**Ebolavirus and Haemorrhagic Syndrome**

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**Abstract:** The Ebola virus is a highly virulent, single-stranded ribonucleic acid virus which affects both humans and apes and has fast become one of the world's most feared pathogens. The virus induces acute fever and death, with haemorrhagic syndrome occurring in up to 90% of patients. The known species within the genus *Ebolavirus* are Bundibugyo, Sudan, Zaire, Reston and Taï Forest. Although endemic in Africa, Ebola has caused worldwide anxiety due to media hype and concerns about its international spread, including through bioterrorism. The high fatality rate is attributed to unavailability of a standard treatment regimen or vaccine. The disease is frightening since it is characterised by rapid immune suppression and systemic inflammatory response, causing multi-organ and system failure, shock and often death. Currently, disease management is largely supportive, with containment efforts geared towards mitigating the spread of the virus. This review describes the classification, morphology, infective process, natural ecology, transmission, epidemic patterns, diagnosis, clinical features and immunology of Ebola, including management and epidemic containment strategies.

**Keywords:** Haemorrhagic Fever, Ebola; Ebolavirus; Hemorrhage; Filoviridae; Pathogenicity Factors; Virulence; Disease Management.

**Ebolavirus** is a single-stranded ribonucleic acid (RNA) virus that has become one of the most feared and virulent pathogens, affecting both humans and great apes. Within a few days, the virus induces acute fever and very often death, and is usually associated with haemorrhagic syndrome in up to 90% of symptomatic individuals. Various species of the genus *Ebolavirus* are known: Bundibugyo, Sudan, Zaire, Reston and Taï Forest. The Reston species does not cause human fatalities, although it kills non-human primates such as chimpanzees and monkeys, as well as other animals like duikers. Whilst Ebola is endemic in regions of Central and West Africa and the Philippines, outbreaks are usually characterised by widespread fear, exacerbated by widespread media hype and concern for the international spread of the virus, including via potential bioterrorism by dissident groups around the world.

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The objective of this integrated review is to describe the classification, morphology, infective process and natural ecology of Ebola, as well as the transmission and epidemic patterns of the virus. This review also details the diagnosis, clinical features and immunology of the virus, including current disease management practices and epidemic containment strategies. A literature review was conducted of peer-reviewed, original research and review papers indexed in PubMed, CINAHL, MEDLINE, Scopus, ScienceDirect and Google Scholar databases and published between January 1990 and October 2014. Selected medical textbooks and online resources that addressed specific aspects related to the Ebola and Marburg viruses were also consulted. Searches were conducted using the following search terms: ‘viral haemorrhagic fevers’, ‘Ebola virus disease’, ‘Filoviridae infection’, ‘ecology’, ‘epidemics’, ‘epidemiology’, ‘diagnosis’, ‘signs and symptoms’, ‘immunology’ and ‘disease management’ in various combinations, in order to retrieve articles published in English that addressed various aspects of Ebola virus disease (EVD).

Classification and Taxonomy

The Ebola virus is classified as a biosafety risk group 4 agent, which is the highest rating on the biosafety scale, due to the high health risk it poses for laboratory personnel and the public.\(^3\) Ebola virus is a lipid-enveloped, single-stranded, negative-sense RNA virus belonging to the genus Ebolavirus in the family Filoviridae and order Mononegavirales.\(^4,7\) Ebola and Marburg viruses are the only filoviruses that cause severe haemorrhagic fever syndrome in humans and non-human primates such as monkeys and chimpanzees.\(^5,8\) The Marburg virus consists of only one strain while the genus Ebolavirus comprises five species, which are named after the country or location in which they were first discovered.\(^1,5,7\) The four species Zaire ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus (formerly Cote d’Ivoire ebolavirus) and Bundibugyo ebolavirus occur in sub-Saharan Africa, whereas the fifth strain, Reston ebolavirus, originated from the Philippines, although it was first isolated in Reston, Virginia, USA.

