

EMERGING (OR NOT) INFECTIOUS DISEASES

Ebola

- Member of genus Filoviridae
- Ebola and Marburg
- Among the most virulent pathogens of humans
- Mortality rate in West Africa now is 70%
- Has approached 90% in past outbreaks



Filoviruses

- Ebola and Marburg also classified as hemorrhagic fever viruses based on their clinical manifestations, which include coagulation defects, a capillary leak syndrome, and shock
- 5 different species
- Zaire species responsible for current outbreak in West Africa
- The filoviruses were first recognized in 1967, when the inadvertent importation of infected monkeys from Uganda into Germany and Yugoslavia resulted in explosive outbreaks of severe illness among vaccine plant workers who came into direct contact with the animals by killing them, removing their kidneys, or preparing primary cell cultures for polio vaccine production. Since that time, with the exception of a few accidental laboratory infections, all cases of filoviral disease have occurred in sub-Saharan Africa. The frequency of recognized outbreaks has been increasing since 1990.

Recent Outbreak

- Although most previous Ebola outbreaks occurred in Central Africa, this outbreak started in the West African nation of Guinea in late 2013 and was confirmed by the World Health Organization in March 2014. The initial case was a two-year-old child in Guinea, who developed fever, vomiting, and black stools, without other evidence of hemorrhage. The outbreak subsequently spread to Liberia, Sierra Leone, Nigeria, and Senegal
- The magnitude of the outbreak, especially in Liberia and Sierra Leone, has probably been underestimated; this is due in part to individuals with Ebola virus disease being cared for outside the hospital setting

Recent Outbreak

- As of September 28, 2014, the cumulative number of probable, suspected, and laboratory-confirmed cases attributed to Ebola virus is 7178, including 3338 deaths. However, Nigeria and Senegal have not reported any new cases since September 5, 2014, and August 29, 2014, respectively.
- On September 30, 2014, the first travel-associated case of Ebola was reported in the United States. An individual who traveled from Liberia to Dallas, Texas first developed clinical findings consistent with Ebola virus disease approximately five days after arriving in the United States

- Perhaps the greatest mysteries regarding the filoviruses are the identity of their natural reservoir and the mode of transmission from the reservoir to wild apes and humans
- Bats have long headed the list of suspects, because they have been present in large numbers at the sites of several filovirus outbreaks and are known to maintain other pathogenic RNA viruses, such as rabies.
- Mosquitos not suspected

- Experiments in laboratory animals indicate that filoviruses can initiate infection via many routes, including ingestion, inhalation, or passage through breaks in the skin. Nonhuman primates can be infected with Marburg or Ebola virus through droplet inoculation of virus into the mouth or eyes, suggesting that cases of human infection result from the inadvertent transfer of virus to these sites from the patient's own contaminated hands
- Person-to-person transmission occurs through direct contact of broken skin or unprotected mucous membranes with virus-containing body fluids (eg, blood, vomitus, urine, feces, semen, and probably sweat) from a person who has developed signs and symptoms of illness. This mode of transmission may lead to outbreaks.

- ●One type of direct contact that leads to transmission is the ritual washing of Ebola victims at funeral. An epidemiologic study found that family members were only at risk of infection if they had physical contact with sick individuals or their body fluids, or helped to prepare a corpse for burial.
- ●Healthcare workers are at risk of infection if they care for a patient with Ebola or Marburg virus disease without appropriate protective measures. Over 370 healthcare workers have become infected during the epidemic in West Africa, **due in large part to shortages of personal protective equipment and/or exposure to patients with unrecognized Ebola virus disease.** Approximately 50 percent have died.

- Ebola virus disease is rarely, if ever, spread from person to person by the respiratory route
- Although aerosolized filoviruses are highly infectious for laboratory animals, in humans, airborne transmission has only been reported among healthcare workers who were exposed to aerosols generated during medical procedures.

