Review Article

Ebola virus: A global public health menace: A narrative review

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Abstract

Ebola virus disease (EVD), a fatal viral hemorrhagic illness, is due to infection with the Ebola virus of the *Filoviridae* family. The disease has evolved as a global public health menace due to a large immigrant population. Initially, the patients present with nonspecific influenza-like symptoms and eventually terminate into shock and multiorgan failure. There exists no specific treatment protocol for EVD and only supportive and symptomatic therapy is the line of treatment. This review article provides a detailed overview of the Ebola virus; it's clinical and oral manifestations, diagnostic aids, differential diagnosis, preventive aspects, and management protocol.

Keywords: Ebola virus, oral manifestations, public health menace, symptomatic therapy

Introduction

Ebola, earlier termed as Ebola hemorrhagic fever (EHF), is a critically lethal ailment which primarily affects the humans and nonhuman primates. Ebola virus disease (EVD) occurs due to a virus infection which belongs to the family *Filoviridae* and genus *Ebolavirus*.[1] EVDs has posed diagnostic challenges and has been a universal public health threat since its discovery. While investigating an alleged yellow fever case, Dr. Peter Piot in the year 1976 first detected the disease in Zaire, Africa (presently the Democratic Republic of Congo).[2] The name "Ebola" was termed as the disease was noticed near the Ebola river in Congo.[3]

Fruit bats of *Pteropodidae* family, such as *Hypsignathus monstrous*, *Epomops franqueti*, and *Myonycteris torquata* serve as the natural hosts of the EBOV in Africa. Nonhuman primates may develop the infection by eating the partly eaten fruits and may also transmit the infection to humans.[4] Indian population is an impending threat to EVD, as India falls in the home range of *Pteropodidae* family of fruit bats.[5]

Ebola virus transmission primarily takes place through close bodily contact with the infected patient or their fluids, contaminated tissue surfaces, and clothing from alive, infected or deceased individuals. Unsafe traditional burial practices also play a pivotal role in the disease transmission.[6] There is documented evidence regarding the sexual mode of disease transmission, although transmission through the air is unlikely.[7]

EVD present with bizarre and atypical manifestations mimicking other viral diseases, especially in the initial disease phase. Constitutional symptoms, such as fever, myalgia, headache, vomiting, and diarrhea are the early presenting features. Hemorrhagic rash, internal and external bleeding are usually the warning manifestations in the late stages.[8] Bleeding from the body apertures is a distinguishing EVD manifestation.[9] Gum bleeding, odynophagia, and atypical oral manifestations constitute the oral features of EVD.[10]

Till date, there is no precise antiviral management or vaccination for EVD. The management protocol mainly relies on supportive

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and symptomatic therapy, along with monitoring coagulopathies and multiorgan dysfunction.[2]

The World Health Organization (WHO) affirmed the EVD outbreak as a "Public Health Emergency of International Concern" on August 8th, 2014.[5]

With the enormous immigrant population, India is estimating the likelihood of a probable EVD outbreak. The Ministry of Health and Family Welfare, Government of India, in collaboration with other agencies has appraised the situation and recommended travel instructions by air, land, and sea and health care professionals.[11]

Taxonomy

The virus belongs to the *Ebola virus* genus, *Filoviridae* family, and *Mononegavirales* order.[12] The genus *Ebolavirus* includes the following species- *Zaire ebolavirus* (EBOV), *Reston ebolavirus* (RESTV), *Bundibugyo ebolavirus* (BDBV), *Taï Forest ebolavirus* (TAFV), *Sudan ebolavirus* (SUDV), and the newly identified *Bombali ebolavirus* (BOMV).[13] Except for exclusive identification of RESTV in the Philippines, all the other species causes endemic West African EVD.[14]

EBOV responsible for the EHF causes the highest human mortality (57%–90%), followed by SUDV (41%–65%) and Bundibugyo virus (40%). TAFV has caused only two nonlethal human infections to date, whereas RESTV causes asymptomatic human infections.[15]

Figure 1 shows the taxonomy of Ebola virus.

Transmission

Based on the Centers for Disease Control and Prevention (CDC) classification, Ebola virus is considered as a biosafety level 4 and category A bioterrorism pathogen with an immense likelihood for massive nationwide transmission.[16]

Source of Infection

Intimate physical contact with the patients in the acute disease stages and contact with the blood/fluids from the

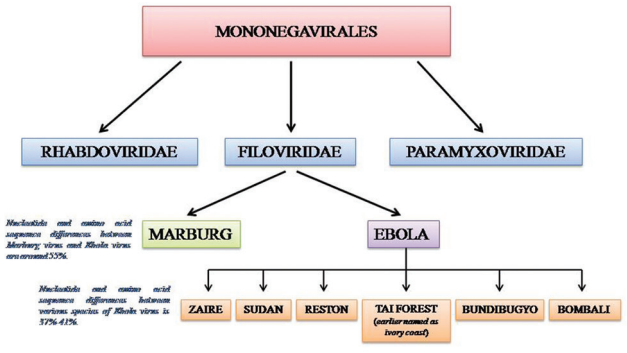

Figure 1: Taxonomy of Ebola virus

dead individuals constitutes the most important modes of transmission.[17]

