This lecture is part three of the *Ebola Virus Disease and Clinical Care* lectures.

This brief lecture will review current standards of care and provide basic information on experimental treatments and vaccines. Some of these have already been used to treat or prevent Ebola virus disease (EVD), while others are in the pipeline. At this time, none of these are approved by the U.S. Food and Drug Administration (FDA), and none have had more than very early and limited testing in humans. Developments in the field are moving rapidly. If you have questions about the use of such treatments or vaccines for exposed or ill healthcare workers, your sponsoring organization can provide information regarding their policies and procedures.

**NOTE:** Information in this presentation will change regularly. Current and updated information can be found at: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

The learning objectives for this lecture are to:

- Recognize supportive care is a cornerstone of clinical management for patients with Ebola
- Understand the types of supportive care used in caring for patients with Ebola
- Understand the role of current investigational therapies and vaccines for the treatment of, or prophylaxis against, Ebola virus disease (EVD)
As has been presented earlier in this course, a cornerstone of Ebola management is supportive care. However, this care should be aggressive.

Patients will often have hypovolemia due to substantial gastrointestinal fluid losses, and later may develop capillary leak, and exhibit a sepsis-like physiology. They might respond well to aggressive IV fluid resuscitation. However, caution should be exercised so that aggressive fluid resuscitation does not result in pulmonary edema. Because intravenous catheter placement and maintenance entails risk to the healthcare worker, some ETUs, at times when high patient census or low staffing levels make use of IV fluids riskier, prefer to use oral rehydration solution (ORS). If your ETU uses IV fluid resuscitation, the intravenous catheter should be placed as soon as need for intravenous hydration has been identified. Catching up with fluid is difficult. IV catheter placement may require additional clinical staff to assist the patient and minimize risks. Fluid requirements by mouth are an excellent alternative. But patients can often be too weak or nauseated to take in enough fluid.

It should be assumed electrolytes are being lost even in the absence of lab testing. Therefore, electrolyte abnormalities from vomiting and diarrheal losses should be replaced. Options include:

- Oral rehydration solution
- Intravenous fluid, with Ringer’s lactate. This is a preferred IV solution because of the presence of potassium and lactate
- Normal saline can be supplemented with Potassium (K+), Magnesium (Mg++), glucose, or Bicarbonate (HCO₃⁻)

Healthcare workers should provide symptomatic management of fever, nausea, vomiting, diarrhea, seizures, myalgia, or abdominal pain.

Most ETUs provide empirical therapy for other infections that can complicate EVD, including broad spectrum antibiotics for possible bacterial infections and antimalarials.
There are currently no approved Ebola-specific prophylaxis or treatments that have proven to be effective.

Some non-human primate data have been used to identify potentially effective Ebola treatments, but data are limited, and human clinical trial data are extremely limited. However, Phase I trials are ongoing.

On this slide you can see listed a few of the investigational therapies or vaccines you might hear about. We go into more detail on several of these in subsequent slides. Therapeutic interventions that have been tried during the current Ebola epidemic include:

- Convalescent plasma and whole blood
- ZMapp, a monoclonal antibody cocktail by Mapp Bio
- TKM-Ebola, a small interfering RNA therapeutic by Tekmira
- Brincidofovir – a nucleotide analog (Chimerix)
- Favipiravir – an RNA-dependent RNA polymerase inhibitor (Toyama)

Several candidate Ebola vaccines are in the early stages of development and show some promise.

At this time, availability of these study products is very limited and they are only used under an investigational protocol.
Convalescent blood products have been used to treat severe viral diseases, including EVD. Ebola survivors may have high titers of antibodies against the virus that might provide some protection for persons currently infected. The World Health Organization (WHO) indicated this approach was reasonable to try in the absence of any other specific therapy, and such blood products could be collected and made available in affected countries. However, in vivo data on effectiveness of convalescent plasma in non-human primates (NHP) have been inconsistent. In humans, seven of eight patients who received convalescent plasma survived in one outbreak in 1995. However, because the blood products were administered to patients later in the clinical course who seemed to be improving, the effectiveness could not be adequately assessed. However, there are potential risks to using this therapy, including:

- Transmission of bloodborne pathogens,
- Transfusion-related acute lung injury (TRALI), and
- Possible antibody-dependent enhancement (ADE) of Ebola virus pathogenesis.

In short, it is unclear if convalescent whole blood or plasma provides any specific benefit for treatment of EVD.

