This lecture is on Ebola virus disease (EVD) and clinical care. This is part one of a three-part lecture on this topic.

This lecture will focus on EVD in the West African setting. The training and information you receive in this course will not cover the use of certain interventions such as intubation or dialysis which are not available in West African Ebola Treatment Units (ETUs). You will need supplemental training to care for patients appropriately in countries where advanced care is available.

The learning objectives for this lecture are to:

- Describe the routes of Ebola virus transmission
- Explain when and how patients are infectious
- Describe the clinical features of patients with Ebola
- Describe screening criteria for EVD used in West Africa
- Explain how to identify patients with suspected EVD who present to the ETU

A number of different viruses cause viral hemorrhagic fever. Some illness from these infections, such as Lassa fever, dengue, or yellow fever, may be encountered in West Africa and can easily be confused with Ebola virus because symptoms are similar.

For example, because Lassa fever is endemic in West Africa and an accepted drug treatment (Ribavirin) exists, it is important to differentiate this from Ebola virus.
This is an electron micrograph of an Ebola virus particle, demonstrating the characteristic filamentous structure of the virus. It is sometimes described as a shepherd's crook or “U” or a “6”. The virus has a lipid envelope and the genome only encodes for 7 genes.

As you can see from this picture the virus has an exceptionally large surface area because of its filamentous area. This makes it more susceptible to disruption of the lipid envelope which results in deactivation of the virus.

Let’s address transmission of the Ebola virus.

Ebola virus belongs to a family of zoonotic RNA viruses, called Filoviridae, which also includes Marburg virus, another hemorrhagic fever virus with similar symptoms and case fatality rates.

The first Ebola virus species was discovered in 1976 in Yambuku, Zaire, now known as the Democratic Republic of the Congo, along the Ebola River, as shown here on the map. In this first recognized outbreak, there were 318 cases, with a case fatality rate of 88%. Since 1976, there have been more than 20 outbreaks of Ebola and Marburg viruses. Ebola virus species now include Zaire, responsible for this outbreak, Sudan, Bundibugyo, Tai Forest, and Reston. Different fatality rates have been associated with the several species. Ebola Zaire is the most virulent, having a case fatality of 88-99%, while Ebola Reston is not associated with any human deaths.
Based on evidence and the known transmission cycles of other similar viruses, researchers believe that Ebola virus is animal-borne. Bats are the most likely reservoir although the exact species is unknown.

This slide depicts the hypothesized natural life cycle of Ebola virus in bats on the left, and spillover infections of other mammals, including humans, that can occur on the right. Preparation of “bush meat,” a term used to describe meat from any wild animal, including monkeys and bats, might be an important opportunity for a spillover event. The event could then start a person-to-person chain of Ebola virus transmission through contact with blood or body fluids.

Transmission occurs via direct or indirect contact with body fluids from Ebola virus infected persons or animals.

Potentially infectious body fluids include blood, respiratory secretions, urine, feces, vomit, saliva, sweat, breast milk, semen, and vaginal secretions.

Detection in semen by viral culture (up to day 82) or by reverse transcriptase polymerase chain reaction (RT-PCR) (up to day 101) has been reported after illness onset and recovery. The transmission risk from semen after recovery is uncertain. However, seminal fluid is an immunologically protected site, meaning that antibodies might not have access to virus present in semen. Hence, it is recommended men use condoms for three months after the Ebola virus is no longer detectable in the patient’s blood.
Important concepts about Ebola virus transmission include:

- Infected persons are not contagious until onset of symptoms.
- Infectiousness of body fluids (e.g., viral load) increases as patients become more ill.
- Corpses are highly infectious even though viral load stops increasing after death. Fresh corpses are a major problem with customary West African body preparation and burial practices.
- Direct contact with ill persons or recently deceased persons are the most common routes of transmission.
- Transmission also occurs through contact with objects or surfaces contaminated by blood or other body fluids containing virus.

Evidence from this epidemic and previous outbreaks indicates direct contact with blood or other body fluids from an infected person or corpse are the major routes of transmission. Levels of Ebola virus in blood and other body fluids are very high, especially when patients are sickest and near death. Since the infectious dose is very low, even small amounts of blood or other body fluids are potentially very infectious. Virus from contaminated hands or fomites, including contaminated personal protective equipment (PPE), can enter through the eyes or other mucous membranes, or breaks in skin that might not be visible. Percutaneous injuries such as a needlestick can also transmit virus.

Other possible routes of transmission include sexual contact or breastfeeding. However, it is hard to distinguish these contacts from other close contacts that would typically occur in a household.

