Ebola Virus: Another Challenge from the Deadly Viral Brigade

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Abstract

Ebola viruses are the causative agents of a severe form of viral haemorrhagic fever in man, designated Ebola haemorrhagic fever, and are endemic in regions of central Africa. The recent west African outbreak of Ebolavirus has brought this filoviral infection again in limelight, Indian government has issued guidelines to various airports to screen travelers coming from Africa and middle east Haj pilgrims to keep a check on this highly virulent infection. This viral hemorrhagic disease has remained confined majorly to Africa but its high outbreak potential makes it essential for all infectious disease clinicians and people dealing with travel medicine to be cautious. Management of these patients with symptomatic therapy is the current strategy which is followed. There is absence of any effective vaccine so further research is warranted in this direction.

Introduction

Ebola virus is a member of the Filovirus family, it is an enveloped nonsegmented negative stranded RNA virus with five reported species namely Sudan, Reston, Zaire, Tai Forest and Bundibugyo. It has been clinically categorized in the group of hemorrhagic viral infections. This viral infection has been endemic in Central Africa and has remained a local health problem but because of its high fatality it has also caused concern world over through the capacity of import of these cases via travel and also through the fear of misuse for bioterrorism tools.

Recently there has been an outbreak of this infection in West Africa and the CDC as of June 18 2014 has officially reported 528 cases and 337 deaths due to Ebola viral disease in the three African countries of Guinea, Sierra Leone and Liberia attributing to a 64% of case fatality rate. This has been the largest ever documented outbreak of this disease. And hence there has been increased focus on this infection.

Epidemiology

Ebola virus is predominantly a zoonotic virus. It was first found as the etiologic agent in the year 1976 in the cases of hemorrhagic fevers in Zaire and Sudan. It caused an epidemic in these areas with a fatality rate of around 50 to 90%. This epidemic was attributed to interhuman spread in hospital settings with practice of sharing unsterilized needles in these resource limited countries. The next epidemic of Zaire Ebola viral disease (EVD) occurred in 1995. Ever since intermittent outbreaks have happened in Gabon district from 1995-2003. Till recent times around 20 outbreaks have been reported around central Africa with the majority caused by species Zaire ebolavirus.

Outside Africa there had been reports of Ebola viral infection in monkeys in Reston region of Virginia in USA in the year 1989 which was concluded to have come through a Philippine exporter. This species has also been reported in Pigs in Philippines and from then onwards have always been on radar of public health personnel because of its implications on food safety and agriculture.
Fruit bats have been labeled as the principal reservoir of this filovirus. There have been reported fatalities in gorillas, chimpanzees etc because of EVD but these seem to be sentinels for the virus and not reservoirs.4 Human to human transmissions have been reported only during outbreak situations.

Pathogenesis

In humans and animals EBOV (Ebola Virus) multiplies in all cells including endothelial cells, macrophages and parenchymal cells of organs as well. During the initiation stage of the disease phagocytic cells are involved. Viral antigens not only cause direct damage but the EBOV infection also leads to a surge of cytokines which cause further severity of illness. Interferon alpha is formed in response to this infection as in any other viral infection but the EBOV antigens render interferon ineffective and thus they do not provide any significant protection. And this mechanism of rendering IFNs ineffective is one of the reasons for increase severity and fatality of this infection.

Clinical improvement occurs when viral antibodies are formed and their titre increase in blood along with a drop of antigen levels.5 In fatal cases this response has been reported to be inhibited and extensive spleen and lymph node damage has been found.

Clinical Manifestations

The incubation period of EVD is around 2-21 days after which patients usually present with nonspecific complaints of malaise, fever, chills, myalgia, headache, nausea, vomiting and diarrhea. These complaints are sudden in onset; the diarrhea usually is bloody in nature. In light skinned patients around 5th day an erythematous nonitchy maculopapular rash has been reported which later undergoes desquamation. Bleeding or hemorrhagic manifestations usually occur around the same time. Bleeding from mucosa, hemoptysis, hematemesis, hematuria, ecchymoses etc have been reported. Edema of face, scrotum and neck has also been seen. In severe cases EVD can lead to hepatic failure, renal failure, MODS (multiorgan dysfunction syndrome), pancreatitis, shock and death.

In mild cases fever undergoes defervesence around 10-12 days. But a recrudescence has also been seen in some patients and delayed complaints of hepatitis, uveitis and orchids has also been observed.