Clinical trials of convalescent plasma treatment for EVD are currently being conducted in Africa.

ZMapp is a mix of three human-mouse monoclonal antibodies produced in tobacco plant cells. The antibodies bind to Ebola virus proteins and render the virus less able to infect cells in mammals. In NHPs, ZMapp completely protected rhesus macaques when treatment was initiated up to five days post exposure. Patients have been treated on compassionate grounds but a formal efficacy study has not been completed. ZMapp is administered by IV. Production capacity is very limited, and there is no current supply. Phase I clinical trials to assess safety are planned for 2015 and will be followed by an efficacy study.
TKM-Ebola is another investigational therapy. It is made by Tekmira and was initially designed for post-exposure prophylaxis. The drug consists of lipid nanoparticle small interfering RNAs that target two essential viral genes to prevent virus replication. In NHP studies, there was 67 to 100% efficacy when treatment was initiated 30 minutes post challenge. TKM-Ebola is administered by IV, and when given to uninfected humans, side effects observed included transient hypotension, headache, dizziness, chest tightness, and raised heart rate. A limited supply of TKM-Ebola has been available for use under emergency investigational new drug (IND) for known patients. It has also been used for post-exposure prophylaxis (PEP). Clinical efficacy trials of a new formulation of TKM-Ebola for treatment are under consideration.

Brincidofovir (BCV) is an oral broad spectrum antiviral with activity against double-stranded DNA viruses. It is a nucleotide analog lipid conjugate targeting viral replication. It was originally selected for pharmaceutical development on the basis of its activity against cytomegalovirus and adenovirus. More than 1,000 persons have received BCV for non-EVD causes without severe adverse reactions; however, elevated liver function tests have been noted. It is currently in Phase III clinical trials for cytomegalovirus and adenovirus. Chimerix announced BCVs in vitro activity against EVD was equivalent to that seen against RNA viruses in September 2014. BCV received FDA Experimental IND approval in October 2014. A clinical trial of BCV for EVD is planned in Liberia.

Favipiravir (Avigan) is an oral antiviral that targets RNA dependent RNA polymerase and viral replication. Favipiravir has been shown in the mouse model and NHPs to have activity against EVD in vivo. Favipiravir is currently in Phase III clinical trials for influenza. More than 1,400 persons have received Favipiravir for non-EVD causes. The dosages used for treatment of patients with Ebola have been well above the doses recommended for treatment of influenza and severe adverse reactions have not been observed. However, nausea and vomiting with this medication have been noted and may reduce its utility. Clinical trials of Favipiravir for treatment of EVD have begun in Guinea.
There are no Ebola virus vaccines that have been approved or proven to be effective, but studies are now underway.

Some limited NHP data suggest some protective benefit from vaccination. Several candidate vaccines have been fast-tracked for study.

One vaccine is a Chimpanzee Adenovirus 3-vectored bivalent vaccine. It was developed by the Vaccine Research Center of the National Institutes of Health (NIH) in collaboration with Okairos, a Swiss-Italian biotech company. The vaccine contains two Ebola virus genes and is a non-replicating vaccine.

Another is a Vesicular Stomatitis Virus (VSV), a vectored monovalent vaccine, developed by the Public Health Agency of Canada. This is a replicating vectored vaccine. In this vaccine, the VSV glycoprotein is deleted and replaced with the Ebola glycoprotein (GP). This vaccine has been used experimentally post exposure to boost immune response. NHP receiving the vaccine were protected from infection. A small number of persons have received VSV vaccine after experiencing a high-risk exposure (e.g., needlestick) while working in an ETU. However, effectiveness of VSV vaccine is unknown when used for post-exposure prophylaxis.

Additional Ebola vaccine development is underway, including vaccines based on recombinant adenovirus, recombinant vaccinia, or rabies vaccines. Studies in NHP are planned for late 2015.

In summary, treatment for patients with Ebola virus disease is supportive with a particular focus on fluid replacement, electrolyte replacement, symptom relief, and use of empiric antibiotics and antimalarials. Currently, there are no specific treatments or vaccines available for EVD.
Experimental treatments and vaccines to prevent Ebola are rapidly evolving. Current information can be found at www.clinicaltrials.gov.

Resources
- The most up-to-date information on experimental treatments and vaccines can be found at:
  - www.clinicaltrials.gov

For more information please contact Centers for Disease Control and Prevention
1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov
Web: www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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