The long-established funeral ceremonies in the African countries entail direct handling of the dead bodies, thus significantly contributing to the disease dissemination. Unsafe conventional burial procedures accounted for 68% infected cases in 2014 EVD outburst of Guinea.[18]

EBOV RNA may be identified for up to a month in rectal, conjunctival, and vaginal discharges and semen specimens may demonstrate the virus presence up to 3 months, thus signifying the presence of EBOV in recuperating patients.[14] The sexually transmitted case of EVD has been reported between a convalescent patient and close family member. Another study demonstrated a case in a recuperating male patient. The patient's semen specimen tested positive with Ebola viral antigen almost 3 months after the disease onset.[19]

Asymptomatic EBOV carriers are not infectious and do not have a major role play in the EVD outburst, and the field practice in Western Africa supported this assumption.[20] However, this presumption was refuted after the documentation of a pioneer asymptomatic carrier case in North Gabon epidemic (1996).[21]

EBOV has been detected from blood, saliva, semen, and breast milk, while RNA has been isolated from sweat, tears, stool, and on the skin, vaginal, and rectal swabs, thus highlighting that exposure to infected blood and bodily secretions constitute the major means of dissemination.[22]

Eating uncooked infected animal meat such as bats or chimpanzees account significantly to oral EVD transmission, especially in the African countries.[23] The demonstration of the Ebola virus in the Filipino pigs in 2008 triggered the likelihood of an extensive range of possible animal hosts.[24]

EVD dissemination has also been reported with hospital-acquired infections, particularly in areas with poor hygiene conditions. The infected needles usage was responsible for the 1976 EVD outbreak in Sudan and Zaire.[25,26] Improper hygiene and sterilization were the crucial factors for the 1967 Yambuku EVD outburst.[27]

EVD dissemination may also occur through the inanimate materials with infected body secretions (fomites).[19] However, disease transmission through the airborne and droplet infection is ambiguous.[10]

Figure 2 shows the primary and secondary transmission of disease.

Table 1 depicts the possible routes of transmission.

Epidemiology

The vast majority of EVD cases and outbursts have been endemic to African continent ever since the disease detection

Table 1: Possible routes of transmission

Mode of transmission	Consensus likelihood of occurring	Known facts	Unknown facts
Airborne/aerosol (small droplet/droplet nuclei)	Unlikely from epidemiology of disease	EBOV can be aerosolized mechanically and cause lethal disease in nonhuman primates at low concentrations[2,3]	Ability of the virus to become airborne through respiratory tract in humans and animals.
		Outbreaks contained without airborne precautions in the affected population[4]	Airborne stability of EBOV in tropical climates.
		EBOV detected after 90 min in experimental small aerosols[5]	Whether aerosol generating procedures (AGPs) produce EBOV aerosols that cause transmission
Fomites	Less likely from environmental sampling	Virus found in dried blood[6]	
		Persists on glass and in the dark for 5.9 days[7]	EBOV stability in tropical climates and on surfaces
Droplet (large droplet)	Likely from epidemiology and experiments	EBOV found in stool, semen, saliva, breast milk[6]	Whether infectious fluids are formed into droplets by humans
		Accidental infections in nonhuman primates, possibly from power washing[8,9]	Range of droplets containing EBOV.
		EBOV infections without direct contact[10]	
Bodily fluids contact	Very likely from epidemiology and experimental data	Sharing needles and handling the deceased or sick are high risk factors[11]	How much virus is shed in different fluids
		EBOV found in a variety of bodily fluids[6]	

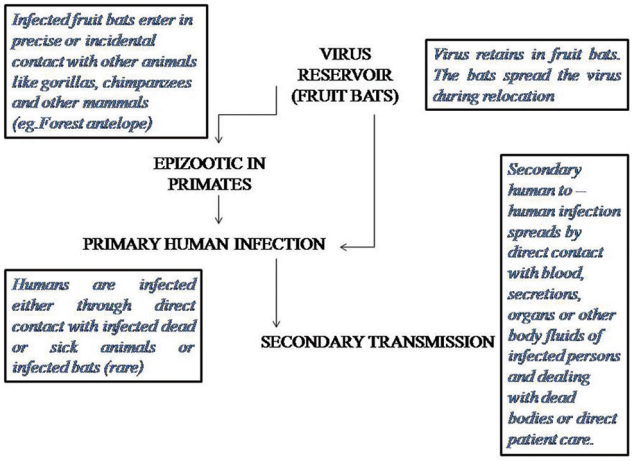

Figure 2: Primary and secondary transmission

in 1976,[28] and 36 such outbreaks have occurred in six African countries.[29]

Table 2 shows Ebola epidemiological outbreaks between 1976 and 2014.

The 2014–2016 EVD started in South East Guinea rural surroundings and eventually became a global public health menace by rapidly disseminating to urban localities and other countries.[28]

Figure 3 depicts the geographical distribution of Ebola virus disease.

The conducive environmental surroundings of the African continent facilitate EVD endemicity. However, intermittent imported Ebola cases have also been noticed in United States, United Kingdom, Canada, Spain, and Thailand.[30,31]

Figure 4 depicts the distribution of Ebola virus disease in West African Countries.

