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Review of Ebola Virus Disease in the Oral Cavity

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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
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국문초록
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 \(\mu\)m 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”. Ebola virus disease outbreaks have primarily been in distant villages in Central Africa over the past decades (Figure 1), but the 2014 epidemic affected West African countries where no Ebola virus outbreak had previously occurred, 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), 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).

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). 

This novel finding about how the Ebola virus infects cells offers new possibilities for treatment of this infection. 

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). 

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 inflammatory 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 responses to Ebola virus infection show differences according to the individual genetic characteristics.\(^8\)

**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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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. 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. 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.\textsuperscript{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:\textsuperscript{19,21}

\begin{itemize}
  \item Use of personal protective equipment (for example, double gloving, leg covers and disposable shoe covers)
  \item Choose gloves of exact size
  \item Follow safe injection practices, handling with care and limiting the use of needles and other sharps
  \item Clean the environmental surfaces, including surfaces that may be touched by hands (not necessarily disinfection)
  \item Perform scrupulous hand cleaning before and after glove use
\end{itemize}
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: 

. 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 deferred 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. 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. 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. 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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{25}

\textbf{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.\textsuperscript{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.\(^3\)

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.\textsuperscript{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.\textsuperscript{31,41} Several potential therapeutic agents are tested in phase I, II, and III clinical trials (Table 5).\textsuperscript{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 Favipirarvivir 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.
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. 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.
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Table 1 Virus families implicated in Viral haemorrhagic fevers

