

Ebola Virus Disease and Clinical Care Part II: Diagnosis and Clinical Management

This lecture is on Ebola virus disease (EVD) and clinical care. It is the second in a three-part series. The lecture will cover Ebola diagnosis and clinical management.

This lecture will specifically focus on EVD in the West African setting. As you will see, there are key differences in screening, diagnosis, and treatment in West African ETUs than what you might encounter in settings in developed countries. For example, in the United States and in other developed countries, there are more aggressive interventions available such as intubation, dialysis, and frequent laboratory testing. You will need additional information in order to care for patients appropriately in countries where more advanced care is available.

The learning objectives for this lecture are to:

- ▶ Describe the diagnostic tests and appropriate samples used to make triage and clinical decisions
- ▶ Describe clinical management of EVD, including treatment of common symptoms
- ▶ Explain criteria for discharge of patients with confirmed and suspected Ebola
- ▶ Describe measures to improve post-discharge outcomes

Preparing Healthcare Workers to Work in Ebola Treatment Units (ETUs) in Africa

Ebola Virus Disease and Clinical Care: Part II: Diagnosis and Clinical Management

This presentation is current as of December 2014. This presentation contains materials from Centers for Disease Control and Prevention (CDC), Malaria Sans Frontières (MSF), and World Health Organization (WHO).



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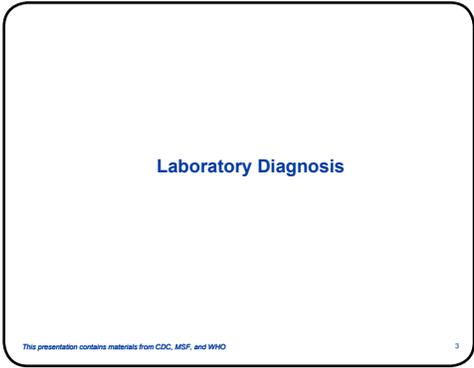
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Learning Objectives

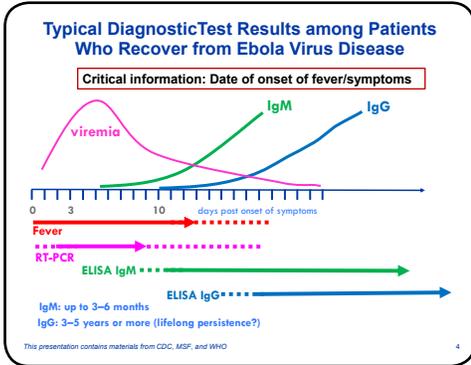
- Describe the diagnostic tests and appropriate samples used to make triage and clinical decisions
- Describe clinical management of Ebola virus disease (EVD), including treatment of common symptoms
- Explain criteria for discharge of patients with confirmed and suspected Ebola
- Describe measures to improve post-discharge outcomes

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Let's begin by discussing laboratory diagnosis of EVD.



This graph depicts the temporal relationships between symptoms, detectable Ebola virus in the blood, and the immune response. The graph illustrates schematically how virus levels and antibody levels change over time in patients who recover. Results for those who die do not look like this. For those patients, Ebola viremia peaks at a higher level and antibody never develops to reach an effective level.

Day zero on this graph is the date of symptom onset, not the date of infection. Viremia increases rapidly and reaches very high levels. This is not well illustrated on this graph because Ebola virus levels will be much higher at the time of the most severe symptoms than at the time when symptoms first occur. IgM antibody levels will not appear for at least seven days after symptom onset. IgG antibody peaks between two and five months after onset.

IgG antibody lasts for at least three to five years and in some people has been detected as long as 11 years post Ebola virus infection. It is believed that immunity after recovery might be lifelong as it is for some other viral illnesses.

How is EVD confirmed with laboratory testing? The current standard to confirm Ebola infection is RT-PCR for detection of Ebola viral RNA. The preferred specimen is blood in a purple-top tube, although a red-top tube can also be used.

Other tests listed on the slide are rarely, if ever, used to make decisions in the ETU. One test is virus isolation. As you can imagine, this type of test requires extreme care and a BSL4 lab.

Immuno-histochemical staining and histopathology can be used to localize Ebola viral antigen in tissue. This might be useful, if available, to test specimens from a patient who died without diagnosis.

An ELISA that detects viral antigen can show the virus is present in blood, serum, or tissue suspensions.

Serologic tests include IgM or IgG and might be used in a patient who survived and is now well but never had RT-PCR testing.