Out of the unparalleled globally reported 28,616 cases and 11,310 casualties, Liberia accounted for almost 11,000 cases and over 4,800 deaths.[32]

Table 3 shows the statistics of the 2014–16 West African outbreak.

Pathogenesis

Ebola viruses penetrate the human body through mucous membranes, skin lacerations/tear, close contact with infected patients/corpse, or by direct parental dissemination.[33] EBOV has a predilection to infect various cells of immune system (dendritic cells, monocytes, and macrophages), endothelial and epithelial cells, hepatocytes, and fibroblasts where it actively replicates by gene modulation and apoptosis and demonstrate significantly high viremia.[34] The virus reaches the regional lymph nodes causing lymphadenopathy and hematogenous spread to the liver and spleen promote an active inflammatory response.[35] Release of chemical mediators of inflammation (cytokines and chemokines) causes a dysregulated immune response by disrupting the vasculature system harmony, eventually causing disseminated intravascular coagulation and multiple organ dysfunction.[36]

Figure 5 demonstrates the pathogenesis of Ebola virus disease.

Clinical Features

Due to the bizarre and atypical manifestations in the initial phase, mimicking dengue fever, typhoid fever, malaria,

Table 2: Ebola outbreaks between 1976 and 2014 (Adapted from WHO 2014)

Year	Country/village	Ebola virus subtype	Number of human cases	Number of deaths	Mortality	Source and spread infection
1976	Sudan, Nzara and Marida	Sudan virus	284	151	53%	Close contact within hospitals, infecting many hospital staff
1976	Zaire, Yambuku	Ebola virus	318	280	88%	Contaminated needles and syringes in hospitals
1976	England	Sudan virus	1	0		Laboratory infection; accidental stick of contaminated needles
1977	Zaire, Tandala	Sudan virus	1	1	100%	Noted retrospectively
1979	Sudan, Nzara and Marida	Sudan virus	34	22	65%	Recurrent outbreak at the same site as 1976
1989	USA, Virginia, Pennsylvania	Reston virus	0	0		Ebola virus was introduced in to quarantine facility by monkeys from the Philippines
1989-1990	Philippines	Reston virus	3	0		Source: Macaques from USA. Three workers (animal facility) developed antibodies, did not get sick.
1990	USA, Virginia		4	0		The same to 1989
1994	Gabon	Ebola virus	52	31	60%	Initially thought to be yellow fever; identified as Ebola in 1995
1994	Cote d'Ivoire	Tai forest virus	1	0		Scientist became ill after autopsy on a wild chimpanzee (Tai Forest)
1995	Democratic Republic of Congo (Zaire)	Ebola virus	315	250	81%	Case-patient worked in the forest; spread through families and hospitals
1996	Gabon	Ebola virus	37	21	57%	Chimpanzee found dead in the forest was eaten by hunters; spread in families
1996-1997	Gabon	Ebola virus				Case-patient was a hunter from forest camp; spread by cloth contact
1996	South Africa	Ebola virus	2	1	50%	Infected medical professional travelled
1996	Russia	Ebola virus	1	1	100%	Laboratory contamination
2000-2001	Uganda	Sudan virus	425	223	53%	Providing medical care to Ebola case-patient without using adequate personal protection measures
2001-2002	Gabon	Ebola virus	65	53	82%	Outbreak occurred over border of Gabon and Republic of Congo
2001-2002	Republic of the Congo	Ebola virus	57	43	75%	Outbreak occurred over border of Gabon and Republic of Congo
2002-2003	Republic of the Congo	Ebola virus	143	128	89%	Outbreaks in the district of Mboma and Kelle in Cuvette Quest Department
2003	Republic of the Congo	Ebola virus	35	29	83%	Outbreaks in the villages of Mboma district, Cuvette Quest Department
2004	Sudan, Yambia	Sudan virus	17	7	41%	Outbreak concurrent with an outbreak of measles, and several cases were later reclassified as measles
2004	Russia	Ebola virus	1	1	100%	Laboratory infection
2007	Democratic Republic of the Congo	Ebola virus	264	187	71%	The outbreak was declared on November 20. Last death on October 10
2007-2008	Uganda	Bundibugyo virus	149	37	25%	First reported occurrence of a new strain
2008	Philippines	Reston virus	6	0		Six pig farm workers developed antibodies; did not become ill
2008-2009	Democratic Republic of the Congo	Ebola virus	32	15	47%	Not well identified
2011	Uganda	Sudan virus	1	1	100%	The Uganda Ministry of Health informed the public that a patient with suspected Ebola died on May 6th 2011
2012	Uganda, Kibaale	Sudan virus	11	4	36%	Laboratory tests of blood samples were conducted by UVRI and CDC
2012	Democratic Republic of the Congo	Bundibugyo virus	36	13	36%	This outbreak has no link to the contemporaneous Ebola outbreak in kibaale, Uganda
2012-2013	Uganda	Sudan virus	6	3	50%	CDC assisted the ministry of Health in the epidemiology and diagnosis of the outbreak
2014	Democratic Republic of the Congo	Zaire virus	66	49	74%	The outbreak was unrelated to the outbreak of West Africa

UVRI: Uganda Virus Research Institute; CDC: Centers for Disease Control and Prevention

meningococcemia, and other bacterial infections, EVD poses diagnostic dilemmas.[37]

