치의학석사 학위논문

에볼라 바이러스 감염의 구강 내 소견에 대한 고찰

Review of Ebola Virus Disease in the Oral Cavity

2016 년 02 월

서울대학교 치의학대학원

치의학과

김 민 지

Abstract

Ebola virus disease is a fatal viral hemorrhagic fever that has been an emerging concern in sub-Saharan Africa from the 1970s. Last year, Ebola virus disease reached epidemic levels in West Africa, and also spread in a limited number of cases to the USA, Europe and Antipodes via infected travelers. Human-to-human transmission of Ebola virus is known only by way of direct contact with tissues, blood, secretions or other bodily fluids, including saliva. Although there been no reported infection cases in the dental healthcare settings, the potential for transmission through saliva suggests a high risk of infection for dental healthcare workers. Therefore, it is imperative that dental healthcare workers be able to identify patients with suspected Ebola virus disease.

This article will review oral signs and symptoms of Ebola virus disease, discuss pathogenesis, treatment and prevention, and propose infection control guidelines for oral healthcare workers.

This review is based on a study of the literature, including research papers and case reports, to analyze the epidemiology, pathogenesis, transmission and prevention of Ebola virus disease. A literature search using PubMed and Google scholar with keywords ['Ebola' AND 'oral' OR 'facial' OR 'dental'] was performed (September 2015) and papers published since 1976 were reviewed. Of the many case reports and studies, those that described orofacial signs and symptoms from early stages of illness were selected and analyzed

for the incidence and descriptions of orofacial signs and symptoms. Management guidelines for infection prevention of Ebola virus disease are based on the standard precautions published by certified health organizations, including the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO).

Ebola virus disease is alarming, with a high mortality rate. Healthcare workers, who are always exposed to risk of infection, need to be especially careful of infection from a patient who is infected with Ebola virus but not yet displaying initial symptoms. To minimize risks, dental practitioners need to obtain accurate information about whether their patients have been in countries suffering from outbreaks of Ebola virus disease within the last 21 days or in contact with someone with Ebola virus disease, as well as assess for the presence of visible initial symptoms of Ebola virus disease (fever, headache, weakness, fatigue, myalgia, diarrhea, vomiting, abdominal pain, unidentified hemorrhage). Above all, in order to reduce the risk of infection and cross-infection by healthcare workers, specific infection control guidelines for healthcare workers should be strictly followed, keeping in mind that all patients have the possibility of infection by Ebola virus.

Keywords : Ebola virus disease, oral signs and symptoms, dental healthcare workers, infection control

Student Number : 2012 – 22147

Contents

I. Introduction

Ebola virus disease is a fatal viral hemorrhagic fever that has been an emerging concern in sub-Saharan Africa from the 1970s. Last year, Ebola virus disease reached epidemic levels in West Africa, and also spread in a limited number of cases to the USA, Europe and Antipodes via infected travelers. Human-to-human transmission of Ebola virus is known only by way of direct contact with tissues, blood, tissues or other bodily fluids, including saliva. Infection in healthcare settings occurs when a healthcare provider treats patients with suspected or confirmed Ebola virus disease, without strictly adhering to infection control precautions. Although there have been no reported infection cases in the dental healthcare setting, the potential for transmission through saliva suggests a high risk of infection for dental healthcare workers.

Gingival bleeding is the most characteristic oral symptom of Ebola virus disease, sometimes accompanied by mucosal lesions and pain. The pathogenesis of Ebola virus disease is based on abnormalities of the immune system, but the precise mechanisms have yet to be defined. Although development of targeted drugs or vaccines is underway, there are no approved drugs or vaccines yet. Treatment of Ebola virus disease has focused on supportive therapy. Accordingly, it is important that dental healthcare workers be able to identify suspected patients based on the knowledge about oral

signs and symptoms of Ebola virus disease to prevent cross infection.

This article will review oral signs and symptoms of Ebola virus disease, discuss pathogenesis, treatment and prevention, and propose infection control guidelines for oral healthcare workers.

II. Studies on Ebola virus disease

Ebola virus disease is an acute viral syndrome with symptoms of fever and bleeding and is also referred to as Ebola hemorrhagic fever. The causative agent of viral hemorrhagic fever includes Ebola virus and Marburg virus, both part of the family *Filoviridae*. Table 1 shows the varied spectrum of different RNA virus families that cause viral hemorrhagic fever.[2] Ebola virus is a lipid-enveloped, non-segmented, negative-stranded RNA virus with particles that are 80 nm in diameter and form twisted filaments of 1.1 μm in length. Fruit bats are considered the natural hosts and can transmit Ebola virus, and human-to-human transmission is also concerned.

II-1. Epidemiology

In 1976, the first reported case of Ebola virus disease appeared in 2 concurrent outbreaks in southern Sudan and the Democratic Republic of Congo. In these 2 cases, the fatality rates hit 53% and 88%, respectively.

After that, 19 Ebola virus disease outbreaks occurred up through 2012, and the mortality rate reached 65%. Ebola virus disease is a classic zoonosis in that humans and other primates are vulnerable to Ebola virus infection. Human-to-human transmission comes from contacts to blood and other bodily fluids of an infected individual.

Five different species of Ebola virus have been reported, including Bundibugyo, Zaire, Sudan, Reston, and Tai Forest. Generally, all hemorrhagic cases have had a fatal consequence within about a week.

The most recent epidemic of Ebola virus disease in 2014 was induced by the Zaire species, and is officially the twenty-fifth outbreaks of Ebola virus disease. The epidemic erupted in Guinea, and the World Health Organization (WHO) officially had notice of the rapidly expanding Ebola virus disease outbreak on March 23, 2014. On August 8, the WHO announced the epidemic to be a "public health emergency of international concern".[3] Ebola virus disease outbreaks have primarily been in distant villages in Central Africa over the past decades (Figure 1),[4] but the 2014 epidemic affected West African countries where no Ebola virus outbreak had previously occured, involving both rural areas, and major capital cities. The 2014 epidemic of Ebola virus infection is far larger than all previous epidemics combined (Table 2),[5] and is also the widest epidemic ever, ranging from Guinea to neighboring countries such as Sierra Leone, Liberia and to distant countries such as the USA, Europe and Antipodes (Figure 2).[6]

II-2. Pathogenesis

Ebola viruses are able to infect a wide range of primate cells as a result of heavily glycosylated surface glycoproteins binding to variable target molecules; their replication results in necrosis of

infected cells. The virus is taken up into endosomes, and crosses the endosomal membrane to reach the cytoplasm. There are three different mechanisms thought to be responsible for the initiation of fusion of the virus to the host cell. One mechanism involves acidic conditions in the endosome inducing conformational changes in viral glycoprotein spikes, and the next mechanism is demonstrated by interactions between 2 domains of envelope glycoprotein 160 (GP160). Chandran et al. suggest a third triggering mechanism, based on their discovery that a conformational change in the surface glycoprotein of Ebola virus is mediated through proteolysis by two endosomal cysteine proteases, cathepsin B and cathepsin L. Cathepsin B and cathepsin L can cleave the C terminus of viral GP1 to yield an approximately 18-kD N-terminal fragment. Successive digestion of this fragment by cathepsin B triggers membrane fusion by GP2, the fusion domain of the glycoprotein molecule (Figure 3).[7] This novel finding about how the Ebola virus infects cells offers new possibilities for treatment of this infection.[7]

The exact mechanisms behind the variety of symptoms in Ebola virus infection have not been clarified, despite numerous studies. Research in macaques has demonstrated that the initial main targets of Ebola virus infection are macrophages and dendritic cells. Macrophages play a major role in initial innate immune anti-viral defense, and dendritic cells initiate the adaptive immune response by presenting antigens to naïve T cells (Figure 4).[8] Ebola virus infection partially damages the functionality of both cell types, but they are still able to trigger inflammation and coagulation. The infected macrophages and dendritic cells inhibit an interferon

response and provokes cytoplasmic-signaling pathways, causing a massive release of proinflammatory mediators and nitric oxide (NO) via a cytokine storm. These mediators increase vascular permeability and express cell adhesion molecules on the surface of endothelial cells. As a result, additional inflamamatory cells and molecules are attracted to the site of infection. Although such changes in the vascular system may dissipate a localized infectious lesion, the systemic spread of Ebola virus induces a breakdown of the circulatory system.[2,8] Ebola virus-infected dendritic cells show limited inflammatory response compared to normal dendritic cells. Virus-infected dendritic cells secrete only a limited range of chemokines, fail to induce co-stimulatory molecules such as CD40, CD80, and CD86 or upregulate major histocompatibility complex (MHC), and are unable to activate differentiation of allogenic lymphocytes.[9] The virus also affects organs, worsening the symptoms of infection. Liver damage disturbs the formation of coagulation proteins, and damage to the adrenal glands destroys the ability to synthesize steroids and leads to circulatory failure. Natural killer (NK) cells and T lymphocytes remain intact, but undergo apoptosis, further deteriorating immune function.[8] The host resposes to Ebola virus infection show differences according to the individual genetic charicteristics.[8]