Blood testing is the standard for RT-PCR. This should preferably be venous blood, collected in an ethylenediamine tetraacetic acid (EDTA) Tube (purple-top tube) with anticoagulant. Venous blood in a dry tube (with a red top) without anticoagulant, can be used for RT-PCR or serology. Finger prick or drop of blood might be useful but this is not standardized. It should only be used if a venous blood sample is not available.

Saliva can be tested, but this is not standard practice in ETUs. Oral swabs which collect saliva and cells shed from the gingiva have been used for testing deceased patients who were not tested while alive. Although this has become the standard approach for sampling deceased patients, sensitivity is less than it is for blood, so a negative saliva test is not useful.

In summary, venous blood for RT-PCR is the most important Ebola virus diagnostic test for making decisions about clinical and infection prevention and control.

How is EVD Confirmed with Laboratory Testing?

- RT-PCR: rapid, provides specific identification of genetic fragments of the virus. **PREFERRED SPECIMEN: BLOOD IN PURPLE-TOP PLASTIC TUBE**
- Current standard to confirm Ebola infection is RT-PCR for detection of Ebola viral RNA
- Other tests—rarely used by ETUs in clinical decisions
 - Virus isolation: requires a Biosafety Level-4 laboratory and can take several days
 - Immuno-histochemical staining and histopathology: localizes viral antigen in tissue, including postmortem
 - Viral antigen ELISA: detects antigen in blood, serum, or tissue suspensions
 - Serologic tests: IgM or IgG



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Patient with Ebola Samples Tested Using RT-PCR

- Blood
 - RT-PCR on venous blood
 - EDTA tube (purple-top, with anticoagulant)
 - Dry tube (red-top, without anticoagulant)
 - Finger prick or drop of blood, only if venous blood sample not available
- Saliva
 - Might encounter, not standard practice in ETUs
 - Saliva has been used for deceased patients who were not previously tested but utility uncertain
 - Sensitivity less than for blood, so a negative test is not useful
- **Venous blood for RT-PCR is the most important diagnostic test for clinical and infection prevention and control decision-making**

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Blood and Other Samples from Patients with Ebola are **Infectious**

- All blood and other samples from symptomatic patients with Ebola are highly infectious
- Specimens are decontaminated and double bagged for disposal
 - This applies for transport of samples collected in the community, healthcare facilities, and within the ETU

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It is important to note blood and other samples from symptomatic patients with Ebola are extremely infectious. Therefore, it is critical to use extreme caution while handling specimens. Specimens must be decontaminated and double bagged for disposal. You will practice the decontamination process during one of the ETU practical exercises. Decontamination and double bagging applies for transport of samples collected in the community, health facilities, and within the ETU.

Considerations for Test-negative Suspected Ebola Cases

- If symptoms started at least three days before a negative RT-PCR, the patient can be discharged
- RT-PCR tests are often negative in patients with symptoms for fewer than three days (72 hours)
 - Repeat the test at 72 or more hours after onset of symptoms
 - Keep in suspect area until a sample taken 72 hours or more after symptoms began is negative
 - Testing negative does not equal immunity
 - Each new presentation of symptoms must be assessed separately
 - Repeat diagnostic testing when indicated

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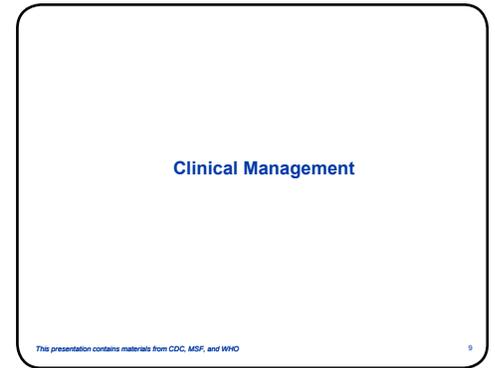
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Let's talk now about specific cases. What happens if you have a patient in the ETU who you thought might have Ebola virus disease but tests negative? We know patients can have a negative test up to three days after symptoms begin, when virus levels are low. If symptoms started at least three days before a negative RT-PCR, the patient can be discharged.

Remember, it is not always easy to elicit an accurate medical history and patients who are afraid may not always be accurate about the onset of symptoms. Therefore, healthcare workers should use the 72-hour cut-off point as a guide. If epidemiologic links or signs and symptoms are suggestive of Ebola for a person who has had one negative test, a second test should be done.

However, what do you do if symptoms have been present less than 72 hours? In this instance, keep the patient in the ETU suspect area, and repeat the test at 72 hours or more after onset of symptoms. Keep the patient in the suspect area until an RT-PCR test is negative. However, testing negative does not equal immunity. Each new presentation must be assessed separately, so don't hesitate to repeat diagnostic testing in a patient who was previously discharged after testing negative.