The incubation period ranges from 2 to 21 days. However, symptoms usually develop 8–11 days following infection.[38,39]

The initial disease phase is represented by constitutional symptoms.[40] High-grade fever of >38° C is the most frequently reported symptom (85–95%), followed by other vague symptoms such as general malaise (85–95%), headaches (52–74%), dysphagia, sore throat (56–58%), and dry cough.[41,42] The progressively advanced disease is accompanied by abdominal pain (62–68%), myalgia (50–79%), nausea, vomiting, and diarrhea (84–86%).[41]

Variety of hemorrhagic manifestations forms an integral component of the late disease phase.[38] Gastrointestinal tract bleeding manifests as petechiae, hematuria, melena, conjunctival bleeding, contusion, or intraperitoneal bleeding. Mucous membrane and venipuncture site bleeding, along with excess clot formation may also occur. As the features advances with time, the patients experience dehydration, confusion, stupor, hypotension, and multiorgan dysfunction, resulting in fulminant shock and ultimately death.[43,44]

Maculopapular exanthema constitutes a characteristic manifestation of all Filovirus infection, including EVD.[45] The rash usually appears during the 5th to 7th day of disease and occur in 25–52% of patients in the past EVD outbreaks.[46]

Table 4 shows the clinical manifestations of Ebola virus disease.

Although EVD has a number of similar features with other viral hemorrhagic fevers (e.g. dengue), there are differences that set them apart.

Table 5 depicts the differentiating features of the Ebola virus and dengue virus infection.

Orofacial features

Gum bleeding, atypical mucosal lesions, and odynophagia comprise the distinctive oral manifestations. Epistaxis

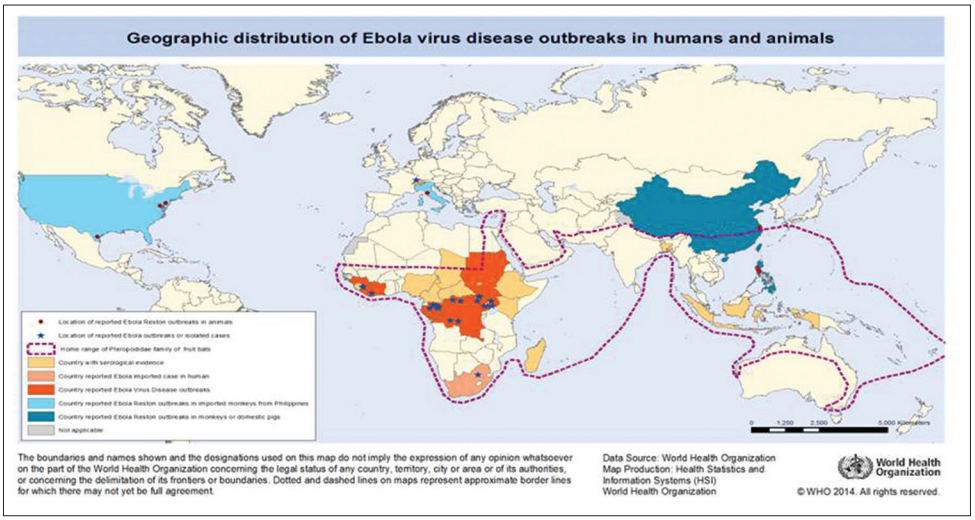

Figure 3: Geographic distribution of Ebola virus disease outbreaks

Table 3: Statistics of 2014-16 West African outbreak

WHO report date	Guinea total cases	Guinea total deaths	Liberia total cases	Liberia total deaths	Siera Leone total cases	Sierra Leone total deaths	Total cases	Total deaths
13th APRIL 2016	3814	2544	10678	4810	14124	3956	28616	11310

Table 4: Clinical manifestations of Ebola virus disease

Days	Phase	Main features	Other features
O-3	Early febrile	Fever	Malaise, fatigue, body ache
3-10	Gastrointestinal	Epigastric pain, nausea, vomiting, diarrhoea	Persistent fever, headache, conjunctival injection, abdominal and chest pain, arthralgia, myalgia, hiccups, delirium
7-12	Shock or recovery	Shock: diminished consciousness or coma Rapid thread pulse, oliguria, anuria, tachypnea	Recovery Resolution of gastrointestinal symptoms, increased apetite, increased energy.
≥ 10	Late complications	Gastrointestinal hemorrhage	Secondary infections: oral/esophageal candidiasis, persistent neurocognitive abnormalities

