

# Understanding Pathophysiology of Marburg Hemorrhagic Fever (MHF)

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## Abstract

The Transmission of a treacherous infectious disease threatens not merely a local population but the world at mass as the result of immigration and increased and faster pace. Any epidemics elicit considerable concern and demands that various precautionary methods be instituted and that the disease be eradicated as quickly as possible. Marburg haemorrhagic fever (MHF) is an old disease, one that may have been present for centenary and was identified decades ago. Fortunately, the disease, MHF was limited to a small geographical area, but the destruction of lives was much greater than that of many pandemics and was a warning of the number of factors, including fear, lack of knowledge regarding the disease, and deception, that can exacerbate the spread of disease and impact implementation of restraints. This article reviews the history of the disease caused by Marburg virus, pathophysiology and its biological components.

**Keywords:** Marburg haemorrhagic fever; Pandemics; Pathophysiology; Biological components

## Introduction

Marburg virus is a highly pathogenic illness that can cause severe disease and mortality rates of up to 90%. The complexity of the outbreak and its unpredictable nature make it difficult to test new vaccines and treatments. It has no approved treatment or vaccines currently [1]. It was detected initially in 1967 following simultaneous outbreaks in Marburg and Frankfurt in Germany [2].

Marburg virus belongs to *Filoviridae* family. MVD is a rare disease that have the capacity to cause an outbreak with greater fatality rate [3]. The illness begins with fever, chills, abdominal pain, and myalgia. A non-pruritic rash may appear within 5 days after onset. The severe symptoms may lead to vomiting, nausea, abdominal pain, and osteodynia. Symptoms become highly severe and leads to hemorrhage and multiorgan failure [4]. Reporting most number of MVD deaths in the second week of infection and transmission of the disease from one person to another occurs through direct contact with the symptomatic MVD patient, their body fluids and their remains [5].

The reservoir of the MHF virus is not known. Although bats have been thought to be the carrier of the disease [6,7]. The disease has been circulating in the wild since 1967 [3,8-10]. Two large outbreaks were reported in 1998 and 2005 [11]. The former involved 154 cases and killed 125 individuals [12,13]. The later (i.e.) in 2005 outbreak it is believed that the virus infected 374 individuals and killed 329 patients [14]. The low number of recognized infectious diseases and the poor quality of clinical documentation have hindered the assessment of human MHF characteristics [15]. Marburg fever can be diagnosed by RT-PCR for the detection of viral nucleic acids [16].

## Mode of Transmission

Human to Human transmission occurs by direct contact (through broken skin or mucous membrane) with secretions like bodily fluids, blood of infected people and with surfaces & materials contaminated with fluids from infected person [5].

Health care workers are frequently infected when treating patients with suspected or confirmed MVD. Transmission through contaminated injection or needle-stick injuries results in more severe disease, rapid deterioration and probably a higher fatality rate [17].

## Clinical Symptoms and Disease Progression

*Marburg Marburgvirus* is a species in genus *Marburg virus* that is represented by 2 viruses MARV and RAVV respectively [18]. Similar

to other infectious diseases MVD starts off with flu like symptoms such as chills, fever, headache, sore throat, myalgia, joint pain and malaise, 2-21 days after the initial infection. This period is the incubation period of the virus. There are three stages or phases for the progression of the disease.

### Generalization Phase:

Within the first 2-5 days of the primary symptoms patients experience abdominal pain, nausea, vomiting, watery diarrhea and lethargy. This phase of the viral cycle is termed as generalization phase.

### Early Organ Phase:

The disease progresses into the later stage called as early organ phase (5-13 days from the onset of the disease). This phase marks the beginning of the severe stage of the disease. Patient may experience high fever throughout this stage and into the late organ phase. Neurological symptoms displayed by the patient include confusion, agitation, increased sensitivity, seizures. During the later part of the early organ phase, patient may exhibit clear hemorrhagic manifestations such as mucosal bleeding, uncontrolled leakage from venipuncture sites, visceral hemorrhagic effusions, blood in stools and hematemesis. During this stage multiple vital organs like pancreas, liver and kidney are affected Figure 1.