Morphology

In their innate states, Ebola viruses exist as filamentous and pleomorphic structures, often taking on different shapes. They may occur in long filaments or branched, U-shaped, 6-shaped or circular forms.\(^1,4\) Ebola viruses have a uniform diameter of 80 nm but vary considerably in length, with some as long as 14,000 nm. Structurally, Ebola viruses consist of three layers: a surface glycoprotein layer, a lipid membrane envelope unit and an internal tubular helical nucleocapsid.\(^4,9\) The virus surface layer consists of glycoprotein spikes, each about 7–10 nm long, spaced at about 10 nm intervals. These spikes aid the entry of the virus into host cells by specifically acting as mediators for receptor binding and cell membrane fusion. The second layer, the lipid membrane, surrounds the internal helical nucleocapsid. This, in turn, houses the third layer, the negative-stranded viral genome, which controls viral replication in cells.\(^5,9\)

Infection of Host Cells and Replication

Ebola viruses infect different cell types, including macrophages, fibroblasts, hepatocytes and endothelial cells, mediated by the glycoprotein spikes that play an important role in endocytosis, a process vital for the entry of the virus into host cells. When an Ebola virus enters the host cells, viral replication starts, resulting in numerous new virus particles.\(^5,10\) The process of viral replication is mediated by the synthesis of a positive RNA strand that serves as a template for the production of additional viral genomes. As replication continues, the new viruses continually bud off, attaining their outer lipid membrane from the host cell membrane, killing them instantly.\(^1,3\) As more and more host cells rupture due to the budding of new viruses, cascades of reactions are triggered, resulting in the lethal Ebola haemorrhagic fever (EHF) syndrome.\(^1,4,7\)

Ecology and Distribution

EHF is considered a classical zoonosis because of its ability to be transmitted naturally from vertebrate animals to humans and other mammalian species.\(^5,11\) Despite the fact that non-human primates have repeatedly been a source of infection for humans, the natural reservoir of the Ebola virus still remains unknown, although bats have been repeatedly implicated as being a natural reservoir of filoviruses.\(^5,11,12\) This declaration followed the detection of viral RNA and antibodies in three specific bat species—Hypsipetes monstrosus, Epomops franqueti and Myonycteris torquata—implying that these bats could be natural reservoirs.\(^5,11,12\) The claim that bats play a central role in Ebola transmission followed the discovery that bats infected experimentally did not die.\(^13\) This claim received further support when laboratory observations in Uganda confirmed that...
African fruit bats (Rousettus aegyptiacus) infected naturally with filoviruses looked healthy and did not show any signs of illness, despite testing positive for Marburg virus isolates and yielding live viruses from liver and spleen tissue samples.\textsuperscript{14} This further supports the claim that these bats could harbour filoviruses in between outbreaks.\textsuperscript{4,15} These findings corroborate reports of studies conducted in Gabon and the Democratic Republic of Congo (DRC), which concluded that bats of the order Chiroptera, among them the African fruit bats of the family Pteropodidae and species R. aegyptiacus, naturally host the Ebola and Marburg viruses.\textsuperscript{11,12,15}

Despite these various investigations, to date none of the Ebola virus strains have ever been isolated from naturally infected animals. What is certain though, is that the virus is endemic in rain forests of Africa and the Philippines and, like humans, non-human primates also become infected directly from as yet unknown natural reservoirs.\textsuperscript{4,5,16}

### Modes of Transmission

The primary mode of Ebola transmission from a natural reservoir to humans or primates remains unknown, although most outbreaks appear to be zoonotic.\textsuperscript{3–5} However, despite being zoonotic, filoviruses are neither spread continuously from person to person nor do they remain latent in primates.\textsuperscript{11,15,16} The main secondary mode of transmission from person to person is nosocomial and starts by contact with blood and body fluids from an infected person. Infection then occurs through direct inoculation from contaminated instruments and infected droplets via mucous membranes or after humans have handled infected primates.\textsuperscript{1,3,5}

In hospitals, health workers may become infected through close contact with patients, especially when they do not use proper infection prevention precautions or barrier nursing techniques.\textsuperscript{2,3,16} In community settings, funeral rituals are a key way in which the virus spreads, particularly where there is direct physical contact while performing cultural rituals like shaving and bathing the deceased.\textsuperscript{3,5,17} Infected humans become contagious after developing early signs and symptoms of the disease—particularly a high fever and headache. Generally, larger Ebola outbreaks tend to occur after infected patients enter healthcare systems where barrier nursing and epidemic control practices are inadequate.\textsuperscript{3,5}

### Clinical Manifestations

Clinically, EHF or EVD, which is the human disease caused by any of the five Ebola virus strains, present with a sudden onset of signs and symptoms following an incubation period of two to 21 days.\textsuperscript{1,3,5} The initial signs and symptoms include a severe frontal headache radiating to the occipital region, acute fever exceeding 39 °C, general weakness, incapacitation, cervical and lower back pain and pains of the large joints.\textsuperscript{3–5} On physical examination, Ebola patients typically look very sick and are often lethargic, presenting frequently with a ‘ghost face’, (i.e. an expressionless face with deep-set eyes). These signs and symptoms are followed by rapid and severe weight loss due to the loss of appetite, and dysphagia resulting from very painful throat lesions and severe disease symptoms.\textsuperscript{16,18,19}