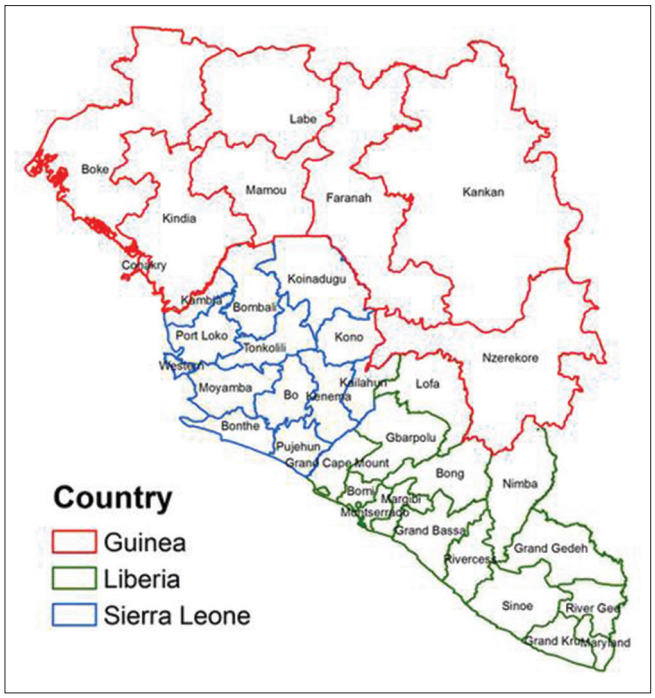

Figure 4: Distribution of Ebola virus disease in West African Countries

(nasal bleed), bleeding from venipuncture sites, conjunctivitis, and cutaneous exanthema are the other manifestations.[9] Bleeding tendencies and gum bleeding is not seen in asymptomatic or initial EBOV patients reporting to the dental hospital.

EVD dissemination in the field of oral and dental health may appear nonsignificant; although, probable situations which may pose a risk to dental health professional have been appraised by Samaranayake *et al.*[21] and Galvin *et al.*[10]

Table 6 depicts the various orofacial manifestations of Ebola virus disease

Diagnosis

EVD patients usually demonstrate altered laboratory parameters based on the stage of the disease.

Table 7 shows the laboratory findings in Ebola virus disease.

The WHO (2014) recommended the sample collection of whole blood or oral swab at suitable centres called Ebola treatment centers.[47] Reverse transcriptase polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) are the most frequently utilized tests for laboratory affirmation of the EVD.[43] RT-PCR is capable of detecting viral RNA in the blood samples of infected patients immediately after the commencement of signs and symptoms,[42,48] has a high sensitivity (up to 100%), and gives results within 1–2 days in cases of epidemics. ELISA detects the immunoglobulins G and M in samples of infected patients, has a low sensitivity (91%) and is not suitable for initial affirmation during an outbreak.[42,49]

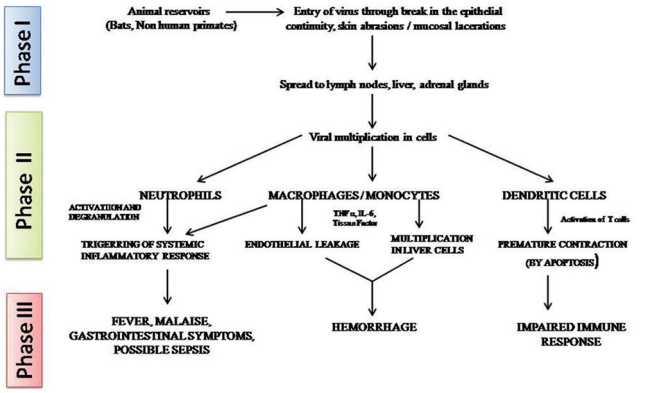

Figure 5: Pathogenesis of Ebola virus disease

Prevention

The most imperative strategy in EVD is to avert the vulnerable population from getting infected and limit the transmission. These preventive strategies entail intensive and rigorous endeavors from the Government, public health amenities, medical units, and personals.[50]

The most essential aspect to curb EVD transmission is to avert direct bodily contact with infected individuals and their body fluids.[51]

Health caregivers are extremely vulnerable and experience an augmented professional threat for EVD.[52] Thus, scrupulous adherence to the universal infection control measures is fundamental in all the hospitals, laboratories, and other health care services.[53] The U.S. CDC has advocated the appropriate use of various personal protective equipment as a mandate for health care professionals.[50]

The risk of rapid importation of Ebola virus into human beings can be prevented by averting the direct bush meat and bats contact.[54]

Unsafe traditional burial procedures, especially in the African continent significantly contributed to the EVD transmission. Hence, it is essential to practice safe and guarded funeral rituals to prevent the disease spread.[55]

WHO recommends the implementation of safe sex practices to combat the sexual transmission of EVD. Strict abstinence or proper and regular condom use in male EVD survivors at least for a period of 12 months of the symptom onset or until their semen has twice tested negative should be followed.[56]

Dental health care personals are extremely susceptible to EVD as they are in regular contact with blood and saliva during the routine diagnostic procedures. There is no documented case of EVD through saliva till date. A study on the identification of EBOV in oral fluids affirmed that patients presenting with demonstrable serum levels of EBOV RNA also exhibit identifiable salivary levels.[57] The incubation period for all body

