

# **Severe Febrile Shock and Hemorrhage: Pathology, Pathogenesis, and Diverse Microbial Etiologies**

## **Yellow Fever and other Viral Hemorrhagic Fevers**

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Although the yellow fever virus is believed to have originated in Africa, the first recorded outbreak was in Mexico in the seventeenth century. This was followed during the eighteenth and nineteenth centuries by numerous outbreaks in the Caribbean, Central and South America and the eastern part of the USA as far north as New York. Epidemics in more temperate regions of the western hemisphere were the result of introductions through seaports and of transport of mosquito vectors and viruses along commercial shipping routes. At the beginning of the last century, yellow fever killed thousands yearly and was the first “filterable agent” proven to be transmitted by an insect, giving birth to a whole new category of viruses: the arboviruses. The work of the US Army Commission in Cuba, including Walter Reed, William Gorgas and other coworkers, established that transmission of yellow fever virus from humans to humans was by infected *Aedes aegypti* mosquitoes. Control measures against this mosquito, along with immunization using a live attenuated virus vaccine, effectively controlled urban yellow fever in the Americas. However, the disease persisted sporadically in rural areas of both Africa and South America as a consequence of sylvatic (jungle) cycles involving monkeys and forest-dwelling mosquitoes. In rural areas, most yellow fever infections occur in people who visit or work in the forests of Africa and South America. Periodically the virus is introduced into urban areas where the highly domesticated mosquito *Aedes aegypti* occurs. This mosquito may become infected by feeding

on a viremic person who was infected in the forest, and secondary transmission can then ensue. Urban epidemics have historically been explosive with many cases because transmission is human to human via the *Aedes aegypti* mosquito, which feeds primarily on humans.

Yellow fever illness varies from a subclinical infection to a fulminating disease terminating in death. After an incubation period of 3-10 days, there is sudden onset of fever, chills, headache and backache. Patients are usually severely ill, restless, with flushed face, swollen lips, and congested tongues and conjunctivae. Many patients suffer from nausea and vomiting and a bleeding tendency may be seen early on. A brief 1-2 day remission may occur and is quickly followed by resumption of the febrile illness. The facial edema and flushing are replaced by a dusky pallor, the gums become swollen and bleed easily, and there is a pronounced hemorrhagic tendency with hematemesis, melena and ecchymoses. In spite of a high fever, the pulse rate is slow and the blood pressure falls, resulting in renal failure with albuminuria, oliguria and anuria. Death, when it occurs, is usually within 6-7 days of onset, and is rare after 10 days of illness. The jaundice, which gives the disease its name, is generally apparent only in convalescing patients. Mortality may be as occur in 20-50%. Most patients with severe disease have leukopenia, thrombocytopenia, elevated hepatic enzymes and coagulation defects. At autopsy the organs most affected are the liver, spleen, kidneys and heart. Typically, midzonal necrosis is apparent in the liver, affecting cells around the periphery of the lobule and sparing areas around the central vein. Acidophilic necrosis is evident and Councilman inclusion bodies are usually present. Viral antigens, as detected by immunohistochemistry, are usually confined to the liver in these fatal cases.

Treatment is supportive and confined to nonspecific measures, including maintenance of fluid and electrolyte balances and replacement of any substantial amounts of blood lost

through hemorrhage. One dose of live, attenuated 17D vaccine provides complete protection for 10 years and is notably free from reactions. Since 1937, this vaccine has protected about 44 million humans from yellow fever. However, since the late 1990s, close to 40 cases of yellow fever vaccine-associated viscerotropic disease have been reported worldwide. The risk of this adverse event is about three per million of doses administered and is highest among people over 60 years old. Virus is widely distributed in various tissues in these cases and is very distinct in cellular tropism as compared to that seen in naturally acquired disease. It is hypothesized that it may be related to be due to genetic susceptibility.

Yellow fever is caused by a flavivirus and is classified as a hemorrhagic fever virus (VHF). VHFs are a special group of viruses, belonging to four different families, transmitted to humans by arthropods and rodents (Table 1). These viruses persist in nature through zoonotic cycles, although in the case of dengue and sometimes yellow fever viruses, human-to-human transmission through the bite of a mosquito vector is an important factor in disease maintenance. Other hemorrhagic fever (HF) of infectious that must be included in the differential diagnosis and excluded are malaria, rickettsial diseases, leptospirosis, shigellosis, and typhoid fever. Characteristic pathologic features of yellow fever and other viral hemorrhagic fevers are provided (Table 2). The presentation will highlight the clinical and pathologic features of yellow fever and other viral hemorrhagic fevers (VHFs). The presentation will prepare pathologists to recognize yellow fever and diagnose these various infections. The differential diagnosis and anatomic pathologic approach to achieve an etiologic diagnosis of these threatening diseases will be discussed.