After two to three days, patients begin to experience gastrointestinal symptoms, including severe, cramping abdominal pain; haematemesis or vomiting blood; nausea, and bloody diarrhoea.\textsuperscript{2,3,5} By the fourth day, patients frequently experience a severe sore throat, commonly perceived as a ‘lump’ in the throat, further worsening the dysphagia.\textsuperscript{5,16,18} By the fifth day, patients present with conjunctivitis, chest pain, coughing, shortness of breath, nasal discharge, dehydration and haemorrhagic symptoms, which may vary from melaena (dark-brown bloody stool) to a slow overt oozing of blood from the gums in severe cases.\textsuperscript{3–5}

After six to eight days, there is involvement of the central nervous system, manifested by somnolence, delirium and coma.\textsuperscript{3–5} There is also severe metabolic disturbance and diffuse coagulopathy.\textsuperscript{4,9} This period also marks a bimodal peak of the prognostic disease pattern, characterised by a binary phenomenon where patients either markedly improve or deteriorate further and then die from multiple organ and system failure and shock.\textsuperscript{18,20}

In non-fatal cases, the symptoms are generally less severe, except that the fever persists for several days. These patients begin to show impressive signs of recovery typically at the turn of the first week, a period associated with the appearance of a humoral antibody response.\textsuperscript{5} However, in fatal cases, the clinical picture is more acute with signs and symptoms appearing early in the first week.\textsuperscript{5,9} As the week progresses, severely sick patients may bleed from the nose, gums, vagina, anus, urethra and injection sites and may even experience the overt vomiting of blood.\textsuperscript{3–5} Other patients develop a pruritic, generalised maculopapular rash, jaundice, tinnitus, haematuria, vertigo, amenorrhoea, oliguria, hiccoughs and lymphadenitis.\textsuperscript{4,16,19} Many severely
ill patients will also develop hepatosplenomegaly, pancreatitis and facial oedema, and typically die between day six and 16 due to multiple organ and system failure and hypovolemic shock.4,9

In patients who survive, recovery is slow, usually lasting several weeks to several months, and is associated with severe incapacitation, weight loss, a persistent headache, poor appetite, body weakness and a reduced libido (among other symptoms). Survivors may also experience psychotic disturbances that typically last between three and nine months after the infection, characterised by episodes of mental confusion, anxiety, fatigue, depression, restlessness and aggressiveness.3–5 In pregnant women, miscarriages are common and clinical findings suggest an increased risk of death among the children of infected mothers, possibly due to transmission of the Ebola virus to their babies, either through breast milk or by direct maternal contact.4,5

Diagnostic Criteria

Clinical diagnosis of EVD is indicated after the occurrence of clusters of cases with prodromal fever, bleeding tendencies and person-to-person transmission, which is frequently associated with prostration, lethargy, wasting, diarrhoea and skin rashes.2–4 Laboratory diagnosis of EVD may be confirmed using acute-phase serum by measuring the level of the specific immunological response or by detecting viral antigens and genomic RNA or isolating viruses.3–5 Immunoglobulin M (IgM) and immunoglobulin G (IgG), the antibodies formed against EVD, can be measured using an immunofluorescence assay (IFA), immunoblot or enzyme-linked immunosorbent assay (ELISA).2,3 The viral antigen and genomic RNA may also be detected using immunohistochemistry, IFA, ELISA and reverse transcription-polymerase chain reaction techniques.2,3 Direct detection of virus particles may be undertaken using electron microscopy.3–5 However, as a general rule and to ensure safety, it is vitally important that all laboratory diagnoses occur only in biosafety level 4 facilities, ensuring maximum biological containment. This is in order to reduce the risk of infection of laboratory personnel.3–5

Immunological Response

Humoral response to Ebola viruses can be detected as early as 10–14 days after infection. The specific antibodies formed against the viruses are directed primarily against the viral surface glycoproteins.4,21 A rapid, high-level, immunological response targeting the viral glycoprotein coat is thought to lead to patient survival.4,21 This observation is based on the findings of studies conducted on survivors of the 1996 Ebola outbreak in Gabon, which concluded that an early immune response appeared to be key to surviving an Ebola infection.4,22–23

In the early stages of infection, survivors tend to produce increased levels of IgG and IgM, which target the viral coat and are associated with a strong inflammatory response, including interleukin β, interleukin 6 and tumour necrosis factor-α. This is followed by clearance of circulating viral antigens and sustained activation of the cytotoxic T cell pathway.4,22–24 Studies further show that patients who die of Ebola have higher concentrations of interferon-γ and their peripheral blood cells show more extensive apoptosis (programmed cell death) compared to that of survivors.4,24 Early and well-regulated inflammatory responses characterised by low levels of interferons and reactive oxygen and nitrogen species indicate higher chances of recovery from Ebola.4,25