Table 5: Differentiating features of Ebola and dengue virus infection

Differentiating features	Dengue	Ebola
Incubation period	3-14 days	2-21 days
Etiology	RNA virus belongs to the genus *Flavivirus* of family Flaviviridae	RNA virus belongs to the genus *Ebola* virus of family Filoviridae
Mode of transmission	Arthropod borne	Direct contact with infected blood/body fluids and environment contaminated with these secretions
Human-human transmission	No	Yes
Mortality	0.04%-0.05%	50%-90%
Typical signs and symptoms		
Fever	Common severely high fever (≥40°) lasts for 4-7 days	Common High fever (≥38°)
Headache	Common and high intensity (usually retrobulbar)	Common and high intensity
Muscle ache and pain	Common and severely intense (known as break bone fever)	Common
Nausea and vomiting	Common	Common
Ocular involvement	Nonpurulent conjunctivitis	Conjunctival injection; subconjunctival hemorrhage
Diarrhea	Uncommon	Common estimated 5 L or more of watery diarrhea per day, lasting for up to 7 days and sometimes longer
Bleeding	Unusual	Usual Bleeding from body orifices is a prominent feature
Rash (maculopapular exanthema)	Moderately elevated; initial rash occurs before or during 1-2 days of fever; 2nd rash is seen 3-5 days later	Elevated; occurs during the 5th-7th day
Neurologic complications	Encephalitis	Persistent neurocognitive abnormalities
Course of disease	Dengue can be divided into undifferentiated fever, dengue fever, and dengue hemorrhagic fever.	Features can be divided into 4 main phases: Early febrile phase, gastrointestinal phase, shock or recovery phase and late complications
Oral manifestations	Erythema, crusting of lips, and tongue and soft palatal vesicles are the prominent oral features. Hemorrhagic bullae, petechiae, purpura, ecchymoses, and bleeding gums may also be seen	Gingival bleeding, mucosal lesions, and pain during deglutination (odynophagia) are the most characteristic oral signs and symptoms.
Typical blood abnormalities		
Platelets	Low	Low
White blood cell count	Low	Low
Hematocrit	High	Low
Hemoglobin	High	Low
Aspartate transferase	Elevated	Elevated
INTERVENTIONS TO CONTROL THE SPREAD AND DISSEMINATION	Control of the vectors and their breeding sites	Avoid direct contact with the infected blood/body fluids and adopting universal infection control measures
TREATMENT	Supportive	Supportive
VACCINE DEVELOPMENT	In progress	In progress

fluids including saliva is 21 days; hence, oral health personals are vulnerable to develop the disease if universal infection control protocol is not followed.[58]

Table 8 demonstrates the various infection control measures to prevent the Ebola virus spread.

Box 1 shows the travel guidelines to EBOV affected regions.

Box 1: Shows the UK Travel guidelines to EBV infested regions.

- Do not handle dead animals or their raw meat
- Avoid contact with patients who have symptoms
- Avoid unprotected sex with people in risk areas
- Wash fruit and vegetables before eating them
- Wash hands frequently using soap and water

Treatment

Till date, there is no precise antiviral management or vaccination for EVD.[51] The management protocol mainly relies on supportive and symptomatic therapy. Public health strategies emphasizing on epidemiological surveillance, contact tracing, and quarantine of the patient have been recommended to combat the dissemination of EVD.[59]

Rehydration, adequate nourishment, analgesics, and blood transfusion form a keystone supportive treatment of EVD

Table 6: Orofacial manifestations of Ebola virus disease

Authors, Year	Oral features			Other features		
	Oral bleeding	Oral mucosal lesions	Odynophagia	Other bleeding sites	Conjuctivitis	Rash
Anonymous, 1978a	Gingival bleeding (48%)	Dry oral cavity Small aphthous like ulcers Posterior pharynx slightly injected Fissures and open sores of the lips and tongue	Painful throat (sensation of dry rope in the throat) (63%)	Epistaxis	Conjunctivae slightly injected but nonicteric	Measles like desquamation (52%)
Anonymous, 1978b	Gingival bleeding (23%)	Herpetiform, grayish exudative patch	Sore throat (32%)	Epistaxis	Conjunctivitis (35%)	Not reported
Piot, 1978	Gingival bleeding (25.6%)	Oral throat lesions (73%) Fissures on the lips Herpetic oral lesions Grayish exudative patches on soft palate and oropharynx	Sore throat (sensation of "ball" in the throat) (79.2%) Dysphagia	Epistaxis (16.7%) Injection sites (6.6%)	Conjunctivitis (58.2%)	Skin rash
Sureau PH 1989	Gingival and oral bleeding	Oropharyngeal bleeding ulcerations in the mouth and in the lips	Sore throat Pharyngitis Dysphagia	Epistaxis Injection sites	Hemorrhagic conjunctivitis	Exanthematous rash on trunk
Bonnet, 1998	Diffuse bleeding in the oral cavity (gums & tongue)	Oral thrush like lesions Bleeding cracks on the lips	Not reported	Bruises and bleeding at the injection sites (late stages)	Not reported	Maculopapular rash and petechiae on flanks and limbs (initially); followed by petechiae on the entire body
Bwaka, 1999	Not reported	Not reported	Odynophagia Dysphagia Sore throat (58%)	Injection sites (5%)	Conjunctival injection (47%)	Maculopapular rash
Ndanbi, 1999	Gingival bleeding (30%)	Oral/mucosal redness (30%)	Dysphagia (48%)	Epistaxis (4%) Injection site (30%)	Conjuctivitis (78%)	Cutaneous eruption (4%) Petechiae (22%)
Mupere, 2011	Gingival bleeding (10%)	Not reported	Sore throat (10%)	Epistaxis (10%) Injection site (10%)	Conjunctival injection (40%)	Not reported
Korepeter, 2011	Not reported	Pharyngeal Arythema	Sore throat	Bleeding from injection/venepuncture site	Conjuctival Hemorrhage	Maculopapular or morbilliform (meseales like) rash/or scar letenoid
Roddy, 2012	Gingival bleeding (4%)	Not reported	Dysphagia (58%)	Epistaxis (8%) Injection site (8%)	Conjuctivitis (50%)	Rash (12%)
Chertow, 2014	Not reported	Oral ulcers and Thrush	Throat pain Dysphagia	Not reported	Conjunctival injection	Not reported
WHO Ebola response team, 2014	Bleeding gums (2.3%)	Not reported	Dysphagia (32.9%) Sore Throat (21.8%)	Unexplained bleeding (18%) Epistaxis (1.9%) Injection site (2.4%)	Conjuctivitis (20.8%)	Rash (5.8%)