Laboratory parameters usually show leucopenia, lymphopenia in early stages with subsequent neutophilia and thrombocytopenia. Hypoproteinemia, proteinuria with deranged coagulation profile in case of DIC is observed.6 Mild elevations in levels of hepatic transaminases are also reported. Increased serum amylase levels indicate pancreatitis in patients. Proteinuria and renal failure also observed in acute stages and in shock.

Pregnant females are at increased risk of miscarriages and can even transmit the virus via breast milk to their offsprings.

The virulence of the EBOV depends on the species and strain. The Zaire species of ebola virus has the highest case fatality rate which is reported to be around 90%.7

Route of Transmission

The EBOV usually enters the human body via the break in mucosa, skin or parenteral introduction. The virus spreads from wild life reservoirs to humans but during outbreaks it can spread from person to person through direct contact of body fluids, like blood, urine, sweat, semen and breast milk.8 Patients can transmit virus during febrile stage, during later stages and also postmortem during funeral rituals. Laboratory exposure through needle-stick injury and blood has been reported.9 The Gabon outbreak of EVD was attributed to killing of chimpanzees for food, also handling and killing of bats has been the cause in another outbreak.10

In human beings the route of infection seems to affect the disease course and outcome,11 with shorter incubation periods of infections acquired by injection route.

Differential Diagnosis

The differential diagnosis of EVD is varied because of the nonspecific nature of symptoms and the multiple diseases presenting with similar clinical syndrome, more so during the early stages of the disease.

Thus malaria, leptospirosis, relapsing fever, meningococcal infection, typhus, rickettsiosis, dengue fever, fulminant viral hepatitis, pneumonic plague, arboviral infections, bacterial septicemias all could present as similar syndromic picture of fever and hemorrhages12 and so are the differential diagnosis of EVD.

History of travel to the endemic areas or cases in endemic areas usually raises the suspicion for the EVD.

Laboratory Diagnosis

The initial diagnosis is usually based on clinical assessment. Blood tests for definitive diagnosis and confirmation are usually done at national and international reference laboratories, which should be contacted immediately in case of suspicion, who advice on proper sample collection and transport. A biosafety level 4 laboratory is only authorized to conduct these tests. These precautions are very essential because of the high infectivity of the virus.
and its potential of spread via medical facilities if appropriate measures are not taken.

Laboratory diagnosis of Ebola virus is arrived at by two ways, first by measurement of host-specific immune responses to infection and second by detection of viral particles or particle components in infected individuals.

Acute infection is diagnosed by RT PCR tests or ELISA to detect viral antigens, these tests can be positive from day 3 to day 15 of infection. Antibodies are tested either by direct IgG and IgM ELISA or IgM capture ELISA. IgM antibodies appear in blood by day 3 and disappear by 30 to 150 days.

While IgG antibodies appear by day 6 and can remain in blood for many years. IgM or rising IgG titre constitutes a strong presumptive diagnosis.

All the above tests are done on materials that have been rendered noninfectious prior to testing. Skin biopsy for detection has been advised on post mortem samples for confirmation of EVD.

Management

There are no definitive antiviral agents available who are effective against EBOV hence the main modality of treatment focuses on i) disease containment, ii) symptomatic relief, iii) management of complications, and iv) supportive therapy.

Treatment thus includes aggressive and appropriate volume and electrolyte management, oral and intravenous nutrition as per patient’s hydration and sensorium, and medications to control fever, gastrointestinal distress, pain, anxiety, and agitation.

Complications should be managed as in any other case and hence transfusion of FFP or platelets in case of DIC, Hemodialysis for renal failure, ionotropic support along with hydration for shock, ventilatory support for ARDS etc are advised. In case of coinfections or superadded infections addition of appropriate antibiotics and antimalarials are also important aspects of patient care.

Studies on EBOV infected Rhesus monkeys with activated protein C and inhibitor of factor VIIa/tissue factor have shown some benefit but there use in humans still needs to be investigated.

In a small, noncontrolled trial, transfusion of blood from patients convalescing from Ebola virus infection had shown lower case fatality rate (12.5%) in comparison with the overall case-fatality rate of 80% during the 1995 DRCepidemic. However, these patients generally received better care than the nontreated patients who had presented earlier during the course of the outbreak. In addition, they were transfused late in the course of illness, when they probably were already on the way to recovery. Thus this modality still remains under scrutiny.