Aerosol transmission is unlikely. Person-to-person transmission of Ebola virus via inhalation has not been demonstrated. While it is possible in an experimental setting to create an infectious aerosol, aerosols are not typically generated in healthcare settings except under certain circumstances, such as during intubation or bronchoscopy. Viruses typically don’t change transmission mechanism under natural conditions.

Direct contact or contact with contaminated fomites can easily explain transmission patterns observed in this epidemic and other Ebola outbreaks.
There are many opportunities for person-to-person transmission when patients are infected with high levels of Ebola virus. Patients often have vomiting and severe diarrhea, and are unable to care for themselves or even get out of bed to use a bathroom. Persons who are providing care for ill family members are at high risk and household transmission is common.

In healthcare settings, providers are potentially exposed whenever they touch a patient. Virus can easily be transferred from contaminated hands or PPE to a healthcare worker’s mucous membranes. This is why it is critical to pay careful attention to infection prevention and control practices.

Handling or preparing corpses is a high-risk activity for transmission of the virus.

Contact with objects contaminated by Ebola virus, including soiled linens, soiled clothes, or used utensils, can also result in virus transmission.

And of course, injuries from contaminated sharps are a major risk for transmission.

The incubation period is defined as the time from exposure to development of symptoms or signs of disease. Nine to eleven days is the most common incubation period. However, after a large inoculation such as one that might occur with a needlestick, the incubation period might be as little as two days. The incubation period can be up to 21 days, and that is the standard typically used for contact tracing. However, incubation periods of more than two weeks are unusual.

We will now talk about the clinical presentation and features of patients with Ebola Virus Disease.
Some of the most common clinical presentations of patients with EVD are listed in this slide. As you can see, there is a wide spectrum of signs and symptoms which can make it difficult to distinguish EVD clinically from other common illnesses in West Africa.

Fever is a very common early sign of EVD, often accompanied by nausea, fatigue, or headache. Onset is often, but not always, abrupt. GI symptoms such as vomiting and diarrhea often follow the initial symptoms. Hemorrhaging is not usually common at presentation and occurs in less than half of patients with Ebola as a late sign.

According to experts who have seen many cases, early symptoms are those of early sepsis, and non-specific. Other diseases that might present with similar symptoms include Lassa fever, malaria, typhoid fever, and meningococcemia. These diseases are commonly found in West Africa and may be a reason some people delay seeking treatment. Co-infections are also possible.

Don’t expect all signs or symptoms to be present in every patient, or for signs and symptoms to present sequentially.

In severe disease, a full-blown sepsis presentation is typical. Signs will include hypovolemia, oliguria, signs of liver injury, and cytokine storm.

Hemorrhagic symptoms are seen in less than 50% of patients, even at this stage. This is a key point. Do not expect to necessarily see hemorrhagic symptoms. Do not discount the possibility of EVD in severely ill patients who do not have hemorrhagic signs. When present, signs of hemorrhagic illness range from gum “oozing” to less commonly frank epistaxis or mucocutaneous bleeding. Gastrointestinal bleeding may be present.

Neuropsychiatric abnormalities such as agitation and confusion are very common in later stages of disease.

In a setting where many persons have poor nutritional status at baseline, acute malnutrition is an issue when patients cannot eat due to GI symptoms or weakness. Illness may be more likely to progress to shock and multiple organ failure, and death.
Routine lab testing is not available in many ETUs. However, when tests are done, typical findings include low platelet count (thrombocytopenia), and low White Blood Cell (WBC) count (leukopenia). Electrolyte abnormalities from fluid shifts related to diarrhea, fever, and interstitial fluid leak are prominent. Signs of poor end organ perfusion such as transaminitis (AST, ALT) and increased creatinine are seen. Clotting abnormalities can be seen, often later than the changes in electrolytes and cell counts. In short, lab findings are that of early sepsis, and non-specific. Clinical studies in the current epidemic indicate that most patients who have died from EVD had acidosis on admission or acidosis that developed during hospitalization. Among patients who died, levels of blood urea nitrogen and creatinine progressively increased over time, suggesting that dehydration and worsening renal function played a significant role in their hospital course. Patients who died were more likely to have sustained elevations in AST, ALT, or alkaline phosphatase (especially AST) than were patients who survived.

Late stage changes prominently feature the findings typical of hemorrhagic fevers. Here you see a patient with hematemesis.

Note this hemorrhagic patient, who has spontaneous gum bleeding, is not prostrate or immobile.
This patient has bleeding from intravenous (IV) site.

There are various characteristics that predict a higher risk of death from EVD. For example, age is a primary risk factor for death. Patients younger than 5 or older than 45 are at higher risk. Limited evidence suggests pregnant women are at increased risk for severe illness and death when infected with Ebola virus. Pregnant women with Ebola also appear to be at a very high risk of fetal loss and pregnancy-associated hemorrhage.

