is characterized by prodromal symptoms like high fever, myalgia, headache, nausea, abdominal pain, and non-bloody diarrhea. This could be complicated by hypotension, relative bradycardia, tachypnea, conjunctivitis, pharyngitis, and cutaneous flushing or rash.[31]

The hemorrhagic phase is short and there is rapid progression to hemorrhagic diathesis. These include petechiae, conjunctival hemorrhage, epistaxis, hematemesis, hemoptysis, and melena.[32] There could be fatal Acute respiratory distress syndrome (ARDS) and diffuse alveolar hemorrhage.[33,34]

The disease is fatal in 40-60% of the cases. In severe cases, death occurs as a result of multiorgan failure, disseminated intravascular coagulation, and circulatory shock.

The convalescent period starts after10-20 days of onset. The physician may note feeble pulse, tachycardia, loss of hearing, loss of memory and hair in some patients.[31]

Reverse-transcriptase PCR (RT PCR) is the investigation of choice for rapid diagnosis and a presumptive diagnosis can be made within 8 hour. Viral culture is the gold standard but cumbersome, not practiced as a diagnostic modality.[30]Serological tests are useful in the second week of illness, so are not routinely used for rapid diagnosis.

The early diagnosis and supportive care in the form of blood, platelet, and plasma replacement has proven to be life-saving.[30] Role of anti-viral drugs is not very clears but World Health Organization (WHO) recommends ribavirin for CCHF. The recommended dose is a bolus of 30 mg/kg followed by 15 mg/kg for four days and then 7.5 mg/kg for six days for a total of 10 days.[35]

The mainstay of prevention and control of CCHF viral infection is to prevent human contact with livestock and minimize the tick burden in the vertebrate hosts.[30] Wearing personal protective equipment, avoiding unpasteurized milk and uncooked meat should be followed always. Human-to-human transmission can be prevented by adopting strict universal precautions when caring for patients. Use of barrier nursing, isolation, use of protective gears (gloves, gowns, face-shields, and goggles) will help prevent the spread. Safe burial practices should be ensured. Since the virus is inactivated by 1% hypochlorite and 2% glutaraldehyde they should be used. Heating at 56°C (133°F) for 30 min can also destroy the virus.[30]

Additionally the frequency of international travel poses risk of other VHFs imported by infected travelers coming into India. In this regard the 2014 Ebola outbreak in West Africa is of particular interest and a screening program has been started by the Ministry of Health and Family Welfare to screen international travelers coming from Ebola infected regions at various international airports in the country.

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