Now we will discuss clinical management used in ETUs in greater detail.



These two guidebooks are the most common clinical care guides currently in use. The left one is provided by the World Health Organization (WHO) and the right one is from Médecins Sans Frontières (MSF). Much of the material that follows is adapted from these guides.



In West African ETUs, clinical management is predominantly supportive. However, this does not mean it is ineffective. It is clear that aggressive replacement of volume loss from diarrhea, vomiting, and capillary leak/3rd spacing is necessary to improve chances of survival. To minimize risks to staff, some ETUs rely exclusively on oral hydration with oral hydration salt solution (ORS). ORS hydration should be used even if patients do NOT have diarrhea or vomiting to keep ahead of fluid loss. Where available, IV resuscitation with Ringer's lactate, which contains some potassium, is recommended. This is especially important for patients whose illness severity or mental status make ORS insufficient. Healthcare workers should replace potassium and magnesium loss, which are likely to be significant for patients with diarrhea. Replace empirically or, if available, base repletion on lab results. Electrolyte imbalances that can occur with aggressive IV hydration are a concern, but in most ETUs electrolytes cannot be measured.

There are no approved therapies specific for EVD.

Clinical Management
Suspected or Confirmed Cases of Ebola

- Clinical management is predominantly supportive
 - Aggressively replace volume loss from diarrhea, vomiting, and capillary leak/3rd spacing
 - Oral hydration with ORS (**even if patients do NOT have diarrhea or vomiting**)
 - IV resuscitation with Ringer's lactate (contains some potassium)
 - Replace potassium and magnesium loss, which are likely to be significant for patients with diarrhea
 - Replace empirically, or base repletion on lab results when available
 - Electrolyte imbalances with aggressive IV hydration a concern but usually cannot measure electrolytes
- There are no approved therapies specific for EVD

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Clinical Management Managing the Treatable Manifestations and Complications of EVD

- **Fever and pain**
 - Paracetamol (acetaminophen)
 - Do NOT use NSAIDs (concern for thrombocytopenia, bleeding)
 - Opioids (caution in hypotensive patients; may reduce gut transit in diarrhea)
- **Nausea and vomiting**
 - Promethazine, metoclopramide, ondansetron
- **Diarrhea**
 - Aggressive oral rehydration
 - IV hydration when possible for those unable to take orally
 - Role of anti-motility agents uncertain
- **Dyspepsia**
 - Cimetidine or omeprazole
- **Agitation**
 - Diazepam or haloperidol
- **Malaria (empiric therapy for all, or treat rapid diagnostic test positives)**
- **Bacterial co-infections or gut translocation**
 - Empiric antibiotic therapy aimed at gut pathogens (e.g., cefepime)

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The ETU focus is on managing the treatable manifestations and complications of EVD.

Patients can be provided with a variety of treatments aimed at relieving their symptoms. Fever and pain can be reduced by using paracetamol or acetaminophen. Do NOT use nonsteroidal anti-inflammatory drugs (NSAIDs) because of concerns about thrombocytopenia or bleeding. Opioids can be used, but with caution in hypotensive patients. Opioids might also help with diarrhea. Nausea and vomiting might respond to promethazine, metoclopramide, or ondansetron. Diarrhea should be managed as effectively as possible with aggressive oral rehydration and intravenous (IV) hydration when possible for those unable to take hydration orally. The role of anti-motility agents, such as loperamide, is uncertain in EVD treatment. Dyspepsia can be reduced with cimetidine but because of toxicity, use omeprazole, if available. Patients with Ebola can become agitated, and this makes treatment and management in the high-risk zone more difficult. In these situations, diazepam or haloperidol might help.

Many patients will have malaria. Most ETUs either provide empiric malaria therapy for all, or treat based on results from rapid diagnostic tests. Remember, if patients are not empirically treated for malaria, a reoccurrence of fever during hospitalization could represent a bout of malaria.

Patients unable to take oral medications may require IV or intramuscular artesunate. The severe GI tract manifestations might make bacterial co-infections caused by gut translocation more common, and some ETUs provide empiric antibiotic therapy such as cefepime aimed at gut pathogens.

Clinical Management Nutrition Support for Patients with Ebola

- **Enteral nutrition**
 - Encourage eating as soon as possible
- **Vitamin supplementation**
 - Retinol
 - B vitamin complex
 - Multivitamin

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Patients might already be malnourished at baseline. Yet, there are considerable catabolic demands from a severe infection like Ebola virus. As much as possible, encourage patients to eat. Some ETUs supplement food with vitamins such as retinol, B vitamin complex, or just a simple multivitamin.