- Prior to the epidemic in West Africa, outbreaks of Ebola and Marburg virus disease were typically controlled within a period of weeks to a few months. This outcome was generally attributed to the relatively inefficient person-to-person transmission of the virus in areas of the African rainforest where population density was low and residents rarely traveled far from home. However, the epidemic in West Africa has shown that Ebola virus disease can spread rapidly and widely as a result of the extensive movement of infected individuals (including undetected travel across national borders) and the avoidance and/or lack of adequate medical isolation centers

- **PATHOGENESIS** — Ebola virus enters the body through mucous membranes, breaks in the skin, or parenterally. The pathogen infects many cell types, including monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, and epithelial cells. Because of the difficulty of performing clinical studies under outbreak conditions, almost all data on the pathogenesis of Marburg and Ebola virus diseases have been obtained from laboratory experiments employing mice, guinea pigs, and a variety of nonhuman primates.

Pathogenesis

- Cell entry and tissue damage — Whatever the point of entry into the body, macrophages and dendritic cells are probably the first cells to be infected. Filoviruses replicate readily within these ubiquitous "sentinel" cells, causing their necrosis and releasing large numbers of new viral particles into extracellular fluid. Spread to regional lymph nodes results in further rounds of replication, followed by dissemination of virus to dendritic cells and fixed and mobile macrophages in the liver, spleen, thymus, and other lymphoid tissues.

Pathogenesis

- **Systemic inflammatory response** — In addition to causing extensive tissue damage, filoviruses also induce a systemic inflammatory syndrome by inducing the release of cytokines, chemokines, and other proinflammatory mediators from infected macrophages and other cells

Pathogenesis

- **Coagulation defects** — The coagulation defects seen in Marburg and Ebola virus disease are also induced indirectly. Virus-infected macrophages synthesize cell-surface tissue factor (TF), triggering the extrinsic coagulation pathway. Proinflammatory cytokines also induce macrophages to produce TF. The simultaneous occurrence of these two stimuli helps to explain the early appearance, rapid development, and ultimate severity of the coagulopathy in filovirus infection
- **Impairment of adaptive immunity** — Failure of adaptive immunity, through impaired dendritic cell function and lymphocyte apoptosis, helps to explain how these viruses are able to cause severe, frequently fatal illness

- Incubation period — Patients with Ebola virus disease typically have an abrupt onset of symptoms 8 to 10 days after exposure (range 2 to 21 days). The incubation period for the individual patient depends, in part, upon the type of exposure (eg, approximately 6 days for percutaneous exposure versus 10 days for contact exposure). **There is no evidence that asymptomatic persons still in the incubation period are infectious to others.** However, all symptomatic individuals should be assumed to have high levels of virus in the blood and other body fluids and appropriate safety precautions should be taken

Signs and Symptoms

- **Nonspecific flu-like symptoms** — Ebola and Marburg hemorrhagic fever typically begin with the abrupt onset of fever, chills, and general malaise. Other signs and symptoms include weakness, anorexia, severe headache, and pain in the muscles of the trunk and lower back. High fever may be accompanied by relative bradycardia, as seen in typhoid fever. A nonproductive cough and pharyngitis, with the sensation of a lump or "ball" in the throat, are also frequently present.
- **Rash** — Some patients develop a diffuse erythematous, nonpruritic maculopapular rash by day five to seven of illness. The rash usually involves the face, neck, trunk, and arms, and can desquamate.
- **Gastrointestinal** — Gastrointestinal signs and symptoms usually develop several days after the initial presentation. These include watery diarrhea, nausea, vomiting, and abdominal pain.
- **Hemorrhage** — Bleeding is often not observed in the early phase of illness, but may manifest later in the course of disease as petechiae, ecchymosis/bruising, oozing from venipuncture sites, and/or mucosal hemorrhage. Frank hemorrhage is seen most commonly in the terminal phase of illness.
- **Other findings** — Patients with Ebola virus disease can present with additional findings such as hiccups, chest pain, shortness of breath, headache, confusion, seizures, and/or cerebral edema. Conjunctival injection and dark red discoloration of the soft palate are common physical findings. Pregnant women may experience spontaneous miscarriages

Laboratory Findings

- **Leukopenia** — Leukopenia usually presents as lymphopenia and is then followed by an elevated neutrophil count, with an increased percentage of immature forms.
- **Thrombocytopenia** — Platelet counts are usually in the range of 50,000 to 100,000/microL . Platelet counts typically reach a nadir around day six to eight of illness.
- **Transaminitis** — Because filoviruses can cause multifocal hepatic necrosis, blood chemistry tests usually demonstrate elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, with the former typically increasing more than the latter
- **Coagulation abnormalities** — Prothrombin (PT) and partial thromboplastin times (PTT) are prolonged and fibrin degradation products are elevated, consistent with disseminated intravascular coagulation (DIC). These changes are most prominent in severe and fatal cases.
- **Renal abnormalities** — Proteinuria is a common finding, and renal insufficiency occurs with progression of illness