II-3. Transmission and prevention

The route of first human transmission has not been identified, but direct physical contact with an infected person during the stage of clinically apparent illness is the most important risk factor for

secondary transmission. Interviews with surviving members of 27 households in which someone had been infected with Ebola virus helped defines modes of human-to-human transmission of Ebola virus disease. In addition to the 27 primary cases, all 28 secondarily infected cases were reported to have physical contacts with an ill person. None of the 78 household members who reported no physical contact during the period of clinical illness became infected. Among those household members who reported direct physical contact with the ill person, adult family members, both those who touched the cadaver and those who were exposed during the late hospital stage were at additional risk. These findings imply that direct physical contact with a clinically ill patient is necessary, but not necessarily sufficient, for secondary transmission.[10]

Although the relative significance of aerosol, conjunctival and oral exposure has not been determined in the natural transmission of Ebola virus disease, numerous researches demonstrate infectivity potential of aerosol and saliva. E. Johnson et al. reported inhalation of virus in rhesus monkeys caused a rapidly fatal disease in 4-5 days and detected cell-associated Ebola virus antigens present in the airway epithelium, alveolar pneumocytes, and macrophages in the lung and pulmonary lymph nodes.[12]

Formenty et al. obtained serum and saliva specimens from 24 suspected patients and analyzed the specimens for immunoglobulin G antibodies by enzyme-linked immunosorbent assay (ELISA) and for Ebola virus by antigen detection ELISA and reverse-transcriptase polymerase chain reaction (RT-PCR). Patients with

seropositive results had no antibody detected in their oral fluid specimens. However, Ebola virus antigens were detected in oral fluid specimens obtained from patients with positive serum RT-PCR results, leading them to conclude that oral fluid samples have the potential to provoke infection of Ebola virus..[13]

As mentioned earlier, no effective treatment or vaccine is available for Ebola virus disease, because Ebola virus itself has highly glycosylated surface glycoproteins and affects monocytes, macrophages and dendritic cells first.[14] Several vaccine candidates, including inactivated virus, DNA vaccines, virus-like particles (VLPs) and vaccines based on recombinant viral vectors, have been tested in rodents and nonhuman primates.[15] The Ebola virus antigens included in the vaccines vary. While the Ebola virus surface GP has been the main antigen in vaccine development, the NP and VP40 matrix proteins have also been used in some candidates, such as the VLPs-based vaccine.[16] As a novel approach, a replication-deficient recombinant Ebola virus lacking the gene encoding for VP30, an important transcription factor that plays an important role in viral replication, was recently proven to protect nonhuman primates against Ebola virus.[17] This vaccine is definitely different from other Ebola virus vaccines, in that it presents all viral proteins and viral RNA to the immune system, which might lead to protective immune responses.

Several vaccine candidates have been initiated into phase I, II and III human clinical trials (Table 3).[18] More leading vaccine candidates

include those based on viral vectors such as adenoviruses and vesicular stomatitis virus modified to express the Ebola virus surface GP.

III. Management guidelines for prevention of Ebola virus infection

With the global impact of the West Africa Ebola virus disease outbreak, international organizations have announced reinforced infection prevention and control guidance for Ebola virus disease patients. Ebola virus disease is highly infectious and often rapidly fatal, but it can be prevented. Because the virus is spread through direct contact with body fluid (blood, stool, saliva, urine, sperm, vomit, etc.), such contact can be minimized. In addition, the Ebola virus can be removed with heat, alcohol-based products, and bleach (sodium hypochlorite). It is susceptible to commonly used disinfectants such as aldehydes, halogens, peroxides, quarternary ammonium compounds, and phenolics.[19] Therefore, if standard precautions are carefully applied in health-care settings, it is possible to prevent Ebola virus transmission and protect health-care providers.

The Centers for Disease Control and Prevention (CDC) emphasizes that early recognition is critical for infection control with the motto ‘Think Ebola'. Figure 5 includes the contents.[20] For the prevention of Ebola virus transmission, it must be assessed whether a patient have been in countries suffering from outbreaks of Ebola virus disease within the last 21 days or had contact with someone with Ebola virus disease. Such history taking is carried out

through an interview. If the patient is unable to answer directly, information must be obtained via protectors, such as family members or friends. At the same time, patients must be assessed for visible initial symptoms of Ebola virus disease (fever, headache, myalgia, weakness, fatigue, diarrhea, vomiting, abdominal pain, and unidentified hemorrhage). During this screening process, medical personnel must comply with standard universal precautions, acting as if all patients are infected with the Ebola virus. If a patient has been exposed to the Ebola virus, or shows initial symptoms of Ebola virus disease, the patient should be isolated immediately and public health authorities contacted.[20]

The CDC and World Health Organization (WHO) regularly declare newly modified infection prevention guidelines. Prevention guidelines from both institutions are generally similar and include the following common precautions:[19,21]

. Use of personal protective equipment (for example, double gloving, leg covers and disposable shoe covers)

. Choose gloves of exact size

. Follow safe injection practices, handling with care and limiting the use of needles and other sharps

. Clean the environmental surfaces, including surfaces that may be touched by hands (not necessarily disinfection)

. Perform scrupulous hand cleaning before and after glove use

The CDC is tightening previous infection control guidance for healthcare workers caring for patients with Ebola virus disease. The modified guidance is centered on three principles:[22]

. All healthcare workers undergo rigorous training and are practiced and competent with personal protective equipment, including putting it on and taking it off in a systematic manner

. No skin exposure when personal protective equipment is worn

. All workers are directed by a trained monitor who watches each worker put on and take off personal protective equipment

The guidance shows how the accurate wear of personal protective equipment is important for the prevention of Ebola virus infection.

The American Dental Association(ADA) presents a standard precaution for the prevention of Ebola virus infection in dental health care workers, receiving the CDC advisories. The main contents are based on the guidelines described in the "Think Ebola". It means ADA also puts emphasis on the early identification of infected patients through the interview before the dental treatment. The ADA also recommends that dental treatment should be deffered for the patient who has no symptoms but has been exposed to Ebola virus-infected patients. However, if requiring necessary preliminary treatment, patients showing serious

dental infection and pain can be treated following standard precautions, consulted by a physician. [23]

IV. Signs and symptoms of Ebola virus disease in the oral cavity

The presence of Ebola virus antigens in the saliva of patients infected with Ebola virus suggests that there is a possibility of transmission of Ebola virus through saliva contamination.[13] Therefore prevention and rapid diagnosis of Ebola virus infection is important for dental healthcare workers who are easily exposed to oral fluids.

The incubation period in human-to-human transmission can be 2 to 21 days, although typically symptoms appear 8-11 days after infection.[3,24] Early nonspecific symptoms of Ebola virus disease are often indistinguishable from those of common tropical diseases, especially malaria, shigellosis, and typhoid fever. Maculopapular rash, however, is a classic symptom of Filovirus infection, including Ebola virus disease.[25] Most reports about Ebola or Marburg virus infection describe the development of a rash in the early stage of illness. In previous outbreaks of Ebola virus disease, a rash was seen in 25-52% of patients. The rash is frequently described as being nonpruitic, erythematous, and maculopapular, then becoming diffuse, generalized, and confluent.[26] In the early stages of Ebola virus disease, patients manifest nonspecific signs and symptoms such as fever (≤40° C), headache, asthenia, arthralgia, myalgia and back pain. Progressive gastrointestinal symptoms often develop

within 3 to 5 days of symptom onset with continuing fever. Gastrointestinal symptoms include abdominal pain, anorexia, nausea, vomiting and diarrhea leading to serious electrolyte imbalance, intravascular volume depletion and shock.[18,25] Conjunctival bleeding, rash, hiccups, respiratory and neurologic manifestations have been reported. Bleeding is a late clinical symptom that only occurs in less than 20% of patients with Ebola virus disease.[27,28,29] Bleeding is generally manifested as oozing from punctured skin, gums, and the nose. Delayed bleeding at intravenous puncture sites is sometimes the first clue for the diagnosis of Ebola virus disease. In general, visible bleeding implies a poor prognosis, but gastrointestinal bleeding such as melena and bloody stools are the exceptions, as they are exhibited by both survivors and nonsurvivors in the early stages of illness.[25]

IV-1. Analysis of preceding research

Clinical examination of orofacial symptoms in patients who visit dental clinics may help healthcare workers identify Ebola virus infected patients. A literature search through PubMed and Google scholar with the keywords ['Ebola' AND 'oral' OR 'facial' OR 'dental'] was performed (September 2015). Among the many surveys and case reports, those that observed patients from the early phases of illness with reported orofacial symptoms were selected. Recorded orofacial manifestations are arranged in Table 4.[3,25-6,30-35]

The three main oral signs and symptoms are:

. Gingival bleeding
. Mucosal lesion
. Pain; Odynophagia

In addition to this, oral healthcare workers should also look for epistaxis, bleeding from injection sites, conjunctivitis and rash.