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<td>Two viruses in the tick–borne encephalitis group that cause VHF: Omsk haemorrhagic fever virus and Kyasanur Forest disease virus</td>
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<td>60</td>
<td>45</td>
<td>Zaire ebolavirus</td>
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<td>Gabon</td>
<td>Mayibout</td>
<td>37</td>
<td>21</td>
<td>Zaire ebolavirus</td>
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<td>Cote d'Ivoire (Ivory Coast)</td>
<td>Tai Forest</td>
<td>1</td>
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<td>Tai Forest ebolavirus</td>
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<td>Gabon</td>
<td>Mekouka</td>
<td>52</td>
<td>31</td>
<td>Zaire ebolavirus</td>
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<td>South Sudan</td>
<td>Nzara</td>
<td>34</td>
<td>22</td>
<td>Sudan ebolavirus</td>
<td>1979</td>
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<td>Dem. Rep. of Congo</td>
<td>Tandala</td>
<td>1</td>
<td>1</td>
<td>Zaire ebolavirus</td>
<td>1977</td>
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<tr>
<td>South Sudan</td>
<td>Nzara</td>
<td>284</td>
<td>151</td>
<td>Sudan ebolavirus</td>
<td>1976</td>
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<tr>
<td>Vaccine candidate names</td>
<td>Sponsor or manufacturer</td>
<td>Location</td>
<td>Stage of evaluation</td>
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<tr>
<td>-------------------------</td>
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<td></td>
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<tr>
<td>VRC–EBODNA023–00–VP (Ebola DNA Plasmid Vaccine)</td>
<td>National Institute of Allergy and Infectious Diseases (NIAID)</td>
<td>Uganda</td>
<td>Phase IB completed</td>
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<tr>
<td>VRC–MARDNA025–00–VP (Marburg DNA Plasmid Vaccine)</td>
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<tr>
<td>VRC–EBODNA023–00–VP (Ebola DNA Plasmid Vaccine)</td>
<td>NIAID</td>
<td>US</td>
<td>Phase I completed</td>
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<tr>
<td>VRC–MARDNA025–00–VP (Marburg DNA Plasmid Vaccine)</td>
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<tr>
<td>Ad5–EBOV (Ebola Adenovirus Vector Vaccine)</td>
<td>Jiangsu Province CDC with Beijing Institute of Biotechnology, Tianjin Cansino Biotechnology, Inc.</td>
<td>China</td>
<td>Phase I ongoing</td>
<td></td>
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<tr>
<td>rVSV△G–ZEBOV (recombinant vesicular stomatitis virus expressing the envelope glycoprotein of Ebola virus Zaire)</td>
<td>US Centers for Disease Control and Prevention (CDC)</td>
<td>Sierra Leone</td>
<td>Phase II/III ongoing</td>
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<tr>
<td>cAd3–EBOZ with MVA–BN® FILO (Prime–Boost regimen)</td>
<td>University of Maryland with Wellcome Trust, NIAID Leidos, Inc.</td>
<td>Mali</td>
<td>Phase IB ongoing</td>
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<tr>
<td>(Bivalent) VRC–EBOAdc069–00–vp (cAd3–EBO)</td>
<td>University of Maryland</td>
<td>Mali</td>
<td>Phase I ongoing</td>
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<tr>
<td>VRC–EBODNA069–00–VP (cAd3–EBO), Ebola Chimpanzee Adenovirus Vector Vaccine</td>
<td>NIAID</td>
<td>US</td>
<td>Phase I ongoing</td>
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<tr>
<td>VRC–EBOMVA079–00–VP (MVA–EbolaZ) (Ebola Modified Vaccinia Virus Ankara Vaccine) with and without boost to VRC–EBOADC069–00–VP (cAd3–EBO)</td>
<td>NIAID</td>
<td>US</td>
<td>Phase I/IB ongoing</td>
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<tr>
<td>VRC–EBOADC069–00–VP (cAd3–EBO) (Ebola Chimpanzee Adenovirus Vector Vaccine)</td>
<td>NIAID</td>
<td>Uganda</td>
<td>Phase IB ongoing</td>
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<tr>
<td>Vaccine candidate names</td>
<td>Sponsor or manufacturer</td>
<td>Location</td>
<td>Stage of evaluation</td>
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<tr>
<td>------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>rVSVΔ−ZEBOV GP (BPSC1001)</td>
<td>Universitätsklinikum Hamburg-Eppendorf</td>
<td>Germany</td>
<td>Phase I ongoing</td>
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<tr>
<td>rVSVΔ−ZEBOV GP (BPSC1001)</td>
<td>Dalhousie University Canadian Institutes of Health Research NewLink Genetics Corp.</td>
<td>Canada</td>
<td>Phase I ongoing</td>
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<tr>
<td>Monovalent Zaire Ebola Viral Vector Candidate Vaccine (cAd3−EBO Z) with MVA−BN® Filo (Prime−boost regimen)</td>
<td>University of Oxford</td>
<td>UK</td>
<td>Phase I A ongoing</td>
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<tr>
<td>MVA−EBO Z alone and cAd3−EBO Z with MVA−EBOZ (prime−boost regimen)</td>
<td>University of Oxford</td>
<td>UK</td>
<td>Phase I ongoing</td>
<td></td>
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<tr>
<td>EBOV GP Vaccine (Ebola Virus Glycoprotein) with or without Matrix−M® adjuvant</td>
<td>Novavax</td>
<td>Australia</td>
<td>Phase I ongoing</td>
<td></td>
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<tr>
<td>VRC−EBOADV018−00−VP (Recombinant Ebola Adenoviral Vector Vaccine)</td>
<td>NIAID</td>
<td>US</td>
<td>Phase I ongoing</td>
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<tr>
<td>VSVG−ZEBOV (Vesicular stomatitis virus−Ebola Zaire) ChAd3−EBO Z (chimpanzee adenovirus 3−Ebola Zaire)</td>
<td>NIAID</td>
<td>Liberia</td>
<td>Phase II ongoing</td>
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<tr>
<td>VSV−ZEBOV</td>
<td>University of Oxford WHO Wellcome Trust and others</td>
<td>Kenya</td>
<td>Phase I ongoing</td>
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<tr>
<td>Ad5−EBOV (Adenovirus type 5 vector−based EBOV)</td>
<td>First Affiliated Hospital of Zhejiang University Beijing Institute of Bioengineering Academy of Military Medical Sciences, Tianjin Cansino Biotechnology Inc.</td>
<td>China</td>
<td>Phase I ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPSC−1001 (VSV ΔG−ZEBOV) (recombinant vesicular stomatitis virus expressing envelope glycoprotein of Ebola virus Zaire)</td>
<td>NewLink Genetics Corp.</td>
<td>US</td>
<td>Phase I ongoing</td>
<td></td>
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</tbody>
</table>
### Table 4
Reports of orofacial and other signs and symptoms of mild-to-moderately severe EVD in addition to fever\(^3,24-5,29-34\)