Pregnant or new mothers are a special situation. Breastfeeding mothers suspected of having Ebola virus disease or those confirmed to have the disease should not have close contact with unaffected infants if safe alternatives exist. If unaffected infants with affected mothers remain in the ETU, the infants (and other children) must be kept in a safe separate area requiring additional staff and logistics to monitor and care for them. These situations also require safe alternatives to breastfeeding. The issue with breast milk is the presence of macrophages, which are often a target of the virus. There are very little data on the risk of transmission from breast milk. However, given what is known about the transmission of Ebola virus, regardless of breastfeeding status, infants whose mothers are infected with EVD are already at high risk of acquiring the virus infection through close contact with the mother, and at high risk of death overall. Until more is known, a mother who survives Ebola should not breastfeed her baby if safe alternatives exist. However, in resource-limited settings where safe alternatives do not exist, breastfeeding may be the only option for providing the nutrition the baby needs.

In pregnant women, vaginal bleeding is a common symptom and often profuse. Mortality is extremely high among these women, who also have high rates of spontaneous abortions and miscarriage. Because of the likelihood of copious contaminated fluids, clear SOPs should be in place on what treatment and infection prevention and control should be used for pregnant women who are miscarrying in the ETU.

Clinical Management ***Special Clinical Situations***

- ❑ **Breastfeeding mothers with suspected or confirmed Ebola**
 - Should not have close contact with unaffected infants
 - Require safe alternatives to breastfeeding
- ❑ **Pregnant women**
 - Vaginal bleeding is a common symptom and often profuse
 - Mortality is extremely high with high rates of spontaneous abortion, miscarriage

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Clinical Management Psychosocial Concerns for Patients

- Provide care with dignity
- Explain what you are doing and why to your patient and to the patient's family
- Recognize that patient anxiety and fear of death during EVD treatment is magnified by the infection prevention and control measures required
 - Isolation
 - Dehumanizing PPE
 - Reduced or absent communication with family and healthcare worker
 - Healthcare worker can only stay in the high-risk zone for a short period

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There are also psychosocial concerns for patients receiving treatment in the ETU. Healthcare workers should do their best to provide care with dignity. Explain what you are doing and why to your patient and to the patient's family. Recognize that patient anxiety during Ebola treatment is magnified by the infection prevention and control measures required.

Anxiety may be caused by

- ▶ Fear of death
- ▶ Isolation
- ▶ Dehumanizing personal protective equipment (PPE)
- ▶ Reduced or absent communication with family and healthcare workers
- ▶ Healthcare workers can only stay in the high-risk zone for a short period

From the patient's point of view, care in the ETU is a completely alien and likely a terrifying experience. In addition to being desperately ill, they are seeing others in the ETU who are even more ill or dying.



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In this picture, a young girl is tested for Ebola virus by a healthcare worker in high-risk PPE. You can imagine how scary this might be to anyone, especially a child.

Patient Discharge

Now we will discuss discharge procedures and issues.

This slide describes the ETU discharge criteria for patients who are suspected to have Ebola. Only a negative RT-PCR test three or more days after symptom onset can be used to make discharge decisions.

If a patient who is suspected to have Ebola but tested negative has had contact with a person with Ebola while in the ETU, as most will, refer the patient to the contact tracing team on discharge. Based on clinical suspicion, do not hesitate to retest patients with suspected cases for Ebola virus even though they previously tested negative.

If the person who has tested negative for Ebola virus still requires ongoing medical care, refer the patient to a local non-ETU healthcare facility. Do not forget subsequent exposures can occur. Testing negative does not equal immunity.

Patient Discharge ETU Discharge Criteria for Patients with Suspected Ebola

- Only a negative test three or more days after symptom onset can be used to make discharge decisions
- If patient suspected of having Ebola who tested negative has had contact with a patient with Ebola while in the ETU, refer case to contact tracing team
- Retest for Ebola virus disease for suspected patients who had previously tested negative based on clinical suspicion
- If the person who has tested negative for Ebola virus disease requires ongoing medical care, refer to a local non-ETU healthcare facility

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The ETU discharge criteria for patients with Ebola are discussed on this slide. Discharge requires both clinical AND laboratory clearance.

In most ETUs, clinical criteria will include three days WITHOUT symptoms that could indicate ongoing shedding of virus, such as fever, vomiting, diarrhea, or bleeding, AND the ability to perform activities of daily living.