Bleeding is a characteristic symptom of Ebola virus disease. Because it generally appears as a late stage symptom, those patients are generally too unwell to seek dental care. Typically, gingival bleeding is concomitant with other forms of bleeding, notably epistaxis and bleeding from injection sites. Synchronistic bleeding at distinct sites is a differential sign of Ebola virus disease.[2]

Diverse findings of mucosal lesions were found in the literature. Mucosal lesions such as grayish exudative ulcers and thrush-like lesions on the throat, tongue and lips were described. Mucosal lesions generally appear 5-10 days after onset of symptoms in the process of deterioration. Chertow et al. posited that oral or esophageal candidiasis and oral ulcers were due to secondary infection that occurred in the process of disease progression.[31]

Odynophagia appears as a result of ulceration and edema of mucosal lesions, ranging from sore throat to severe dysphasia.

Early conjunctivitis, normally bilateral, is one of the most frequent signs of Ebola virus disease, reported in 35–50% of cases. Rash is also reported in 15–50% of cases, and is a characteristic symptom of viral hemorrhagic fever that makes it distinguishable from other tropical diseases. Rashes appears particularly in traumatized areas, and may be red, morbid form, maculopapular or petechial.

IV–2. Diagnosis and treatment

Gingival hemorrhaging can be reflective of systematic microvascular pathology for scurvy, leukemia, vitamin K deficiency, and Von Willebrand disease, along with viral hemorrhagic fever, including Ebola virus disease.[36] Gingival bleeding in patients with Ebola virus disease is distinguishable in that it is concomitant with other forms of bleeding. Mucosal lesions need further definition, as each report described various symptoms.

In the patients suspected with Ebola virus disease through oral findings, immediate clinical examination must be conducted for definite diagnosis.[37] Diagnosis of suspected patients is confirmed by Ebola virus–specific laboratory tests, including RT–PCR, that detect the Ebola virus genome, or ELISA that measures the Ebola virus antigen or specific antibodies.[38] ELISA has more recently been replaced by RT–PCR, a rapid and highly sensitive nucleic acid amplification test that has become the gold standard for Ebola virus disease. The sensitivity and specificity of RT–PCR are approximately 100% and 97%, respectively.[40] However, viral

genomes may not be detected during the first three days of illness, possibly leading to false-negative results. To minimize such errors, proper sampling and careful RT-PCR protocols are needed to avoid cross-contamination.[31]

To date, there is no approved treatment for Ebola virus disease. Clinical supportive care is the foundation of management and treatment of Ebola virus disease and its complications. Supportive care includes rehydration, nutrition, analgesics and blood transfusion when needed. A key purpose of supportive care is to maintain intravascular volume with oral rehydration solution or intravenous fluids. Antiemetics and antidiarrheal agents may be also used for patients with consistent vomiting and diarrhea. When secondary infections and septicemia are suspected, prophylactic antimicrobial agents may be given.[31,41] Several potential therapeutic agents are tested in phase I, II, and III clinical trials (Table 5).[18] The targeted antiviral compounds/drugs that inactivate the virus by targeting includes TKM-Ebola, based on the concepts of small interfering RNA agents (siRNAs), and Favirpirarvir and Brincidofovir (CMX001), which are nucleotide analogs that perform as viral polymerase inhibitors. Immunotherapy, a method of administering whole blood or plasma of patients in the recovery phase of Ebola virus disease, has been studied and reported to be effective in 87.5% of patients in the Democratic Republic of the Congo in 1995. ZMapp, a combination of three different monoclonal

antibodies against Ebola virus antigen, has been found effective in the treatment of monkeys and is in clinical trials for humans.[18]

V. Discussion: Approaches to Ebola virus disease in dental patients

Since Ebola virus-infected patients appeared in Texas in the United States during 2014, a region where Ebola is not endemic, the disease has emerged as a threat to healthcare workers throughout the world. In particular, the fact that there are potentially contagious asymptomatic or mildly symptomatic patients infected with Ebola virus possibly visiting medical clinics puts healthcare workers at a high risk for infection. Considering the presence of viral antigens in the saliva of patients with Ebola virus disease, dental practitioners also have a high risk of infection through direct contact with saliva. Immediate orofacial clinical examination is necessary to identify patients suspected with Ebola virus disease to best protect dental healthcare workers. When oral symptoms such as gingival bleeding and mucosal lesions are displayed, Ebola should be suspected. Realistically, however, these oral symptoms occur late in the disease process and patients exhibiting them would probably be too unwell to seek dental treatment.[42] Accordingly, dental practitioners need to be on the alert for patients who have been infected with Ebola virus but have not yet displayed any initial symptoms. To minimize risks, dental practitioners need to obtain accurate information about whether a patient has been in countries with outbreaks of Ebola virus disease within the last 21 days or in

contact with an individual with Ebola virus disease. At the same time, assessing visible initial symptoms of Ebola virus disease (fever, headache, myalgia, weakness, fatigue, diarrhea, vomiting, abdominal pain, and unidentified hemorrhage) is critical. If patient has a concerning travel or contact history and symptoms, they must be isolated immediately and public health officials informed. If the patient has no symptoms but has been exposed to Ebola virus-infected patients, dental treatment should be deferred if possible for 21 days (the maximum incubation period) after the potential exposure. However, if requiring necessary preliminary treatment, patients showing serious dental infection and pain can be treated following standard precautions, consulted by local health department. Above all, in order to reduce the risk of infection and cross-infection, specific infection control guidelines directed to healthcare workers must be strictly followed, while keeping in mind that all patients have the possibility to be infected by the Ebola virus.

References

1. Centers for Disease Control and Prevention (CDC). CDC Public health image library ID# 10816[Internet]. Atlanta, USA: Centers for Disease Control and Prevention (CDC); [cited 2015 Oct 8]. Available from:

http://phil.cdc.gov/phil/details.asp?pid=10816

2. Samaranayake L, Scully C, Nair R G, Petti S. Viral Hemorrhagic fevers with emphasis on Ebola virus disease and oro-dental healthcare. Oral Dis 2015;21:1-6.

3. WHO Ebola Response Team. Ebola virus disease in West Africa - the first 9 months of the epidemic and forward projections. N Engl J Med 2014;371(16):1481-1495.

4. Casillas A M, Nyamathi A M, Sosa A, Wilder C L, Sands H A. Current review of Ebola virus: pathogenesis, clinical presentation, and diagnostic assessment. Biol Res Nurs 2003;4(4):268-275.

5. Centers for Disease Control and Prevention (CDC). Cases of Ebola virus disease in Africa, 1976-2015[Internet]. Atlanta, USA: Centers for Disease Control and Prevention (CDC); 2015 Oct [Cited 2015 Oct 8]. Available from:

http://www.cdc.gov/vhf/ebola/outbreaks/history/distribution-map.html

6. Centers for Disease Control and Prevention (CDC). Ebola distribution map[Internet]. Atlanta, USA: Centers for Disease Control and Prevention (CDC); 2015 Oct [Cited 2015 Oct 8].

Available from:
http://www.cdc.gov/vhf/ebola/outbreaks/history/distribution-map.html

7. Kawaoka Y. How Ebola virus infects cells. N Engl J Med 2015;352(25):2645-2646.

8. Bray M, Geisbert T W. Ebola virus: the role of macrophages and dendritic cells in the pathogenesis of Ebola hemorrhagic fever. Int J Biochem Cell Biol 2005;37:1560-1566.

9. Mahanty S, Bray M. Pathogenesis of Filoviral haemorrhagic fevers. Lancet 2004;4(8):487-488.

10. Dowell S F, Mukunu R, Ksiazek T G, Khan A S, Rollin P E, Peters C J. Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. J Infect Dis 1999;179(Suppl 1):S87-91.

11. Jaax N, Jahrling P, Geisbert T, Geisbert J, Steele K, McKee K, Nagley D, Johnson E, Jaax G, Peters C. Transmission of Ebola virus(Zaire strain) to uninfected control monkeys in a biocontainment laboratory. Lancet 1995;346:1669-1671.

12. Johnson E, Jaax N, White J, Jahrling P. Lethal experimental infections of Rhesus monkeys by aerosolized Ebola virus. Int J Exp Pathol 1995;78:227-236.

13. Formenty P, Leroy E M, Epelboin A, Libama F, Lenzi M, Sudeck H, Yaba P, Allarangar Y, Boumandouki P, Nkounkou V B, Drosten C, Grolla A, Feldmann H, Roth C. Detection of Ebola virus

in oral fluid specimens during outbreaks of Ebola virus hemorrhagic fever in the Republic of Congo. Clin Infec Dis 2006;42:1521-1526.

14. Hwang E S. Preparedness for prevention of Ebola virus disease. J Korean Med Sci 2014;29:1185.

15. Marzi A, Feldmann H. Ebola virus vaccines: an overview of current approaches. Expert Rev Vaccines 2014;13(4):521-531.