### Late Organ Phase:

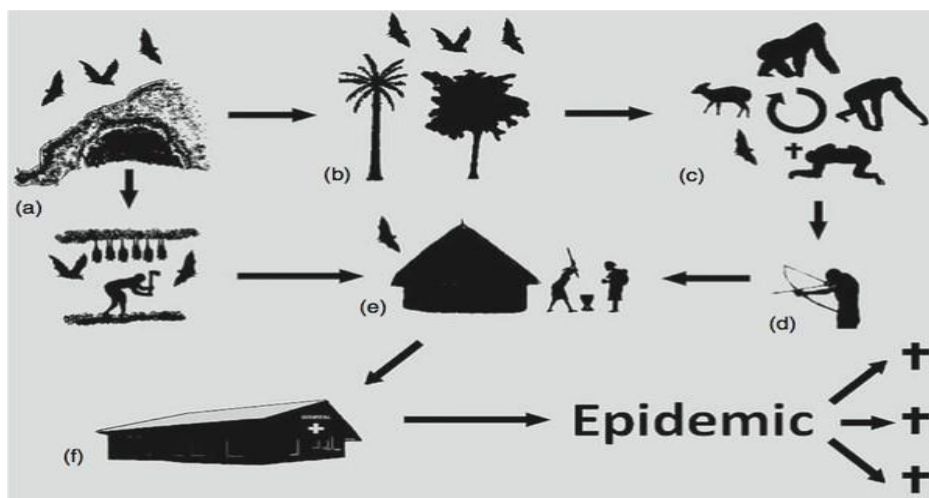
The late organ phase, the third stage of the disease lasts from day 13 until 21 days in the course of disease. In this stage, the patient condition worsens into critical state in which the person experiences convulsions, multiple organ failure, shock, severe metabolic disturbances and diffuse coagulopathy. In this phase multiorgan dysfunction and anuria occurs due to the reduction in circulation as a result of severe dehydration. Patients exhibit neurological symptoms like restlessness, confusion, dementia and coma before death. Spontaneous abortion results in the additional complication in the pregnant patients Figure 2.

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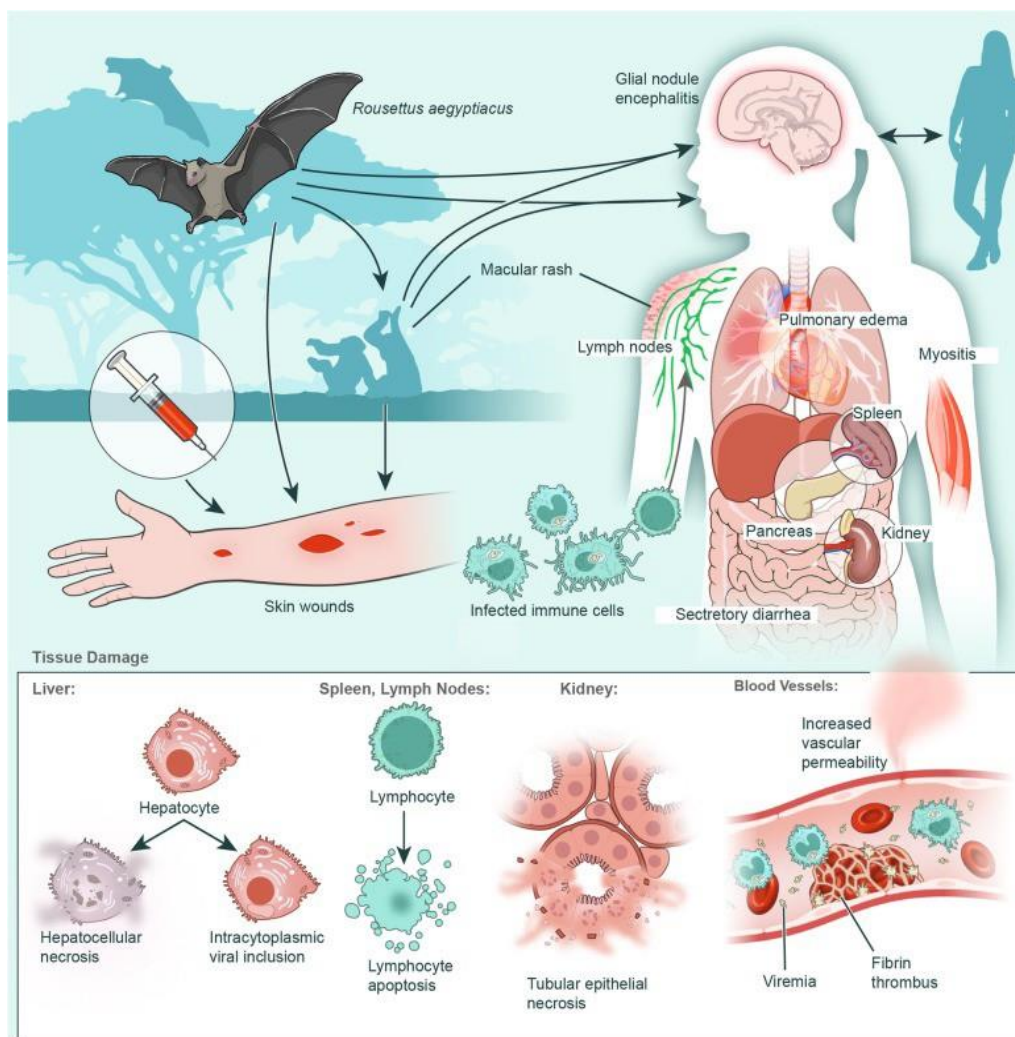
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**Figure 1:** Transmission of Marburg Hemorrhagic fever a) Cave dwelling fruit bats are potential reservoir hosts. Mining and touristic activities in caves are risk factors. b) Trees and oil palm plantations are feeding areas for fruit bats. c) Fecal- Oral transmission between fruit bats, gorilla and chimpanzees. d) Hunting and carcass contact as severe risk factors. e) Spread of virus in villages due to burial rituals. f) Nosocomial infection occurring in hospitals and health care workers.