In a study done on vitro samples and in mice had shown that S-adenosyl homocysteine hydrolase inhibited replication of Ebolavirus. But its role in effective manufacturing of a drug effective against EBOV still needs to be researched upon.

Thus the standard strategy of therapy still remains symptomatic and supportive.

Investigational Treatment Modalities

As there is no definitive therapy in EVD, various antiviral strategies have been tested with varying results. To mention a few:

a. RNA-based treatment strategies to interfere with transcription and replication include the use of antisense oligonucleotides or RNA interference. This modality has shown promising results in rats and nonhuman primates, but there use might be limited by the fact that it has to be administered intravenously and also as it is viral species specific therapy.

b. The nematode-derived anticoagulation protein rNAPc2 has shown 33% efficacy in the treatment of non-human primates infected with Zaire Ebola virus in managing coagulation abnormalities. Use of inhibitor of Factor X and Activated Protein C to manage DIC has also been tried.

c. Recombinant vaccines against Ebola virus based on vesicular stomatitis virus have shown remarkable usefulness when given as a postexposure treatment against Ebola haemorrhagic fever in non-human primates. Its use and efficacy in humans still needs to be studied.

d. EBOV virulence also depends on its entry to immune cells via its surface glycoproteins thus Compound 7 is a benzodiazepine compound that binds directly to the EBOV entry glycoprotein, blocking infectivity. Compound 8a also inhibited EBOV entry, although the mechanism has yet to be determined. Both of these compounds displayed potent inhibition at low concentrations, but have yet to be evaluated for in vivo efficacy.

Methods to Control Outbreak Situations

EBOV has been reported to cause outbreaks, recent one in West Africa being the burning example of same. Thus it is very important to be aware of various methods to follow in order to prevent outbreaks and its spread.

Keys to prevent outbreaks includes: 1. active case identification and isolation of patients; 2. identifying contacts of ill or deceased persons and tracking the
contacts daily for the entire incubation period; 3. investigation of retrospective and current cases to document all historic and ongoing chains of virus transmission; 4. identifying deaths in the community and using safe funeral practices; 5. daily reporting of cases; and 6. education of health-care workers regarding safe infection-control practices, including appropriate use of personal protective equipment.22

Prevention

Initially the development of vaccine against EBOV was disputed because of the rarity of disease and its focal endemicity, but frequent outbreaks in the past and recent times and its potential of bioterrorism tool along with import of such cases due to travel have changed the view.

A protective vaccine against EBOV is very valuable not only for at-risk medical personnel, first responders, military personnel, and researchers, but also for targeted vaccination in affected populations, especially during outbreaks, for use in ring vaccination strategy.

Any vaccine first has to show its efficacy on two animal models of which one has to be a non-primate human only then it would be allowed to be tested further as per regulatory authorities and this requirement has only been passed by few vaccine platforms.

Among the replication-deficient platforms, human-adenovirus-type-5 vectors have been the first successful strategies to protect non-human primates from lethal Ebola virus challenge.23 The second successful approach with replication-deficient platforms is based on Ebola virus-like particles generated by coexpression of the viral matrix protein (VP40), nucleoprotein, and glycoprotein.24

Live-attenuated viruses are more advantageous than are non-replicating vaccines because of ease of production and their potent stimulation of innate and adaptive (humoral and cellular) immune responses. However, this is not feasible in case of EBOV because of difficulties in ensuring the safety of live attenuated Ebola virus strains.

In spite of the above mentioned studies correlates and mechanisms of protection have not been well defined for most of the vaccine candidates. Thus currently the research is still ongoing on the subject of vaccine against EVD

Conclusion

Ebola virus infection as of today is still quite mesmerizing and challenging for clinicians because of its nonspecific symptomatology, high mortality and high infectivity. Its outbreak potential, absence of any specific antiviral agents or therapy and non availability of vaccine further threatens the population at risk and treating physicians.

The latest outbreak of West Africa has shown the limited ability of public health systems to respond to rare, highly virulent communicable diseases. The medical and public health sectors thus need to improve education and vigilance. Rapid diagnostic facilities should be made available in the affected areas at affordable prices. Also the information should be shared in real-time and in perspective to prevent spread as well as to prevent panic among people.

References