Larger inoculums that transmit more virus are also a risk factor. This might occur with a hollow bore needlestick injury, or during exposure without protective equipment to a corpse or patient with advanced disease.

Clinical characteristics that predict a higher risk for death include:

- Short incubation time
- Rapid progression of symptoms
- Liver and kidney involvement
- Unexplained bleeding (specific hemorrhagic symptoms have been rarely reported in the current epidemic (in <1% to 6% of patients). Unexplained bleeding, however, was reported in 18% of cases)
- Altered mental status
For patients with Ebola who survive, long-term medical issues may occur. These could include:

- Frequent, severe, and persistent arthralgia or myalgia
- Cardiac injury
- Cerebral complications including seizures and encephalopathy
- Eye problems
- Malnutrition
- Mental health issues
- Prolonged fatigue

Many diseases in West Africa can be similar to EVD. A long list appears on this slide. More common conditions that mimic EVD include Lassa fever, malaria, typhoid fever, and shigellosis. However, be alert for others, such as meningitis, plague, or leptospirosis. It is important to consider and manage other treatable infections including malaria or Lassa fever, when appropriate, in the ETU.

Appropriate and standard screening methods are important for EVD diagnosis.
Careful screening of patients who present with symptoms that could be EVD must be conducted as early as possible to distinguish them from persons with other illnesses such as the ones listed on the previous slide. Applying a uniform case definition is critical for case identification, tracking, and control of the epidemic. Adherence to a strict case definition should not prevent astute healthcare workers from using their clinical judgment in assessing the patients. Case definitions for screening differ by location. It is critical to use the locally relevant case definition for your ETU.

Screening of all patients who might have EVD must occur before they enter an ETU or healthcare facility. This is necessary to reduce the risk to other patients and caregivers. Triage is not done in high-risk PPE, so healthcare workers performing triage should maintain a distance of at least one meter (three feet) from potential cases. Triage means screening by a nurse or other medical staff member at the entry point of the ETU by questioning the patient and/or family. It does not include laboratory testing, which takes many hours before results are available. The goal of triage is to quickly isolate patients who might have EVD and obtain diagnostic testing.

Most ETUs perform triage screening using the case definition recommended by the World Health Organization (WHO) for suspected EVD in Africa. However, slightly different case definitions could be used in different locations.

If the screening assessment indicates a patient is suspected of having EVD, then the screening healthcare workers must isolate the patient immediately. This will mean admitting the patient to the suspect area of the ETU if they are on site, or arranging transfer to the ETU if they are somewhere outside the facility.
WHO has published screening criteria for EVD in healthcare facilities. Case definitions vary slightly between West African countries. This is an example of a WHO screening algorithm that has been used in Guinea. It is important to use a standard algorithm so patients can be assigned to the proper risk category.

Key points in the WHO case definition include:

- Presence of fever among persons not feeling well is the first step. Fever and known contact are immediate grounds for classifying as a suspected case.
- Persons with fever but no known contact become a suspected case if they have three or more of the listed symptoms such as headaches, vomiting, anorexia/loss of appetite, diarrhea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, hiccups.
- Any unexplained bleeding, regardless of fever, is a suspected case.
- Finally, even if there is no fever, patients can be classified as suspected if there was contact and other symptoms are present.

Clinical judgment is needed to use an algorithm, and getting a clear history from ill and often frightened patients can be a challenge, as you will see in the triage tabletop exercise.

WHO has defined a contact as any person having been exposed to a suspect, probable or confirmed case of Ebola in at least one of the following ways:

- Has slept in the same household with a case
- Has had direct physical contact with the case (alive or dead) during the illness
- Has had direct physical contact with the (dead) case at the funeral
- Has touched his/her blood or body fluids during the illness
- Has touched his/her clothes or linens
- Has been breastfed by the patient (baby)

This list is by no means exhaustive and common sense should always be employed. For example, having shared a meal with a person with suspected, probable, or confirmed Ebola can be defined as contact with that person.

The contact’s exposure must have taken place less than 21 days before their identification as a contact.
In summary:

- The incubation period range is 2-21 days, but most commonly 9-11 days after contact.
- No transmission occurs before system onset.
- Transmission is by direct contact with ill people, body fluids, contaminated materials, corpses, and less commonly, animals.
- EVD is characterized by non-specific early symptoms progressing to signs of sepsis: hypovolemic shock, multi-organ failure, and sometimes hemorrhagic disease.
- Appropriate triage of patients with signs and symptoms that could be EVD is critical to reducing risk for healthcare workers, other patients and the community.