16. Martinez M J, Volchkova V A, Raoul H, Alazard-Dany N, Reynard O, Volchkov V E. Role of VP30 phosphorylation in the Ebola virus replication cycle. J Infect Dis 2011;204(Suppl 3):S934-940.

17. Marzi A, Halfmann P, Hill-Batorski L, Feldmann F, Shupert W. L, Neumann G, Feldmann H, Kawaoka Y. an Ebola whole-virus vaccine is protective in nonhuman primates. Science 2015;348(6233):439-442.

18. Martinez M J, Salim A M, Hurtado J C, Kilgore P E. Ebola virus infection: overview and update on prevention and treatment. Infect Dis Ther 2015:1-26.

19. World Health Organization (WHO). Interim infection prevention and control guidance for care of patients with suspected or confirmed Filovirus haemorrhagic fever in health-care settings with focus on Ebola. Geneva: WHO 2014.

20. Centers for Disease Control and Prevention (CDC). Think Ebola: early recognition is critical for infection control[Internet]. Atlanta, USA: Centers for Disease Control and Prevention (CDC); 2015 Sept [Cited 2015 Oct 8]. Available from:

http://www.cdc.gov/vhf/ebola/healthcare-us/evaluating-patients/think-ebola.html

21. Centers for Disease Control and Prevention (CDC). Infection prevention and control recommendations for hospitalized patients under investigation(PUIs) for Ebola Virus Disease(EBOLA VIRUS DISEASE) in U.S. hospitals[Internet]. Atlanta, USA: Centers for Disease Control and Prevention (CDC); 2015 Sept [Cited 2015 Oct 8]. Avaliable from:

http://www.cdc.gov/vhf/ebola/healthcare-us/hospitals/infection-control.html

22. Centers for Disease Control and Prevention (CDC). CDC tightened guidance for U.S. healthcare workers on personal protective equipment for Ebola[Internet]. Atlanta, USA: Centers for Disease Control and Prevention (CDC); 2014 Oct [Cited 2015 Oct 8]. Available from:

http://www.cdc.gov/media/releases/2014/fs1020-ebola-personal-protective-equipment.html

23. American Dental Association (ADA). Oral Health Topics - Ebola Resources[Internet]. Chicago, USA: American Dental Association (ADA); 2014 Oct [Cited 2015 Oct 8]. Available from:

http://www.ada.org/en/member-center/oral-health-topics/ebola-resources

24. Dallatomasina S, Crestani R, Squire J S, Declerk H, Caleo G M, Wolz A, Stinson K, Patten G, Brechard R, Gbabai O B, Spreicher A, Herp M V, Zachariah R. Ebola outbreak in rural West Afica:

epidemiology, clinical features and outcomes. Trop Med Int Health 2015;10(4):448-454.

25. Bwaka M A, Bonnet M J, Calain P, Colebunders R, Roo A D, Guimard Y, Katwiki K R, Kibadi K, Kipasa M A, Kuvula K J, Mapanda B B, Massamba M, Mupapa K D, Muyembe-Tamfum J J, Ndaberey E, Peters C J, Rollin P E, Enden E V. Ebola hemorrhagic fever in Kikwit Democratic Republic of the Congo: Clinical observations in 103 patients. J Infect Dis 1999;179(Suppl 1):S1-7.

26. Kortepeter M G, Bausch D G, Bray M. Basic clinical and laboratory features of Filoviral hemorrhagic fever. J Infect Dis 2011;204:S810-816.

27. Qin E, Bi J, Zhao M, wang Y, Guo T, Yan T, Li Z, Sun J, Zhang J, Chen S, Wu Y, Li J, Zhong Y. Clinical features of patients with Ebola virus disease in Sierra Leone. Clin Infect Dis 2015;61(4):481-485.

28. Yan Ti, Mu J, Qin E, Wang Y, Liu L, Wu D, Jia H, Li Z, Guo T, Wang X, Qin Y, Li Y, Chen S, Zhang Y, Zhang J, Wu Y, Wang S, Li J. Clinical characteristics of 154 patients suspected of having Ebola virus disease in the Ebola holding center of Jui government hospital in Sierra Leone during the 2014 Ebola outbreak. Eur J Clin Microbiol Infect Dis 2015;34:2089-2095.

29. Bah E I, Lamah M C, Fletcher T, Jacob S T, Brett-Major D M, Sall A A, Shindo N, Fischer ll W A, Lamontagne F, Saliou S M, Bausch D G, Moumie B, Jagatic T, Sprecher A, Lawler J V, Mayet T, Jacquerioz F A, Baggi M F M, Ballenas C, Clement C, Mardel S,

Faye O, Faye O, Soropoqui B, Magassouba N, Koivoqui L, Pinto R, Fowler R A. Clinical presentation of patients with Ebola virus disease in Conarky, Guinea. N Engl J Med 2015;372:40-47.

30. Bonnet M J, Akamituna P, Mazaya A. Unrecognized Ebola hemorrhagic fever at Mosango hospital during the 1995 epidemic in Kikwit, Democratic Republic of the Congo. Emerg Infect Dis 1998;4(3):508-510.

31. Chertow D S, Kleine C, Edwards J K, Scaini R, Giuliani R, Sprecher A. Ebola virus disease in West Africa - clinical manifestations and management. N Engl J Med 2014;371(22):2054-2057.

32. Piot P, Bureau P, Breman G, Heymann D, Kintoki V, Masamba M, Mbuyi M, Miatudila M, Ruppol F, Van Nieuwenhove S, white M K, Vandergroen G, Wulff H, Johnson K M. Clinical aspects of Ebola virus infection in Yambuku area, Zaire, 1976. In: Pattyn S R, ed. Ebola virus haemorrhagic fever. Amsterdam: Elsevier/Morth-Holland Biomedical Press 1978:7-14.

33. Isaacson M, Sureau P, Courteille G, Pattyn S R. Clinical aspects of Ebola virus disease at the Ngaliema hospital, Kinshasa, Zaire, 1976. In: Pattyn S R, ed. Ebola virus haemorrhagic fever. Amsterdam: Elsevier/Morth-Holland Biomedical Press 1978:22-26.

34. Smith D H, Francis D P, Simpson D I H. African haemorrhagic fever in the Southern Sudan, 1976: clinical manifestations. In: Pattyn S R, ed. Ebola virus haemorrhagic fever. Amsterdam: Elsevier/Morth-Holland Biomedical Press 1978:27-30.

35. Sureau P H. Firsthand clinical observations of hemorrhagic manifestations in Ebola hemorrhagic fever in Zaire. Rev Infect Dis 1989;11(4):790-793.

36. Hujoel P P, Stott-Miller M. Retinal and gingival hemorrhaging and chronic hyperglycemia. Diabetes Care 2011;34(1):181-184.

37. Martin P, Laupland K B, Frost E H, Valiquette L. Laboratory diagnosis of Ebola virus disease. Intensive Care Med 2015;41(5):895-898.

38. Shaw M, Palese P. Fields virology. Philadelphia, PA: Lippincott williams & Wilkins 2013:1151-1185.

39. Rowe A K, Bertoli J, Khan A S, Mukunu R, Muyembe-Tamfum J J, Bressler D, Williams A J, Peters C J, Rodriguez L, Feldmann H, Nichol S T,, Rollin P E, Ksiazek T G. Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of the Congo. J Infect Dis 1999;179(Suppl 1):S28-35.

40. Leroy E M, Baize S, Lu C Y, McCornick J B, Georges A J, Georges-Courbot M-C, Lansoud-Soukate J, Fisher-Hoch S P. Diagnosis of Ebola haemorrhagic fever by RT-PCR in an epidemic setting. J Med Virol 2000;60(4):463-467.

41. Schieffelin J S, Shaffer J G, Goba A, Gbakie M, Gire S K, Colubri A, Sealfon R S G, Kanneh L, Moigboi A, Momoh M, Fullah M, Moses L M, Brown B L, Andersen K G, Winnicki S, Schffner S F, Park D J, Yozwiak N L, Jiang P P, Kargbo D, Jalloh S, Fonnie M,

Sinnah V, French I, Kovoma A, Kamara F K, Tucker V, Konuwa E, Sellu J, Mustapha I, Foday M, Yillah M, Kanneh F, Saffa S, Masssally J L V, Boisen M L, Branco L M, Vandi M A, Grant D S, Happi B, Gevao S M, Fletcher T E, Fowler R A, Bauch D G, Sabeti P C, Khan S H, Garry R F. Clinical illness and outcomes in patients with Ebola in Sierra Leone. N Engl J Med 2014;371:2092-2100.

42. Galvin S, Flint S R, Healy C M. Ebola virus disease: review and implications for dentistry in Ireland. J Ir Dent Assoc 2015;61(3):141-143.

