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Ebola Virus Disease: A Perspective for the United States

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ABSTRACT

Ebola virus caused an epidemic of unprecedented extension in West Africa. There was concern that the outbreak would not be controlled for a prolonged period of time. Two cases of infected returning travelers have been reported in the US. One of the cases has been associated with secondary transmission and other infected subjects have been repatriated for treatment. This article reviews the etiology, pathogenesis, transmission, clinical manifestations, diagnosis, treatment, and prevention of the disease with emphasis on the identification and management in the US.

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KEYWORDS: Diagnosis; Ebola; Filovirus; Prevention; Treatment

The recent repatriation of several health care workers affected with Ebola virus disease to the US and the arrival of an infected traveler from Liberia and an infected health aid worker from Guinea have galvanized the interest in a disease that is ravaging West Africa. This article summarizes current knowledge and perspectives on Ebola, and pretends to be a primer for clinicians working in the US.

ETIOLOGY

The Ebola virus, named after a tributary of the River Congo, belongs to the family *Filoviridae*. *Filoviridae* is a family of long filamentous viruses that include 3 genera: *Cuevavirus*, *Marburgvirus*, and *Ebolavirus*. The last 2 are pathogenic in humans.

There are 5 species in the genus *Ebolavirus*: Taï Forest (previously known as Ivory Coast), Sudan, Zaire, Reston, and Bundibugyo.[1] Sudan and Zaire are the species associated with higher lethality. Reston seems to cause asymptomatic disease in Asia. The species *zaire* is causing the current epidemic in West Africa.

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The Ebola virus genome contains a nonsegmented, single-stranded linear RNA molecule of negative polarity. The full viral sequence of the genome based on isolates from previous outbreaks is available online.[2] The RNA genome is wrapped around proteins NP, VP35, VP30, and L. Surrounding the nucleocapsid there is a lipid envelope with embedded glycoproteins. Between the outer envelope and the nucleocapsid there are additional viral proteins VP40 and VP24. The **Table** shows the function of each protein and **Figure 1** shows the structure of the virus.

PATHOGENESIS

Although previous studies using modified Ebola virus have suggested clathrin-mediated endocytosis or caveolin-mediated endocytosis as the entry mechanism into the cell, experiments with the wild virus showed macropinocytosis, a form of endocytosis associated with cell surface ruffling, as the primarily internalization process via interaction of viral glycoproteins and cell surface receptors.[3]

Once inside the cell, the viral polymerase complex proceeds along the ribonucleoprotein initiating the transcription. It is likely that VP24 holds the ribonucleoprotein in a condensed state, preventing the complex from proceeding along the template. On the other hand, VP30 has the opposite effect, favoring the viral genome transcription.[4]

The viral polymerase complex has 2 functions: transcribing the negative single-stranded genome into monocistronic pieces of positive mRNA and replicating the

positive-stranded mRNA to synthesize the viral progeny genome.

Recently, it has been reported that VP40 has a crucial role in viral replication. Contrary to the biology dogma that a gene encodes a single protein with a unique tridimensional shape, it seems VP40 can assume 3 different shapes: one while the virus travels through the infected cells, at the time of transcription (serving as a regulator), and as an important component of the liner structure in the newly formed virions, thus helping with the budding and release of the viruses from the cell.[5]

After entering the body via small lesions in the skin or mucous membranes, the virus targets monocyte/macrophages and dendritic cells. Interaction of the virus with the immune system may actually be detrimental by triggering an antibody-dependent enhancement of the Ebola virus infection: complexes formed by virus, antibodies, and C1 may actually promote endocytosis of the organism, and may potentially explain the virulence of certain strains.[6]

After acquisition, the infection spreads via the lymphatic vessels to regional lymph nodes and from there, causes viremia infecting the spleen, liver, and adrenal glands (**Figure 2**).

CLINICAL SIGNIFICANCE

- Ebola virus disease (EVD) is transmitted by direct contact of infected fluids with skin lesions or mucous membranes.
- EVD is highly contagious, but stringent use of personal protective equipment, contact follow-up, and infection control measures can contain outbreaks.
- EVD carries high mortality, mainly due to delayed care and inefficient foreign health systems.
- There are no vaccines or specific treatment for Ebola virus, however, supportive treatment is of upmost importance.

Macrophages and dendritic cells play a key role in the pathogenesis of Ebola virus infection by secreting cytokines, chemokines, and other immune mediators. The consequences of the release of those substances include: mobilization of neutrophils and monocytes, which, in turn, contribute to a spiraling "inflammatory storm," lymphocyte apoptosis, necrosis of hepatocytes, endothelial damage, and coagulopathy, eventually leading into septic shock and disseminated intravascular coagulation.[7]

Very limited information is available on the tissue pathology of Ebola virus; similar to infections caused by Marburg virus, extensive liver necrosis with large intracytoplasmatic eosinophilic inclusion bodies seems to be the most common postmortem finding.

EPIDEMIOLOGY

There is evidence that bats serve as a reservoir for Ebola virus. The initial evidence came from epidemiological observation of cases of Marburg virus infection associated with mining. Subsequently, antibodies against Ebola virus have been detected in several fruit bat species from Africa and Asia, however, only a Marburg virus has ever been isolated from a bat (*Rosettus aegyptiacus*). Laboratory experiments have

Table Protein Components of the Ebola Virus and Their Function

Protein	Location	Function
L	Wrapped around viral RNA	Caps and polyadenylates mRNAs
NP	Wrapped around viral RNA	Needed for the formation of the nucleocapsids
VP24	Between the outer envelope and the nucleocapsid	Reduces transcription and replication of the virus genome by direct association with the ribonucleoprotein complex
VP30	Wrapped around viral RNA	Essential activator of viral transcription
VP35	Wrapped around viral RNA	Blocks the virus-induced phosphorylation and activation of interferon regulatory factor 3, a transcription factor critical for the induction of alpha/beta interferon expression
VP40	Between the outer envelope and the nucleocapsid	Multipurpose protein that regulates transcription and serves as a component of the liner structure in newly formed virions

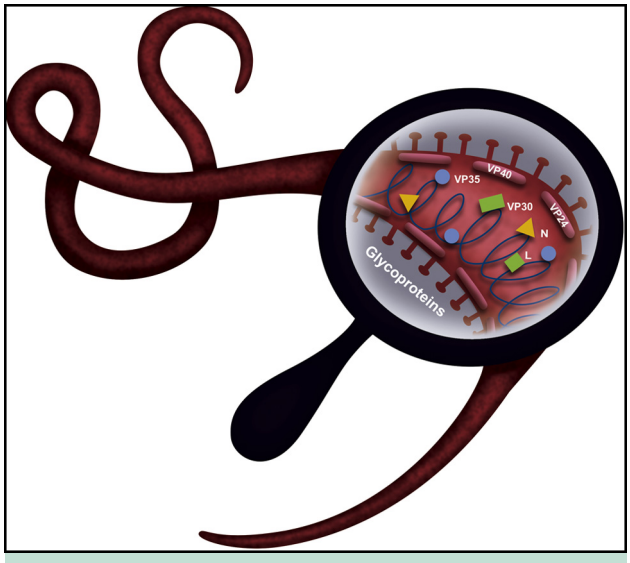

Figure 1 Structure of the Ebola virus. The negative single stranded RNA of the Ebola virus is wrapped around proteins NP, VP35, VP30, and L. Additional proteins VP40 and VP24 lie between the nucleocapsid and the lipid. Glycoproteins spike from the envelope.