**Figure 2:** Pathophysiology of Marburg Hemorrhagic Fever.

Increase in alanine and aspartate aminotransferase (ALT and AST) and increased serum creatinine levels indicate hepatic and kidney damage. Lymphopenia, Thrombocytopenia and Disseminated Intravascular Coagulation appear generally within 1<sup>st</sup> week of the symptom. In the next stages of the disease neutrophilia becomes more effective than lymphopenia. Patients either recover from the disease or die because of dehydration, internal bleeding, organ failure or some combination of systemic factors aided by dysregulated immune response. During the recovery phase these patients suffer with complications such as myalgia, arthralgia, hepatitis, ocular disease, asthenia and psychosis.

Autopsies of RAVV infected patients revealed swelling of heart, kidneys, brain, spleen and lymph nodes along with hemorrhage of mucous membrane, soft tissue and various other organs. Tissues examined exhibited some form of hemorrhage and focal necrosis was seen in almost all organs but prominent in lymphatic and liver tissues as well as in testes and ovaries. Damage to the hepatic tissues were severe and there was extensive hepatocellular swelling and degeneration was seen. Basophilic Cytoplasmic Inclusions found in eosinophils near necrotic areas were positive for viral antigen. In spleen there was moderate necrosis in the red and white pulp regions. Red pulp had the deposits of cellular and fibrin debris. Severe necrosis and bleeding were observed in the germinal centers. Despite severe necrosis viral antigens were not found in germinal centers unlike marginal zone of red pulp region and macrophages. Kidneys were swollen, pale and hemorrhagic as well as tubule necrosis and parenchymal damage was also observed. Alveoli of the lungs were congested; hemorrhaged and alveolar macrophages surrounded by fibrin were present which occasionally stained positive for viral antigen.

## Methodology

### Pathology of the Disease

MVD have been studied in the four main species of NHP (Non-Human Primates). These NHP are cynomolgus macaque (*Macaca fascicularis*), rhesus macaque (*Macaca mulatta*), common marmoset (*Callithrix jacchus*), African green monkey (*Cercopithecus aethiops*). Imported African green monkey carrying MARV were the cause of 1967 outbreak in Germany and Yugoslavia.

Cynomolgus and rhesus monkeys are the most common NHP models used in the study of MVD as the pathogenesis is similar to humans. Compared to the rhesus macaque, cynomolgus monkeys infected with MARV experience a more accelerated disease course. Several inoculation routes have been used to challenge NHP with MARV and studies showed that the overall outcome is almost similar in all routes. For instance, in NHP inoculated by the aerosol route but not i.m route exhibited a early infection of the lymphoid tissue of Lungs but, both routes result in a systemic infection with same levels of dissemination. Fever usually appears at 4-6 dpi, proceeded by anorexia, weight loss, and the development of maculopapular rash of different severities. Hemorrhagic symptoms started at 6-7 dpi and resulted in the bleeding from gums and venipuncture sites. At 7-12 dpi, 1-2 days before the human endpoint, animals showed lethargy, diarrhea, hypothermia, lack of reaction or interest in environment and dehydration.

Viral loads in the blood, liver and spleen were the highest but virus was detected in most of the examined tissues including brain indicating a systemic infection. In the blood lymphopenia was seen until 6-7 dpi, Thrombocytopenia was observed in the middle stages of the disease sometimes recovering in the middle to late phase of the disease. Blood

analysis displayed an increase in AST, ALP and total bilirubin indicating liver damage. Increase in the blood urea nitrogen and creatinine levels indicated renal damage. Serum samples were analyzed for cytokine responses to MARV infection which began at 6-8dpi and continued till the human endpoint. Initially there were increased levels of IFN- $\alpha$ , IL-6, MIP-1 $\alpha$ , MIP-1 $\beta$ , MCP-1 and eotaxin. Later in the course of the disease IFN- $\beta$ , IFN- $\gamma$ , IL-1R, IL-2R, IL-8, IL-6, IL-1 $\beta$  and TNF- $\alpha$  were detected at increased levels. This influx of pro and anti-inflammatory cytokines indicates dysregulation of host immune system by MARV.

Detailed necropsy, histology and immunohistochemistry studies showed enlarged, congested and discolored livers which contained increased numbers of mononuclear cells, Kupfer cells containing MARV antigen and debris, eosinophils with viral inclusion bodies and lesions of necrotic hepatocytes. The spleen had MARV antigen through out the red pulp. As the disease progressed necrotic lesions grew in size and number, cellular necrosis and lymphopenia in white pulp, RBC in red pulp and fibrin deposition in Red pulp and marginal zones were observed. Within the lungs hemorrhage was seen along with edema and fibrin in the alveoli which indicates interstitial pneumonia.

## Conclusion

To understand and taking a proper precaution is the main key to put any type of pandemics and diseases at bay. Marburg Hemorrhagic Fever is a type of disease seems to be rare but its fatality is very severe, can cause high mortality and results in to dangerous disease as well. This review might help to provide some awareness regarding the unknown disease and helps the researchers to find a relevant treatment before it becomes a pandemic.

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