43. Topazian R G, Goldberg M H, Hupp J R. Oral and maxillofacial infections. Saunders 2002.

44. William E D, Robert J H. Focus on Ebola virus research. Viral Immuol 2015;28(1):1-2.

45. Peters C J, LeDuc J W. An introduction to Ebola: the virus and the disease. J Infect Dis 1999;179(1):9-16.

46. Audet J, Kobinger P K. Immune evasion in Ebolavirus infections. Viral Immunol 2015;28(1):10-18.

47. Geisbert T W, Feldmann H. Recombinant vesicular stomatitis virus-vased vaccines against Ebola and Marburg virus infections. J Infect Dis 2011;204:1075-1081.

48. Kreuels B, wichmann D, Emmerich P, Schmidt-Chanasit J, Heer Gd, Kluge S, Sow A, Renne T, Gunther S, Lohse A W, Addo M M, Schmiedel S. A case of severe Ebola virus infection complicated by gram-negative septicemia. N Engl J Med 2014;371:2394-2401.

49. Kawaoka Y. How Ebola virus infects cells. N Engl J Med 2005;352(25):2645-2646.

50. Geisbert T W, Feldmann H. Recombinant vesicular stomatitis virus-based vaccines against Ebola and Marburg virus infections. J Infect Dis 2011;204:S1075-1081.

51. Kerstiens B, Matthys F. Interventions to control virus transmission during an outbreak of Ebola hemorrhagic fever: experience from Kikwit, Democratic Republic of the Congo, 1995. J Infect Dis 1999;179(Suppl 1):S263-267.

52. Leffel E K, Reed D S. Marburg and Ebola viruses as aerosol threats. Biosecur Bioterror 2004;2(3):186-191.

53. Geisbert T W, Daddario-DiCaprio K M, Geisbert J B, Reed D S, Feldmann F, Grolla A, Stroher U, Fritz E A, Hensley L E, Jones S M, Feldmann H. Vesicular stomatitis virus-based vaccines protect nonhuman primates against aerosol challenge with Ebola and Marburg viruses. Vaccine 2008;26:6894-6900.

54. Murray M J. Ebola virus disease: a review of its past and present. Anesth Analg 2015;121(3):798-809.

55. Choi W Y, Hong K J, Hong J E, Lee W J. Progress of vaccine and drug development for Ebola preparedness. Clin Exp Vaccine Res 2015;4:11-16.

56. Jones S M, Feldmann H, Daddario-DiCaprio K M, Geisbert J, Stroher U P, Geisbert T. The magic bullet; VSV vaccines and therapy. In: Proceedings of the Filoviruses: recent advances and future challenges. 2006; Winnipeg, Canada.

57. Feldmann H, Jones S M, Daddario-DiCaprio K M, Geissbert J B, Stroher U, Grolla A, Bray M, Fritz E A, Fernando L, Feldmann F, Hens-ley L E, Geisbert T W. Effective post-exposure treatment of Ebola infection. PLOS Pathog 2007;3:2.

58. Geisbert T W, Lee A C H, Robbins M, Geisbert J B, Honko A N, Sood V, Johnson J C, Jong Sd, Tavakoli I, Judge A, Hensley L E, MacLachlan I. Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study. Lancet 2010;375(9729):1896-1905.

59. Furuta Y, Gowen B B, Takahashi K, Shiraki K, Smee D F, Barnard D L. Favipiravir(T-705), a novel viral RNA polymerase inhibitor. Antiviral Res 2013;100(2):446-454.

60. Florescu D F, Keck M A. Development of CMX001(Brincidofovir) for the treatment of serious diseases or conditions caused by dsDNA viruses. Expert Rev Anti Infect Ther 2014;12(10):1171-1178.

61. Mupapa K, Massamba M, Kibadi K, Kuvula K, Bwaka A, Colebuners R. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. J Infect Dis 1999;179(Suppl 1):S18-23.

62. Qiu X, Wong G, Audet J, Bello A, Fernando L, Alimonti J B, Fausther-Bovendo H, Wei H, Aviles J, Hiatt E, Johnson A, Morton J, Swope K, Bohorov O, Bohorova N, Goodman C, Kim D, Pauly M H, Velasco J, Pettitt J, Olinger G G, Whaley K, Xu B, Strong J E, Zeitlin

L. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. Nature 2014;514(7520):47-53.

Tables

Table 1 Virus families implicated in Viral haemorrhagic fevers[2]

Families	Viral haemorrhagic fevers
Arenaviridae	Lassa fever haemorrhagic fever
	Lujo virus haemorrhagic fever
	Argentine haemorrhagic fever
	Bolivia haemorrhagic fever
	Brazilian and Venezuelan haemorrhagic fever
Bunyaviridae	Hantavirus genus that causes haemorrhagic fever with renal syndrome (HFRS)
	Crimean-Congo haemorrhagic fever(CCHF)
	Virus from the Nairovirus genus
	Garissa virus and Ilesha virus from the Orthobunyavirus
	Rift Valley fever (RVF) virus from the *Phlebovirus* genus
Filoviridae	Ebola virus and Marburg virus
Flaviviridae	Dengue
	Yellow fever
	Two viruses in the tick-borne encephalitis group that cause VHF: Omsk haemorrhagic fever virus and Kyasanur Forest disease virus

Table 2 Cases of Ebola Virus Disease in Africa, 1976−2015[5]

Country	Town	Cases	Deaths	Species	Year
Dem. Rep. of Congo	multiple	66	49	*Zaire ebolavirus*	2014
Multiple countries	multiple	28424	11311	*Zaire ebolavirus*	2014
Uganda	Luwero District	6	3	*Sudan ebolavirus*	2012
Dem.Rep. of Congo	Isiro Health Zone	36	13	*Bundibugyo ebolavirus*	2012
Uganda	Kibaale District	11	4	*Sudan ebolavirus*	2012
Uganda	Luwero District	1	1	*Sudan ebolavirus*	2011
Dem. Rep. of Congo	Luebo	32	15	*Zaire ebolavirus*	2008
Uganda	Bundibugyo	149	37	*Bundibugyo ebolavirus*	2007
Dem. Rep. of Congo	Luebo	264	187	*Zaire ebolavirus*	2007
South Sudan	Yambio	17	7	*Zaire ebolavirus*	2004
Republic of Congo	Mbomo	35	29	*Zaire ebolavirus*	2003
Republic of Congo	Mbomo	143	128	*Zaire ebolavirus*	2002
Republic of Congo	Not specified	57	43	*Zaire ebolavirus*	2001
Gabon	Librevile	65	53	*Zaire ebolavirus*	2001
Uganda	Gulu	425	224	*Sudan ebolavirus*	2000
South Africa	Johannesburg	2	1	*Zaire ebolavirus*	1996
Gabon	Booue	60	45	*Zaire ebolavirus*	1996
Gabon	Mayibout	37	21	*Zaire ebolavirus*	1996
Dem. Rep. of Congo	Kikwit	315	250	*Zaire ebolavirus*	1995
Cote d'Ivoire (Ivory Coast)	Tai Forest	1	0	*Tai Forest ebolavirus*	1994
Gabon	Mekouka	52	31	*Zaire ebolavirus*	1994
South Sudan	Nzara	34	22	*Sudan ebolavirus*	1979
Dem. Rep. of Congo	Tandala	1	1	*Zaire ebolavirus*	1977
South Sudan	Nzara	284	151	*Sudan ebolavirus*	1976
Dem. Rep. of Congo	Yambuku	318	280	*Zaire ebolavirus*	1976

Table 3 Overview of EVD developing vaccines[18]

Vaccine candidate names	Sponsor or manufacturer	Location	Stage of evaluation
VRC-EBODNA023-00-VP (Ebloa DNA Plasmid Vaccine)	National Institute of Allergy and Infectious Diseases (NIAID)	Uganda	Phase IB completed
VRC-MARDNA025-00-VP (Marburg DNA Plasmid Vaccine)			
VRC-EBODNA023-00-VP (Ebola DNA Plasmid Vaccine)	NIAID	US	Phase I completed
VRC-MARDNA025-00-VP (Marburg DNA Plasmid Vaccine)			
Ad5-EBOV (Ebola Adenovirus Vector Vaccine)	Jiangsu Province CDC with Beijing Institute of Biotechnology Tianjin Cansino Biotechnology, Inc.	China	Phase I ongoing
rVSV△G-ZEBOV (recombinant vesicular stomatitis virus expressing the envelope glycoprotein of Ebola virus Zaire)	US Centers for Disease Control and Prevention (CDC)	Sierra Leone	Phase II/III ongoing
cAd3-EBOZ with MVA-BN® FILO (Prime-Boost regimen)	University of Maryland with Wellcome Trust, NIAID Leidos, Inc.	Mali	Phase IB ongoing
(Bivalent) VRC-EBOAdc069-00-vp (cAd3-EBO)	University of Maryland	Mali	Phase I ongoing
VRC-EBODNA069-00-VP (cAd3-EBO), Ebola Chimpanzee Adenovirus Vector Vaccine	NIAID	US	Phase I ongoing
VRC-EBOMVA079-00-VP (MVA-EbolaZ) (Ebola Modified Vaccinia Virus Ankara Vaccine) with and without boost to VRC-EBOADC069-00-VP (cAd3-EBO)	NIAID	US	Phase I/IB ongoing
VRC-EBOADC069-00-VP (cAd3-EBO) (Ebola Chimpanzee Adenovirus Vector Vaccine) VRC-EBOADC076-00-VP (cAd3-EBOZ), Ebola Chimpanzee Adenovirus Vector Vaccines	NIAID	Uganda	Phase IB ongoing

