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REVIEW ARTICLE

Ebola virus disease in nonendemic countries

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The 2014 West African outbreak of Ebola virus disease was unprecedented in its scale and has resulted in transmissions outside endemic countries. Clinicians in nonendemic countries will most likely face the disease in returning travelers, either among healthcare workers, expatriates, or visiting friends and relatives. Clinical suspicion for the disease must be heightened for travelers or contacts presenting with compatible clinical syndromes, and strict infection control measures must be promptly implemented to minimize the risk of secondary transmission within healthcare settings or in the community. We present a concise review on human filoviral disease with an emphasis on issues that are pertinent to clinicians practicing in nonendemic countries.

Introduction

The largest outbreak of Ebola virus disease (EVD) in history has renewed interest in filoviruses and has provided an unprecedented impetus to the development of new therapeutics and vaccines for this highly lethal infection. Hemorrhagic fevers caused by Ebola and Marburg viruses—also collectively known as filoviral hemorrhagic fever (FHF)—previously caused dramatic, albeit limited, outbreaks in central Africa. Their impact on global health was rather small (except in the realm of biological warfare research) because of the high mortality rate, lack of effective antiviral therapies and vaccines, and potential for person-to-person transmission.[1] The 2014 West African outbreak of EVD proved that these filoviruses should no longer be considered as merely regional problems. A short review of EVD and its clinical relevance to the nonendemic countries is presented. The current epidemic is caused by *Zaire ebolavirus*; however, references will also be made to the related *Marburgvirus*, which shares many virological, clinical, and epidemiological characteristics.

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Virology and pathogenesis

The order *Mononegavirales* consists of enveloped, nonsegmented, negative-sense, single-stranded RNA viruses. The Family *Filoviridae* comprises three genera: *Cuevavirus*, *Ebolavirus*, and *Marburgvirus*.[2] In 2011, the sole species of *Cuevavirus*, *Lloviu cuevavirus*, was described. It was discovered during an investigation of massive die-offs of *Miniopterus schreibersii* bats in France, Spain, and Portugal in 2002; and the virus was detected in bat carcasses collected from northern Spain.[3] The genus *Ebolavirus* (*EBOV*) includes five species, *Bundibugyo ebolavirus* (*BEBOV*), *Reston ebolavirus* (*REBOV*), *Sudan ebolavirus* (*SEBOV*), *Taï Forest ebolavirus* (*TAFV/CIEBOV*; previously called *Ivory Coast ebolavirus* or *Côte d'Ivoire ebolavirus*), and *Zaïre ebolavirus* (*ZEBOV*). The genus *Marburgvirus* consists of one species: *Marburg marburgvirus* (*MARV*).

The name "filovirus" describes a unique morphological characteristic of the viruses. The virions are generally filamentous (in Latin, *filum* means "thread") with a diameter of approximately 80 nm and a highly variable length of 800–14,000 nm. They may also appear as branched filaments, short rods, U-shaped, circular, or hairpin-shaped.[4,5] The genomes of *EBOV* and *MARV* are approximately 19 kb and consist of seven genes (from the 3′ to 5′ end): nucleoprotein (NP), VP35, VP40, glycoprotein (GP), VP30, VP24, and RNA-dependent RNA polymerase (L).[4,6] *Ebolavirus* expresses an additional protein through transcriptional editing of the GP gene. In addition to GP, a smaller secreted glycoprotein (sGP) is produced and excreted extracellularly.[4,7]

At 20°C, *EBOV* and *MARV* are stable and resist desiccation, which probably explains their stability in aerosol droplets.[7,8] They are however inactivated by heat and common disinfectants such as detergents, phenolics, and hypochlorites.[7] The usual heat treatment of clinical samples at 56°C for 30 minutes may fail to render the specimen noninfectious. Thermal inactivation at 60°C for 60 minutes or 75°C for 30 minutes is necessary.[9–11] Gamma irradiation readily inactivates the filoviruses, although this method may not be readily available in routine clinical or laboratory settings.[12]

The genetics and molecular biology of the filoviral genome have been previously reviewed.[4,7] In addition to the essential functions for viral replication and assembly, many viral proteins exert their effects on the host immune system and may contribute to the pathogenesis of the infection (Table 1).[4,7,13–15,26,191,192] For example, VP35 and VP24 inhibit the normal antiviral activities of type I interferons at multiple steps of the pathway, whereas sGP may contribute to immune evasion by absorbing anti-GP antibodies (i.e., antigenic subversion).[13–15] Because of the essential roles of many viral proteins in replication and assembly, some viral proteins (e.g., VP30 and VP35) are potential targets for antiviral agent development.[16,17]

In recent years, the pathogenesis of FHF has been better elucidated.[18] Filoviruses are pantropic with the ability to infect different host cell types. The initial cells in which the viruses replicate are likely dendritic cells, macrophages, monocytes, and Kupffer cells at the site of entry. A large number of lectins (e.g., DC-SIGN and L-SIGN) and immunorecognition receptors [i.e., triggering receptors expressed in myeloid cells (TREM)] can serve as receptors for the viruses.[19] After the initial multiplication in the aforementioned cell types, the viruses are transported to the reticuloendothelial system (e.g., lymph nodes, spleen, liver) and other organs where infection of other cell types occur. The resulting massive necrosis and end organ damage are reflected in the histopathology of human and primate infection models with necrosis in the liver, kidneys, lungs, lymphoid tissues, and other organs.[20,21] In addition, various mechanisms contribute to the development of coagulopathy and disseminated intravascular coagulation, which is a hallmark of viral hemorrhagic fevers. Patients with FHF develop significant platelet dysfunction (which is not merely accountable for by thrombocytopenia), and this is contributed to by platelet activation and decreased vascular endothelium production of prostacyclin.[22] Another important target in the pathogenesis of FHF is the endothelium. Human and primate endothelial cells are susceptible to infection by *EBOV*, although direct cyopathic effects are not an important factor in the development of vasculopathy and coagulopathy.[23] The release of vasoactive

Table 1 Filovirus genes and their functions.[4,7,13–15,26,191,192]

Viral genes and proteins	Function in the viral life cycle	Effects on hosts
Nucleoprotein	Viral nucleocapsid assembly; budding	May be a main virulence mechanism
VP35	Viral nucleocapsid assembly	Type I interferon antagonist
VP40 (matrix protein)	Viral nucleocapsid assembly; budding; structural integrity of viral particles	
Glycoprotein	GP: a transmembrane protein; viral attachment to and entry into host cells Likely receptors: cell surface lectins	GP: induces proinflammatory cytokines sGP: possibly contributes to immune evasion by antigenic subversion
VP30	RNA-binding protein, stabilizes nascent RNA; activates RNA transcription; regulates the replication cycle	
VP24 (matrix protein)	Viral assembly; budding	Inhibits interferon signaling and activation May be a main virulence mechanism
RNA-dependent RNA polymerase (L)	Viral transcription	

GP = glycoprotein; NP = nucleoprotein; sGP = secreted glycoprotein.