In contrast, a defective antibody response associated with increased blood concentrations of nitric oxide, resulting from an inappropriate response to the virus particles, is associated with death.4,21 Similarly, studies on serial plasma indicate that survival appears to be related to orderly and well-regulated humoural and cellular responses.26 These findings suggest that impaired humoral responses with absent specific IgG and barely detectable IgM seem to indicate failure to control virus replication, thus leading to death.25,26 These findings imply that the absence of a vigorous immune response and lymphopaenia, or low levels of T cells due to an ineffective immunological response, characterise individuals who do not survive Ebola.4,26,27 These studies further suggest that both cellular and humoral responses are essential in protecting patients against Ebola infection. In the same way, the levels of immunological response that patients generate determine whether they will survive or succumb to EVD.

Therapeutic Interventions and Vaccination

While several candidate treatment options are being tested, no specific chemotherapeutic or immunisation strategy yet exists for Ebola.4,26,27 The danger posed by Ebola has been compounded by the discovery of newer virus strains and the existence of Ebola virus antibodies in fruit bats in Bangladesh, which extends the horizon of future Ebola infection far beyond...
Africa and the Philippines.\textsuperscript{7,4,12} Although no specific therapy exists, convalescent serum has been used in critical situations. This was the case during the 1995 \textit{Zaire ebolavirus} outbreak in Kikwit, DRC, when eight Ebola patients received blood transfusions from Ebola survivors, seven of whom recovered.\textsuperscript{28} In the current outbreak in West Africa, an experimental serum has been successfully used to treat five medical workers—two Americans and three West Africans—following approval by a World Health Organization panel of experts.\textsuperscript{29} The sixth recipient, a Spanish priest, died despite receiving ZMapp\textsuperscript{TM}, the experimental drug being co-developed by Mapp Biopharmaceutical, Inc. (San Diego, California, USA) and Defyrus, Inc. (Toronto, Canada).\textsuperscript{30}

The ZMapp\textsuperscript{TM} experimental drug is classified as a humanised monoclonal antibody, harvested from the serum of Ebola-infected mice with major components produced in the \textit{Nicotiana benthamiana} strain of tobacco. The drug works by attacking specific proteins on the surface of the Ebola virus, thereby reducing its virulence.\textsuperscript{29,30} Another drug currently undergoing human testing is TKM-Ebola, which has been developed by Tekmira Pharmaceuticals Corp. (Burnaby, British Columbia, Canada). TKM-Ebola is a systemically delivered, small interfering RNA therapeutic that is administered using novel lipid nanoparticle delivery technology. TKM-Ebola interrupts the genetic coding of the Ebola virus by blocking the expression of the L proteins of the RNA polymerase of the Ebola virus, thus hampering replication of the virus within the host cells.\textsuperscript{31}

Since there is still no specific therapy in response to EVD, the most appropriate treatment during outbreaks is supportive therapy. This involves balancing patients’ electrolytes, maintaining optimal oxygenation and blood pressure levels and ensuring their adequate nutrition and comfort.\textsuperscript{5,5,30} In addition, there should be prompt treatment of any complications such as super-infections and dehydration to prevent cardiovascular collapse and renal insufficiency.\textsuperscript{32} Further, it is recommended that while providing this supportive therapy, caregivers should adhere to strict barrier nursing practices, which are characterised by careful handling of blood and body fluids. Finally, it must be ensured that deceased individuals are buried promptly in order to prevent transmission of the virus to others.

Conclusion

Ebola virus infection, and the haemorrhagic syndrome that ensues, leads to a high rate of case fatalities largely due to the lack of specific post-exposure prophylactic treatments or a vaccine. The disease process is characterised by rapid immune suppression and multisystem involvement, leading to the impairment and eventual collapse of various organs and systems, and resulting in hypovolemic shock and death. Current patient management practices mainly involve supportive care, including meeting patients’ needs for hydration, electrolyte balance, nutrition and comfort. This care should be provided in designated health facilities with isolation units so as to limit the further spread of the Ebola virus. In summary, in the absence of specific treatments, the most cost-effective outbreak management and containment interventions are preventative in nature and are largely aimed at breaking the human-to-human infection transmission cycle at both institutional and community levels. These measures include early case identification, patient isolation, use of personal protective equipment and safe burial procedures, as well as on-going community education and mobilisation.

References


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