Table 3 Continued[18]

Vaccine candidate names	Sponsor or manufacturer	Location	Stage of evaluation
rVSV△-ZEBOV GP (BPSC1001)	Universitatsklinikum Hamburg-Eppendorf	Germany	Phase I ongoing
rVSV△-ZEBOV GP (BPSC1001)	Dalhousie University Canadian Institutes of Health Research NewLink Genetics Corp.	Canada	Phase I ongoing
Monovalent Zaire Ebola Viral Vector Candidate Vaccine (cAd3-EBO Z) with MVA-BN® Filo (Prime-boost regimen)	University of Oxford	UK	Phase IA ongoing
MVA-EBO Z alone and cAd3-EBO Z with MVA-EBOZ (prime-boost regimen)	University of Oxford	UK	Phase I ongoing
EBOV GP Vaccine (Ebola Virus Glycoprotein) with or without Matrix-M® adjuvant	Novavax	Australia	Phase I ongoing
VRC-EBOADV018-00-VP (Recombinant Ebola Adenoviral Vector Vaccine)	NIAID	US	Phase I ongoing
VSVG-ZEBOV (Vesicular stomatitis virus-Ebola Zaire) ChAd3-EBO Z (chimpanzee adenovirus 3-Ebola Zaire)	NIAID	Liberia	Phase II ongoing
VSV-ZEBOV	University of Oxford WHO Wellcome Trust and others	Kenya	Phase I ongoing
Ad5-EBOV (Adenovirus type 5 vector-based EBOV)	First Affiliated Hospital of Zhejiang University Beijing Institute of Bioengineering Academy of Military Medical Sciences, Tianjin Cansino Biotechnology Inc.	China	Phase I ongoing
BPSC-1001 (VSV △G-ZEBOV) (recombinant vesicular stomatitis virus expressing envelope glycoprotein of Ebola virus Zaire)	NewLink Genetics Corp.	US	Phase I ongoing

Table 4 Reports of orofacial and other signs and symptoms of mild-to-moderately severe EVD in addtion to fever[3,24-5,29-34]

	Oral features			*Other features*		
First author, Year	*Oral bleeding*	*Oral mucosal lesions*	*Odynophagia*	*Other bleeding*	*Conjunctivitis*	*Rash*
Bonnet, 1998[34]	bleeding cracks on the lips diffuse bleeding (i.e., gums, tongue)	Oral thrush-like lesions	NR	bleeding at injection sites	NR	maculopapular and petechial
Bwaka, 1999[35]	NR	NR	Odynophagia dysphagia Sore throat (58%)	Injection site (5%)	Conjunctival injection (47%)	Maculopapular rash
Chertow, 2014[37]	NR	Oral ulcers and thrush	Troat pain dysphagia	NR	Conjunctival injection	NR
Piot P, 1978[38]	Gingival bleeding (25.6%)	Oral-throat lesions(73.6%) fissures on the lips Herpetic oral lesions Grayish exudative patches	Sore throat (79.2%) Dysphagia	Epistaxis (16.7%) Injection site (6.6%)	Conjunctivitis (58.2%)	Skin rash
Isaacson M, 1978[39]	Gingival bleeding	Reddening of the tongue and throat	Sore throat Dysphagia	Injection site	NR	Morbiliform rash
Smith DH, 1978[40]	Bleeding from nose, mouth and gums (50% in fatal cases)	NR	Dry painful throat(63%)	Epistaxis Vaginal hemorrhage	Subconjunctival hemorrhage	Measles like, papular or maculo-papular rash (52%)
WHO Ebola Response Team, 2014[41]	Bleeding gums (2.3%)	NR	Difficulty swallowing (32.9%) Sore throat (21.8%)	Unexplained bleeding (18%) Epistaxis (1.9%) Injection site (2.4%)	Conjunctivitis (20.8%)	Rash (5.8%)
Kortepeter MG, 2011[42]	NR	Pharyngeal erythema	Sore throat	Injeftion site	Conjunctival hemorrhage	Maculopapular rash
Sureau PH, 1989[44]	Gingival and oral bleeding (25.6% in fatal cases, none in nonfatal cases)	Oropharyngeal bleeding ulceration	Pharyngitis Dysphagia	Epistaxis (16.7% in fatal, none in nonfatal cases) Injection site (6.6% in fatal, none in nonfatal)	Hemorrhagic conjunctivitis	Erythematous maculopapular rash

NR; Not reported

Table 5 Overview of Ebola virus therapeutics in development[18]

Agent	Manufacturer	Stage of evaluation
TKM-Ebola	Tekmira (Burnaby, British Columbia, Canada)	Phase I ongoing
TKM-Ebola	Tekmira (Burnaby, British Columbia, Canada)	Phase I terminated
T-705 (Favipiravir)	Institut National de la Sante Et de la Recherche Medicale, France	Phase II ongoing
CMX001 (Brincidofovir)	Chimerix (Durham, NC)	Phase II (withdrawn prior recruitment)
JK-05	Sihuan Phamaceutical Holdings Group Ltd and Academy of Military Medical Sciences (Beijing, China)	Animal studies completed; now considered for use in emergency situations for army only
BCX4430	BioCryst Pharmaceuticals Inc. Durham, NC	Phase I ongoing
AVI-6002	Sarepta Therapeutics (Cambridge, MA)	Phase I completed
Anti-Ebola hyperimmune globulin	None identified	Animal studies completed
ZMapp	National Institutes of Health Clinical Center (National Institute of Allergy and Infectious Diseases (NIAID))	Phase I/II ongoing

N/A not Applicable

Figure legends

Figure 1. EHF diagnosed cases and fatalities by country in Africa, 1976–2002.[4]

Figure 2. Ebola virus disease distribution map displaying the cases in Africa, 1976–2015.[6]

Figure 3. Entry of Ebola virus into a cell by the action of two endosomal proteases, cathepsin B and cathepsin L.[7]

Figure 4. Roles of macrophages and dendritic cells infected by Ebola virus in inducing the clinical features of Ebola hemorrhagic fever.[8]

Figure 5. Evaluation protocols when caring for patients under investigation or patients with confirmed Ebola Virus Disease (EVD). The phrase "Think Ebola." mean early recognition is critical for infection control.[20]

Figures

Figure 1.

* River near the town of Yamabuku where the first case of EHF was documented.

Countries in red denote regions where new subtypes of Ebola virus (pathogenic to humans)

Countries in black denote regions where additional EHF outbreaks in Africa have occurred.

- COTE D'IVOIRE - 1 case, no fatalities
- LIBERIA - 1 case, no fatalities
- SUDAN - 318 cases, 163 fatalities
- DR CONGO (ZAIRE) - 634 cases, 526 fatalities
- Republic of CONGO - 58 cases, 44 fatalities
- UGANDA - 428 cases, 224 fatalities
- GABON - 205 cases, 151 fatalities
- SOUTH AFRICA - 2 cases, 1 fatality

TOTAL in AFRICA - 1644 cases, 1109 fatalities

Figure 2.