The lab criteria include one negative RT-PCR result for Ebola virus.

Patient Discharge ETU Discharge Criteria for Patients with Confirmed Ebola

- Discharge requires clinical AND laboratory clearance
- **Clinical criteria**
 - Three days WITHOUT symptoms that could indicate ongoing shedding of virus (e.g., fever, vomiting, diarrhea, bleeding)
 - AND ability to perform activities of daily living (ADL)
- **Lab criteria**
 - One negative RT-PCR for Ebola virus

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Patient Discharge *Ebola Virus Shedding after Recovery*

- Viral shedding might persist up to three months in
 - Semen
- Viral shedding might persist for several weeks in
 - Breast milk
 - Vaginal secretions
 - Other body fluids, e.g., urine
- Counsel convalescent patients and provide condoms

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The importance of viral shedding after recovery is uncertain.

Shedding of Ebola virus might persist for at least three months in semen, which is an immunologically protected place – antibodies don't penetrate well. Men are advised to use condoms for at least three months after recovery.

Viral shedding into breast milk might also continue after a patient recovers. Some experts have stated it is not likely Ebola virus shedding occurs in breast milk for longer than 1-2 weeks after recovery, although there are very little data to support this. It is generally recommended that lactating patients cease breastfeeding, and some healthcare workers use medications to stop their lactation during their inpatient stay for this reason. There is no current recommendation on when a woman can resume breastfeeding after recovery.

In addition, based again on very small numbers of patients, Ebola RNA has been detected by RT-PCR in vaginal secretions 2-3 weeks after the patient's recovery. Viral shedding in other body fluids such as urine may also persist for some time after recovery. The role of such findings in transmission is not well-established.

Patient Discharge *Psychosocial Issues For Patients after Discharge*

- Difficulty restarting normal life
 - Loss of family members
 - Unemployment
 - Loss of personal belongings
 - Loss of community
- Stigmatization
 - Persons recovered from Ebola
 - Persons who were suspected of having Ebola but tested negative by RT-PCR

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Recovered patients often face substantial psychosocial issues after discharge. Patients might have difficulty restarting normal life, due to:

- ▶ Loss of family members
- ▶ Unemployment
- ▶ Loss of personal belongings
- ▶ Loss of community structure in hard hit areas

Stigmatization by others in the community can occur among those who were ill. Even patients suspected of having Ebola but tested negative by RT-PCR - in other words, were shown not to have Ebola virus infection - have reported stigmatization as well.

When discharging a recovered patient, it is recommended the ETU provide:

- ▶ Disinfection supplies
- ▶ Replacement provisions such as clothing, food, and in some instances money
- ▶ Condoms for three months
- ▶ Vitamin supplements

Discharge planners should discuss with patients why using condoms or sexual abstinence for three months is important.

Patients should also be referred for appropriate follow-up care.

Patient Discharge **Procedures for Recovered Patients with Ebola**

- **Provide**
 - Disinfection supplies
 - Replacement provisions (e.g., clothing, food, possibly money)
 - Condoms
 - Supply of vitamin supplements
- **Discuss why using condoms or abstinence for three months is important**
- **Refer for follow-up care**

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A key point to remember is medical care, nursing care, and psychosocial support increase chances of patient survival and reduce suffering. BUT please minimize your risks as healthcare workers by using PPE properly, and keeping interventions that could result in healthcare worker exposure to the absolute minimum required.

As WHO's motto states "We protect ourselves so that we can save lives."

Medical care, nursing care, and psychosocial support increase chances of patient survival and reduce suffering

BUT

Minimize Your Risks!

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Summary

- ❑ RT-PCR testing of venous blood is used to make key admission and discharge decisions
- ❑ Accurate case identification is essential for patient isolation and treatment
- ❑ Clinical treatment is supportive, including aggressive rehydration necessary for most patients
- ❑ Nutrition and psychosocial support are important during hospitalization and after discharge
- ❑ Healthcare workers can provide clinical care that relieves some symptoms, but must minimize risk to self and other personnel

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In summary:

- ▶ RT-PCR testing of venous blood for Ebola virus is used to make key admission and discharge decisions.
- ▶ Accurate case identification is essential for patient isolation and treatment.
- ▶ Clinical treatment is supportive, including aggressive rehydration necessary for most patients.
- ▶ Nutrition and psychosocial support are important during hospitalization and after discharge.
- ▶ Healthcare workers can provide clinical care that relieves some symptoms, but must minimize risk to self and other personnel.

<http://www.cdc.gov/vhf/ebola>

For more information please contact Centers for Disease Control and Prevention

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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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