Levels of Exposure

- High-risk exposure — The CDC recommends medical evaluation using infection control precautions for all persons with onset of fever within 21 days of having a high-risk exposure. The same approach is indicated for persons with a high-risk exposure **without** a fever if there are other compatible clinical symptoms present and laboratory findings are abnormal (ie, platelet count <150,000 cells/microL and/or elevated transaminases) or unknown.
- A **high-risk exposure** includes any of the following:
 - ● Percutaneous or mucous membrane exposure to blood or body fluids of a person with Ebola virus disease
 - ● Direct skin contact with or exposure to blood or body fluids of a patient with Ebola virus disease without appropriate personal protective equipment.
 - ● Processing blood or body fluids of a confirmed patient with Ebola virus disease without appropriate personal protective equipment or standard biosafety precautions
 - ● Direct contact with a dead body without appropriate personal protective equipment in a country where an Ebola virus disease outbreak is occurring

Levels of Exposure

- Low-risk of exposure — The CDC recommends medical evaluation using infection control precautions for persons with low-risk of exposure who develop fever with or without other clinical findings.
- A **low-risk exposure** includes:
 - Household contact with an Ebola virus disease patient
 - Other close contact with an Ebola virus disease patient in health care facilities or community settings

Medical Therapy - ZMapp

- ZMapp, being developed by Mapp Biopharmaceutical Inc., is an experimental treatment, for use with individuals infected with Ebola virus. The product is a combination of three different monoclonal antibodies that bind to the protein of the Ebola virus
- Used on two health care workers returning to the US. Both lived. Used on two others who died, probably because of the late progress of the disease at the time of administration.

Medical Therapy

- brincidofovir, a broad-spectrum antiviral that has shown promise against Ebola in test tubes and is now being tested in animals, and has been administered to the patient in Dallas. It has not been widely tested against Ebola in humans.
- The drug's manufacturer, North Carolina-based Chimerix, announced that it has received special permission from the Food and Drug Administration to provide the drug to Ebola patients. Requests for the special permission came from patients' doctors

Summary

- The filoviruses, Ebola and Marburg, are among the most virulent human pathogens. Case-fatality rates in large epidemics in central Africa have reached 80 to 90 percent.
- ●Ebola and Marburg viruses are also classified as "hemorrhagic fever viruses" based on their clinical manifestations, which include coagulation defects, a capillary leak syndrome, and shock.
- ●With the exception of the first outbreak in Marburg, Germany, and a few subsequent accidental laboratory infections, all cases of filoviral disease have occurred in sub-Saharan Africa.
- ●The largest outbreak of Ebola virus disease is currently occurring in West Africa and is caused by the Zaire species of the virus. This outbreak started in the West African nation of Guinea in late 2013 and was confirmed by the World Health Organization in March 2014. The outbreak subsequently spread to Liberia, Sierra Leone, Nigeria, and Senegal. On September 30, 2014, the first travel-associated case of Ebola was reported in the United States. As of October 2014, over 7000 confirmed, probable, or suspected cases and over 3300 deaths have been reported.
- ●Person-to-person transmission requires direct contact with blood or other virus-containing body fluids.

Summary

- The reservoir host of the filoviruses is not known. Evidence is accumulating that various bat species serve as a source of infection for both humans and wild primates.
- ●In addition to causing extensive tissue damage, filoviruses also induce a systemic inflammatory syndrome by causing the release of cytokines, chemokines, and other proinflammatory mediators from infected macrophages.
- ●The incubation period is typically 8 to 10 days, but can range from 2 to 21 days.
- ●Patients with Ebola and Marburg virus disease usually have an abrupt onset of non-specific symptoms, such as fever, malaise, and myalgias. As the illness progresses, patients develop worsening prostration, stupor, and hypotension. Signs of impaired coagulation generally remain limited to conjunctival hemorrhages, easy bruising, and failure of venipuncture sites to clot.
- ●Ebola virus can persist for some time in certain bodily fluids, such as semen and breast milk. In one known instance, viral persistence in semen led to virus transmission through sexual contact.