**TABLE 1. Hemorrhagic Fever (HF) Viruses**

<b>VIRUS</b>	<b>DISEASE NAME</b>	<b>CASE FATALITY</b>	<b>VERTEBRATE HOST</b>	<b>ARTHROPOD VECTOR</b>
<b>ARENAVIRUSES</b>				
Junin	Argentine HF	15-30%	Rodents ( <i>Calomys musculus</i> )	None
Machupo	Bolivian HF	15-30%	Rodents ( <i>Calomys callosus</i> )	
Guanarito	Venezuelan HF	15-30%	Rodents ( <i>Zygodontomys brevicauda</i> )	None
Sabia	Brazilian HF	15-30%	Presumably an unidentified rodent	None
Lassa	Lassa fever	~ 15%	Rodents ( <i>Mastomys</i> )	None
<b>BUNYAVIRIDAE</b>				
Rift Valley fever	Rift Valley fever	~ 50%	Vertebrates (Sheep, cattle)	Mosquito, <i>Aedes</i> and others
Crimean Congo HF	Crimean Congo HF	15-30%	Vertebrates (Birds, hares, large ungulates)	Ticks, especially <i>Hyalomma</i>
Hantaan, Seoul, Puumala, and others	Hemorrhagic fever with renal syndrome (HFRS)	1-15%	Rodents	None
Sin Nombre, Black Creek Canal, and others	Hantavirus pulmonary syndrome (HPS)	50%	Rodents	None
<b>FILOVIRIDAE</b>				
Marburg	Marburg HF	25%	Unknown	Unknown
Ebola	Ebola HF	50-90%	Unknown	Unknown
<b>FLAVIVIRIDAE</b>				
Yellow fever	Yellow fever	20%	Primates	Mosquito, especially <i>Aedes</i>
Dengue	Dengue HF, dengue shock syndrome (DHF/DSS)	5%	Primates, humans	Mosquito, especially <i>Aedes aegypti</i>
Kyasanur Forest disease (KFD)	KFD	0.5-9%	Rodents	Ticks
Omsk hemorrhagic fever (OHF)	OHF	0.5-9 %	Rodents	Ticks

**Table 3. Pathologic features in viral hemorrhagic fevers.**

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<b>DISEASE</b>	<b>PATHOLOGIC FEATURES*</b>
Argentine HF	Multifocal hepatocellular necrosis with minimal inflammatory response, interstitial pneumonitis, myocarditis, and lymphoid depletion. Extensive parenchymal cell and reticuloendothelial infection, more than morphologic lesions would suggest.
Bolivian HF Venezuelan HF Lassa fever	
Rift Valley fever	Widespread hepatocellular necrosis and hemorrhage, sometimes with midzonal distribution, minimal inflammatory response, DIC, lymphoid depletion, and encephalitis. RVF antigens in very few individual hepatocytes.
Crimean Congo HF	Widespread hepatocellular necrosis and hemorrhage with minimal or no inflammatory cell response and lymphoid depletion. Hepatic and endothelial cell infection and damage.
Hemorrhagic fever with renal syndrome (HFRS)	Retroperitoneal edema in severe HFRS, mild to severe renal pathologic changes. Congestion and hemorrhagic necrosis of renal medulla, right atrium of the heart, and anterior pituitary. Extensive endothelial infection mainly in renal and cardiac microvasculature.
Hantavirus pulmonary syndrome (HPS)	Large bilateral pleural effusions and heavy edematous lungs, mild to moderate interstitial pneumonitis, immunoblasts and atypical lymphocytes in lymphoid tissues and peripheral blood. Extensive infection of endothelial cells in pulmonary microvasculature.
Ebola HF	Extensive and disseminated infection and necrosis in major organs such as liver, spleen, lung, kidney, skin, and gonads. Extensive hepatocellular necrosis associated with formation of characteristic intracytoplasmic viral inclusions. Lymphoid depletion, microvascular infection and injury.
Marburg HF	Similar to Ebola HF
Yellow fever	Midzonal hepatocellular necrosis; minimal inflammatory response. Councilman bodies and microvesicular fatty change. Hepatocellular and Kupffer cell infection.
Dengue HF/DSS	Centrilobular and midzonal hepatocellular necrosis with minimal inflammatory response; Councilman bodies and microvesicular fatty change. Hyperplasia of mononuclear phagocytic cells in lymphoid tissues and atypical lymphocytes in peripheral blood. Widespread infection of mononuclear phagocytic and endothelial cells.
Kyasanur Forest Disease (KFD)	Focal hepatocellular degeneration, fatty change, and necrosis. Pulmonary hemorrhage, depletion of malpighian follicles, sinus histiocytosis, erythrophagocytosis, mild myocarditis, and encephalitis.
Omsk HF	Little known; scattered focal hemorrhage, interstitial pneumonia, and normal lymphoid tissues

\* These features represent the more characteristic pathologic findings in the different VHFs. More general findings seen to variable degrees in all HF are not listed in this table.