<table>
<thead>
<tr>
<th>First author, Year</th>
<th>Oral features</th>
<th>Other features</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Oral bleeding</td>
<td>Oral mucosal lesions</td>
</tr>
<tr>
<td>Bonnet, 1998(^{34})</td>
<td>Oral thrush-like lesions</td>
<td>NR</td>
</tr>
<tr>
<td>Bwaka, 1999(^{35})</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chertow, 2014(^{37})</td>
<td>Oral ulcers and thrush</td>
<td>NR</td>
</tr>
<tr>
<td>Piot P, 1978(^{38})</td>
<td>Gingival bleeding (25.6%)</td>
<td>Oral–throat lesions (73.6%) fissures on the lips Sore throat (79.2%) Grayish exudative lesions</td>
</tr>
<tr>
<td>Isaacson M, 1978(^{39})</td>
<td>Gingival bleeding</td>
<td>Reddening of the tongue and throat</td>
</tr>
<tr>
<td>Smith DH, 1978(^{40})</td>
<td>Bleeding from nose, mouth and gums (50% in fatal cases)</td>
<td>NR</td>
</tr>
<tr>
<td>WHO Ebola Response Team, 2014(^{41})</td>
<td>Bleeding gums (2.3%)</td>
<td>NR</td>
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<tr>
<td>Kortepeter MG, 2011(^{42})</td>
<td>Pharyngeal erythema</td>
<td>Sore throat</td>
</tr>
<tr>
<td>Sureau PH, 1989(^{44})</td>
<td>Gingival and oral bleeding (25.6% in fatal cases, bleeding ulceration Dysphagia)</td>
<td>Oropharyngeal Pharyngitis</td>
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</table>

NR: Not reported
<table>
<thead>
<tr>
<th>Agent</th>
<th>Manufacturer</th>
<th>Stage of evaluation</th>
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<tr>
<td>TKM–Ebola</td>
<td>Tekmira (Burnaby, British Columbia, Canada)</td>
<td>Phase I ongoing</td>
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<tr>
<td>TKM–Ebola</td>
<td>Tekmira (Burnaby, British Columbia, Canada)</td>
<td>Phase I terminated</td>
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<tr>
<td>T–705</td>
<td>Institut National de la Sante Et de la Recherche Medicale, France</td>
<td>Phase II ongoing</td>
</tr>
<tr>
<td>CMX001</td>
<td>Chimerix (Durham, NC)</td>
<td>Phase II (withdrawn prior recruitment)</td>
</tr>
<tr>
<td>JK–05</td>
<td>Sihuan Phamaceutical Holdings Group Ltd and Academy of Military Medical Sciences (Beijing, China)</td>
<td>Animal studies completed; now considered for use in emergency situations for army only</td>
</tr>
<tr>
<td>BCX4430</td>
<td>BioCryst Pharmaceuticals Inc. Durham, NC</td>
<td>Phase I ongoing</td>
</tr>
<tr>
<td>AVI–6002</td>
<td>Sarepta Therapeutics (Cambridge, MA)</td>
<td>Phase I completed</td>
</tr>
<tr>
<td>Anti–Ebola hyperimmune globulin</td>
<td>None identified</td>
<td>Animal studies completed</td>
</tr>
<tr>
<td>ZMapp</td>
<td>National Institutes of Health Clinical Center (National Institute of Allergy and Infectious Diseases (NIAID))</td>
<td>Phase I/II ongoing</td>
</tr>
</tbody>
</table>

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.
Figure 2.
Figure 3.
Figure 4.
에볼라 바이러스 감염의 구강 내 소견에 대한 고찰

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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 될 것이다. 물론 아니라, 교차 감염에 의해 에볼라 바이러스가 확산되는 것을 방지할 수 있도록, 구강 내를 관리하는 의료 종사자들을 위한 감염 예방 수칙을 제시해보고자 한다.


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 해당되다면 표준 지침에 따라 해당 환자를 즉시 격리해야 하며, 증상은 없지만 에볼라 바이러스 감염 환자에 노출된 경험이 있다면 치과 치료는 에볼라 바이러스 감염의 최대 잠복기인 21일 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