Table 7: Laboratory findings in Ebola virus disease

Timing	Common laboratory findings
Early illness	Leukopenia, lymphopenia, and thrombocytopenia Elevated hemoglobin and hematocrit Elevated aspartate aminotransferase and alanine aminotransferase (ratio≥3:1) Elevated prothrombin time, activated partial thromboplastin time, and D-dimer
Peak illness	Leukocytosis, neutrophilia, and anemia Hyponatremia, hypo- or hyperkalemia, hypomagnesemia, hypocalcemia, hypoalbuminemia, hypoglycaemia Elevated creatinine phosphokinase and amylase Elevated blood urea nitrogen and creatinine Elevated serum lactate and low serum bicarbonate
Recovery	Thrombocytosis

Table 8: Infection control measures to prevent Ebola virus spread

Personal protective equipments (PPE)	Ebola virus infection may be transmitted through broken skin and mucosa.	Gown, gloves (possibly double gloves), surgical mask, eye visor/goggles, or face shield to protect conjunctival, nasal, and oral mucosae at the same time. use additional personal protective equipment (such as double gloving, leg covers and disposable shoe covers, when there is contact with blood and bodily fluids Choose PPE of exact size. Gloves or other PPE that becomes contaminated by blood or bodily fluids must be cleaned or changed before touching other instruments or surfaces. Gloved/ungloved hand hygiene. Use alcohol-based hand rub or soap and running water. undertake scrupulous hand cleaning before and after glove use	Strength of the evidence High
Sharp instruments	Sharp instruments are extremely dangerous because they become contaminated by blood or bodily fluids and may break skin/mucosae even if protected by PPE.	Use of needles and other sharp instruments must be limited. These instruments must be handled with extreme care and disposed after use in dedicated seal containers.	Strength of the evidence High
Nonsharp instruments	Indirect transmission through nonsharp contaminated instruments is not demonstrated Preventive measures are recommended under the Precautionary Principle	Use of disposable medical equipment is recommended or, alternatively, nondisposable medical equipment must be cleaned and disinfected after use according to manufacturer's instructions	Strength of the evidence Low
Droplets	Airborne transmission is not demonstrated preventive measures are recommended under the precautionary principle	If aerosol generating procedures or events, such as coughing or sputum induction, occur, the use of powered air-purifying respirator or respirator (FFP2 or EN certified equivalent or US NIOSH-certified N95) is recommended	Strength of the evidence Low
Environmental surfaces	Environmental surfaces do not pose a risk of infection. However, Ebola virus is nonenveloped and is able to survive in the environment for long time. Preventive measures regarding surfaces visibly contaminated with blood and bodily fluids are recommended under the precautionary principle.	Use of standard hospital detergents and disinfectants (e.g., 0.5% chlorine solution or a solution containing 5000 ppm available free chlorine), preceded by cleaning to prevent inactivation of disinfectants by organic matter, is recommended	Strength of the evidence Low

patient.[60] Intravenous fluids and oral rehydration solution endow with proper electrolytes substitute and maintain the intravascular volume. Unrelenting vomiting and diarrhea are taken care of by the use of antiemetics and antidiarrheal drugs.[35,60,61] Suspected cases of secondary bacterial infections and septicemia are best managed by the use of prophylactic antibiotic regimen (third generation I.V. cephalosporins).[62] Concurrent parasitic coinfections may also be seen and require prompt investigations and management.[63]

A number of investigative clinical trials emphasizing on the development of vaccine, antibody therapies, and antiviral drugs have been conducted for EVD.[64]

Table 9 shows experimental treatment for Ebola virus disease.

Various clinical trials in Africa, Europe, and the United States suggest that Ebola vaccines are in various development stages (Phase I–III). A number of candidate vaccines employ diverse platforms, including recombinant viral vectors (most evolved vaccine candidate), DNA vaccines, inactivated viral particles, subunit proteins, recombinant proteins, and virus-like particles. Example of viral vectors expressing ebolavirus glycoproteins include recombinant simian adenovirus (cAd3), recombinant vaccinia virus, recombinant human adenovirus (Ad26), and a live vesicular stomatitis virus used alone or in prime-booster regimens.[65]

However, Ebola virus having the glycosylated surface proteins and preferentially infecting the immune cells impedes the development of an effective vaccine.[66]

Dental Management

Dental health care professionals in Europe have not encountered a case of EVD so far. However, health care personals (including dental surgeons) are more prone to EVD while treating patients in West or sub-Saharan Africa. Dental professionals are more likely to encounter asymptomatic EVD patients or those with early-stage vague symptoms.[27]