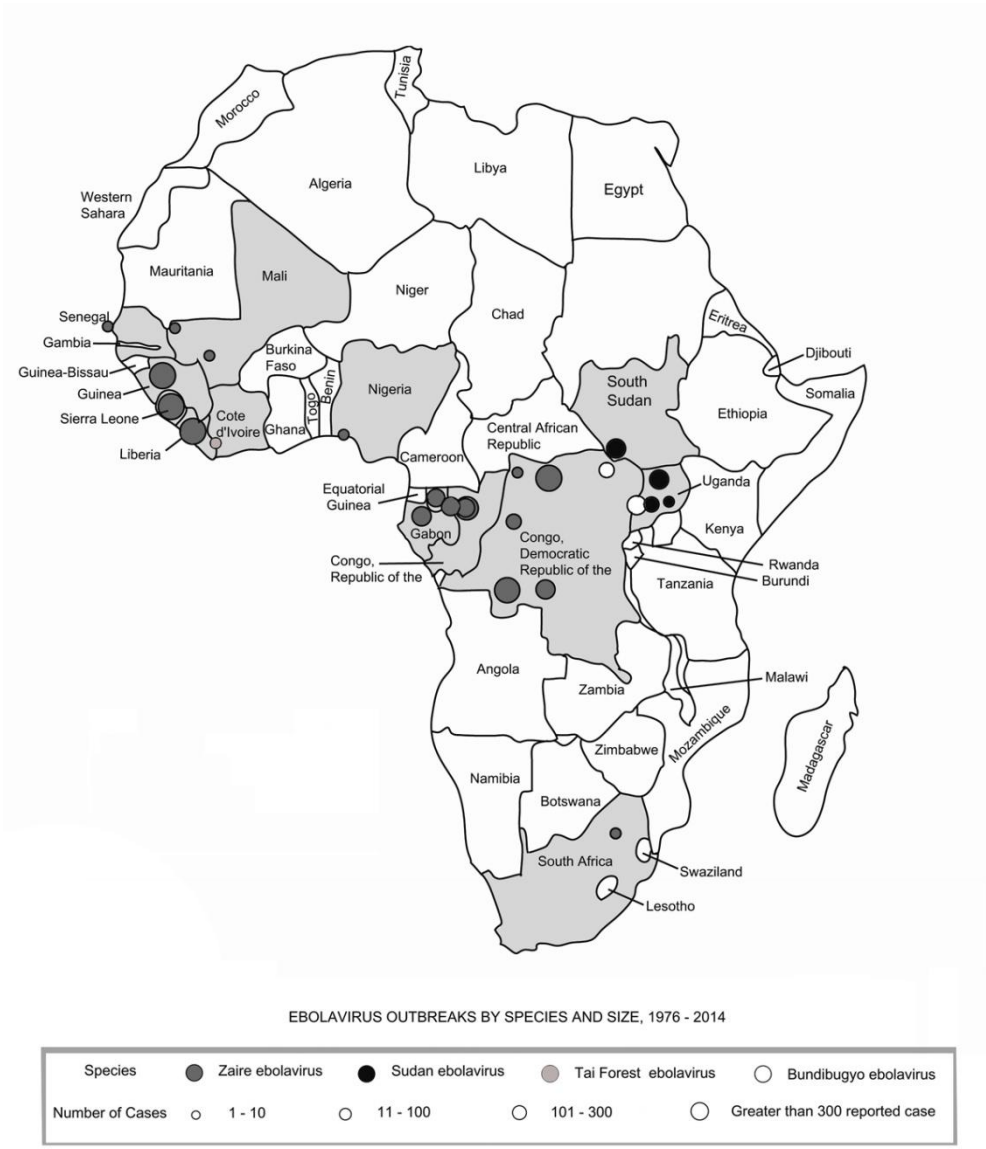

Morocco
Tunisia
Algeria
Libya
Egypt
Western Sahara
Mauritania
Mali
Niger
Chad
Eritrea
Djibouti
Senegal
Gambia
Guinea-Bissau
Guinea
Sierra Leone
Liberia
Burkina Faso
Togo
Benin
Nigeria
Cote d'Ivoire
Ghana
South Sudan
Somalia
Ethiopia
Central African Republic
Cameroon
Uganda
Equatorial Guinea
Gabon
Kenya
Congo, Democratic Republic of the
Congo, Republic of the
Rwanda
Burundi
Tanzania
Angola
Zambia
Malawi
Zimbabwe
Mozambique
Madagascar
Namibia
Botswana
South Africa
Swaziland
Lesotho
EBOLAVIRUS OUTBREAKS BY SPECIES AND SIZE, 1976 - 2014
Species
Zaire ebolavirus
Sudan ebolavirus
Tai Forest ebolavirus
Bundibugyo ebolavirus
Number of Cases
1 - 10
11 - 100
101 - 300
Greater than 300 reported case

Figure 3.

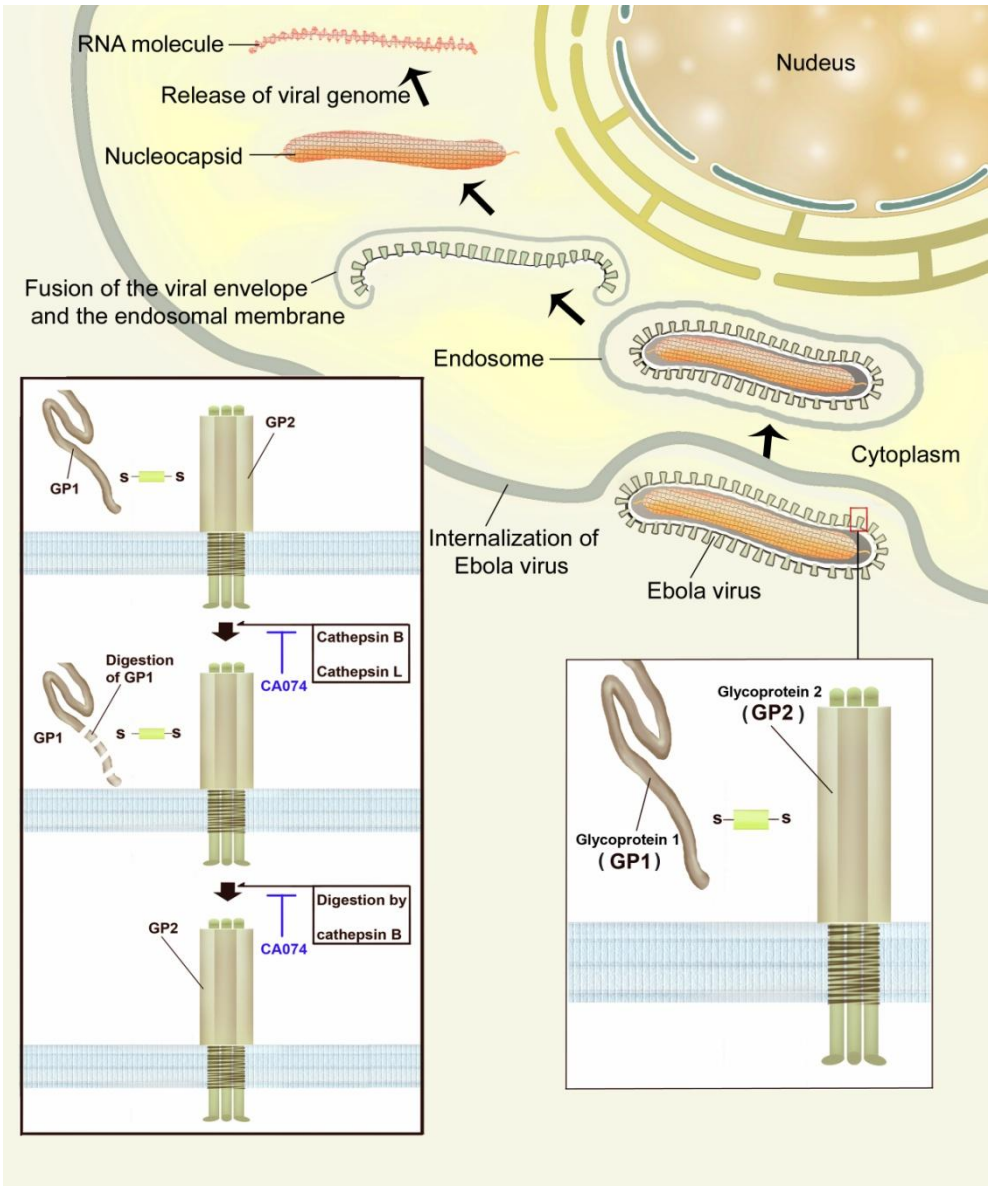

RNA molecule
Release of viral genome
Nucleocapsid
Nudeus
Fusion of the viral envelope
and the endosomal membrane
Endosome
Cytoplasm
Internalization of
Ebola virus
Ebola virus
GP1
S
S
GP2
Cathepsin B
Cathepsin L
CA074
Digestion
of GP1
GP1
S
S
Digestion by
cathepsin B
CA074
GP2
Glycoprotein 2
(GP2)
S
S
Glycoprotein 1
(GP1)

Figure 4.

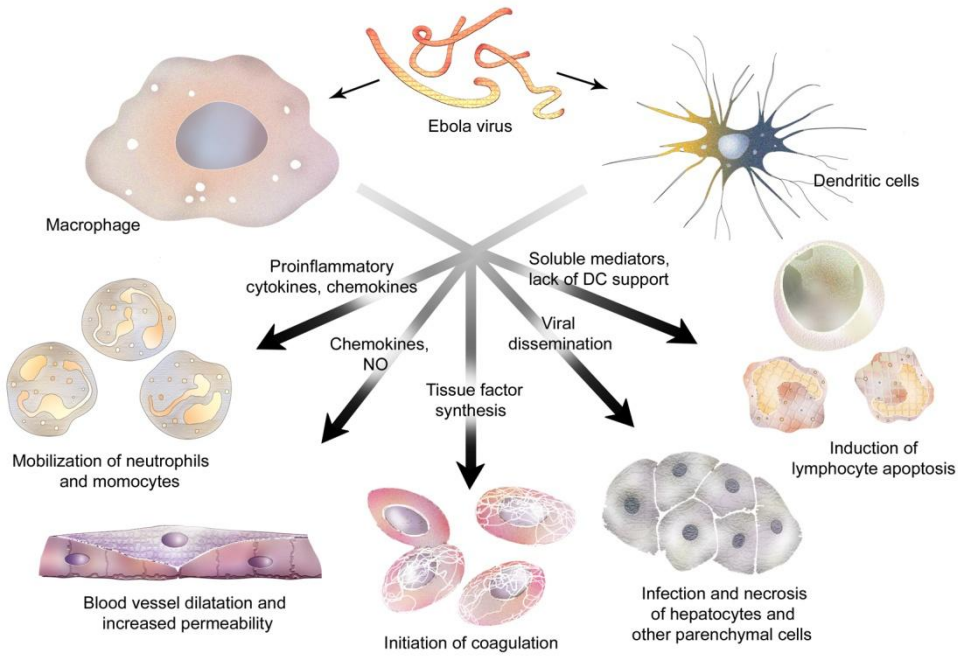
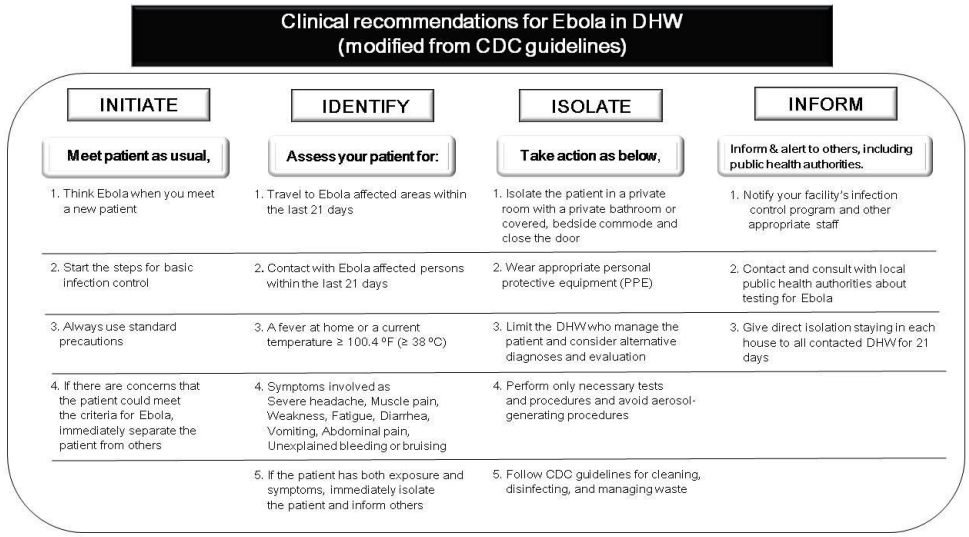

Ebola virus
Macrophage
Dendritic cells
Proinflammatory cytokines, chemokines
Soluble mediators, lack of DC support
Chemokines, NO
Viral dissemination
Tissue factor synthesis
Mobilization of neutrophils and momocytes
Induction of lymphocyte apoptosis
Blood vessel dilatation and increased permeability
Initiation of coagulation
Infection and necrosis of hepatocytes and other parenchymal cells

Figure 5.


Clinical recommendations for Ebola in DHW
(modified from CDC guidelines)
INITIATE
Meet patient as usual,
1. Think Ebola when you meet a new patient
2. Start the steps for basic infection control
3. Always use standard precautions
4. If there are concerns that the patient could meet the criteria for Ebola, immediately separate the patient from others
IDENTIFY
Assess your patient for:
1. Travel to Ebola affected areas within the last 21 days
2. Contact with Ebola affected persons within the last 21 days
3. A fever at home or a current temperature ≥ 100.4 °F (≥ 38 °C)
4. Symptoms involved as Severe headache, Muscle pain, Weakness, Fatigue, Diarrhea, Vomiting, Abdominal pain, Unexplained bleeding or bruising
5. If the patient has both exposure and symptoms, immediately isolate the patient and inform others
ISOLATE
Take action as below,
1. Isolate the patient in a private room with a private bathroom or covered, bedside commode and close the door
2. Wear appropriate personal protective equipment (PPE)
3. Limit the DHW who manage the patient and consider alternative diagnoses and evaluation
4. Perform only necessary tests and procedures and avoid aerosol-generating procedures
5. Follow CDC guidelines for cleaning, disinfecting, and managing waste
INFORM
Inform & alert to others, including public health authorities.
1. Notify your facility's infection control program and other appropriate staff
2. Contact and consult with local public health authorities about testing for Ebola
3. Give direct isolation staying in each house to all contacted DHW for 21 days

국문초록

에볼라 바이러스 감염의 구강 내 소견에 대한 고찰

김 민 지
치의학과
치의학전문대학원
서울대학교

에볼라 바이러스 감염(Ebola virus disease)은 치명적인 바이러스성 출혈열(viral hemorrhagic fever)을 일으키며, 사하라 사막 이남의 아프리카 지역에서 처음 발병하였다. 지난 2014년, 서아프리카 지역을 중심으로 에볼라 바이러스 감염이 창궐한 이후, 미국, 유럽 등지에서도 감염자가 나타나면서 화두에 올랐다. 아직까지 치과 의료 환경에서 전염 사례가 보고된 바는 없으나, 에볼라 바이러스의 전염이 타액과 같은 인간의 분비물로부터 이루어진다는 사실은 치과 의료 종사자들의 에볼라 바이러스 감염에 대한 감염 위험성이 높음을 시사한다. 따라서 치과 의료 종사자들에게 있어서, 구강 내 소견을 통해 에볼라 바이러스 감염을 예측하여 전염을 예방할 수 있도록 하는 것이 중요하다.

본 논문에서는 에볼라 바이러스 감염의 구강 내 증상을 고찰하고, 그러한 증상이 나타나는 발병기전 및 가능한 치료, 예방법에 대하여 논해 볼 것이다. 뿐만 아니라, 교차 감염에 의해 에볼라 바이러스가 확산되는 것을 방지할 수 있도록, 구강 내를 관리하는 의료 종사자들을 위한 감염 예방 수칙을 제시해보고자 한다.

본 논문은 문헌을 통한 조사 연구를 기반으로 한다. 에볼라 바이러스 감염의 역학, 발병기전, 전염, 예방에 대한 연구와 증례보고를 분석하였다. PubMed 와 Google 학술검색을 통해 ['Ebola' AND 'epidemiology'/'Pathogenesis'/'Transmission'/'Prevention']을 키워드로 문헌을 수집하였고, 1987 년 이후에 발표된 문헌들을 선별하였다. 에볼라 바이러스 감염의 구강 내 증상에 관한 연구를 위해 [‘Ebola' AND 'oral' OR 'facial' OR 'dental']을 키워드로 문헌 검색을 시행했다. 그 중, 질환의 초기부터 환자의 증상을 관찰하였고, 에볼라 바이러스 감염의 구강 및 안면에 대한 증상을 언급한 문헌을 선별하여, 증상의 빈도와 묘사된 양상을 비교하여 분석했다. 에볼라 바이러스 감염의 감염 예방을 위한 관리 지침은 공인된 보건 기구인 미국 질병관리본부(Centers for Disease Control and Prevention, CDC)와 세계 보건 기구(World Health Organization, WHO)에서 발표된 표준 수칙을 기반으로 하였다.

에볼라 바이러스 감염은 높은 사망률을 보이는 두려운 질환이다. 의료계 종사자들은 언제나 감염의 위험에 노출되어 있지만, 잠재적인 감염성은 가지면서 증상이 없는 에볼라 바이러스 감염 환자에 대한 주의가 필요하다. 에볼라 바이러스에 감염된 환자의 타액 내에서 에볼라 바이러스의 항원이 검출되었다는 결과는 치과 의료계 종사자의 감염 위험성이 높음을 시사한다. 환자의 해외 체류 경력이나 에볼라 바이러스

감염 환자와의 접촉 여부에 대한 정보 수집과 에볼라 바이러스 감염의 초기 증상에 대한 임상 검사를 통해 의료진의 감염 위험을 최소화할 수 있다. 만일 환자가 두 경우에 모두 해당된다면 표준 지침에 따라 해당 환자를 즉시 격리해야 하며, 증상은 없지만 에볼라 바이러스 감염 환자에 노출된 경험이 있다면 치과 치료는 에볼라 바이러스 감염의 최대 잠복기인 21 일 뒤로 연기하는 것이 바람직하다. 무엇보다, 의료진의 감염 및 교차 감염의 위험을 줄이기 위해서는, 모든 환자에 있어 에볼라 바이러스에 대한 감염 가능성을 염두에 두고 표준 예방 지침을 엄격히 준수하는 것이 중요하다.

주요어 : 에볼라 바이러스 감염, 구강 내 소견, 치과, 감염 예방

학 번 : 2012 – 22147