Table 9: Experimental treatment for Ebola virus disease

Drug	Drug type	Mechanism of action	Ebola virus clinical trial phase	Result/status	Other clinical trials
FAVIPIRAVIR (T-705) (Fujifilm Holding Corp)	Nucleotide analogue and viral RNA polymerase inhibitor	Prevents viral replication by RNA chain termination and/or lethal mutaggenesis	Phase II (NCT02329054): JIKI; NCT02662855: Sierra Leone)	Efficacy in patients with low to moderate levels of virus	Administered with ZMapp to a patient who recovered; administered to a patient with convalescent plasma who recovered; retrospective study indicated increased survival and lower viral loads.
BCX4430 (BioCryst Pharmaceuticals Inc., Durham, NC)	Synthetic adenosine analogue	Inhibits viral RNA polymerase and results in RNA chain terminaton	Phase I (NCT02319772)	Phase I complete; results not available yet	Not Applicable
TKM-Ebola (Tekmira Pharmaceutical Corp.)	Small Interfering (si) RNA agents Lipid nano-particle with si RNA-Ebola virus specific compound	Gene silencing	TKM-100802 Phase I (NCT02041715) TKM-130803 Phase II (PACTR201501000997429)	Terminated Terminated early; did not demonstrate efficacy [77]; development has been suspended	100802 administered to two patients in combination with convalescent plasma; both survived
Brincidofovir CMX001 (Chimerix Durham, NC)	Nucleotide analogue	Inhibits viral replication by inhibiting DNA polymerase	Phase II (NCT02271347)	Terminated due to low enrollment; not currently under further development as EBOV therapeutic agent	Administered to 5 patients during the outbreak, often in combination with other therapies
AVI-6002 AVI-7537 (Sarepta Therapeutics Cambridge, MA)	Small Interfering (si) RNA agents Phosporo-diamidate morpholino oligomer Ebola virus specific compound	Gene silencing	Phase I AVI-6002: NCT01353027; AVI-7537: NCT01593072	AVI-6002: Favorable safety and tolerability AVI-7537: Terminated prior to enrollment; further development has been suspended	Not Applicable
Z-Mapp (Mapp Pharmaceuticals)	Combination of 3 different monoclonal antibodies-Ebola specific compound	Virus neutralisation	Phase II (NCT02363322)	Inconclusive efficacy due to insufficient statistical power	Administered to patients during the outbreak, often in combination with other therapies
JK-05 (Sihuan Pharmaceutical Holdings Group Ltd and Academy of Military Medical Sciences (Beijing, China)	Broad spectrum antiviral drug	Inhibits viral RNA polymease	Not Applicable Animal studies completed; now considered for use in emergency situations for Army only	Not Applicable	Not Applicable
Convalescent plasma or blood	Derived from surviving or cured Ebola patients	contains anti Ebola antibodies	Phase I/II: NCT02333578 Phase II/ III (NCT02342171; ISRCTN13990511)	Completed; results from one study found no improvement in efficacy in treated group	Whole blood: 1995 Kikwit outbreak—7 out of 8 survivors; administered to patients during the outbreak, often in combination with other therapies
GS-5732	Small molecule monophosphoramidate prodrug of an adenosine analogue	Inhibition of RNA-dependent RNA polymerase	Phase I	Phase I complete; Phase II for efficacy in survivors with viral persistence in semen (NCT02818582)	Administered to a newborn in combination with ZMapp and buffy coat transfusion; patient survived
IFN- β	Cytokine family member	Inhibits the viral infection by activating the innate and adaptive immune response	Phase I/II (ISRCTN17414946)	Results not yet released	Not Applicable

Contd...

Table 9: Contd...

Drug	Drug type	Mechanism of action	Ebola virus clinical trial phase	Result/status	Other clinical trials
Amiodarone	Multi-ion channel blocker for treatment of cardiac arrhythmias	Inhibits filovirus entry in vitro by reducing virus binding to target cells	Phase II (NCT02307591)	Terminated early; reduction in case-fatality rate; not statistically significant	-
FX-06	Fibrin derived peptide	Treats hemorrhagic shock by reducing vascular leakage	Not Applicable	Not under current investigation for EBOV indication	2014 3-day treatment course (400 mg/kg loading dose+200 mg/kg maintenance dose) was administered to a patient in combination with self-administration of amiodarone and intermittent treatment with favipiravir; patient survived

Individuals with a travel history to Ebola endemic regions, but with no direct intimate contact with the disease fall in the low-risk category and may undergo any medical/dental health care procedures without restrictions. However, all the nonessential procedures should be postponed for 21 days in individuals with direct exposure to the virus. The regional Health Service Executive Department of Public Health needs to be notified when the exposed patient's treatment cannot be deferred or controlled with pharmacotherapy.[10]

Conclusion

EVD has emerged as a significant global public health menace due to multiple disease outbreaks in the last 25 years. Recent advancements are being carried out in the form of effective Ebola virus vaccine and anti-Ebola virus drugs. However, rapid geographic dissemination, nonspecific clinical presentation, lack of vaccine, and specific diagnostic test are the possible challenges to combat this dreaded public health menace.

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Conflicts of interest

There are no conflicts of interest.

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