ECHO Summary,7/JUN/2024
Session Title: Emergency Approach to Viral Hemorrhagic Fever

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Background

Viral hemorrhagic fevers are a group of febrile illnesses caused by highly infectious RNA viruses from several viral families leading to potentially lethal disease syndromes characterized by fevers, malaise, vomiting, mucosal and gastrointestinal bleeding, edema, and hypotension. *These are reportable diseases.*[1] Specifically, *Ebola virus disease (EVD) should be reported to the district surveillance person AND you should text ALERT to 6767.*

Epidemiology

- Transmission is via direct contact with the body fluids of an infected person, highly contacted fomites, or ingestion of /contact with infected animals[1]
    - *The most common transmission method is person-to-person via body fluids*
- Filoviruses are known to cause Ebola and Marburg hemorrhagic fevers. Ebola has an incubation period of 2-21 days; its reservoirs lie in fruit bats of the Pteropodidae family, chimpanzees/other monkeys, and forest antelopes
- Arenaviridae family is known to cause rodent-borne diseases such as Lassa fever
- Bunyaviruses are transmitted by arthropods and rodents causing diseases such as Hanta Fever, Crimean Congo hemorrhagic fever, and Rift Valley virus fever (and the latter is commonly found in the cattle corridor districts in Uganda)
- Flaviviruses are transmitted by arthropods are known to cause diseases such as Zika virus and Dengue fever via transmission by the Aedes aegypti or Alobticus mosquitoes

Risk Factors

- Travel to communities where viral hemorrhagic fevers commonly occur such as game parks and endemic areas
- Cultural practices such as burials
- Poor infection control measures
- History of exposure to infected people in the last 2-21 days including sexual partners, breastfeeding partners
- Recent contact with infected animals like monkeys, bats, infected game meat[1]

Pathogenesis

- Entry through mucosal surfaces or break in skin viral replication in macrophages and dendritic cells spreading to lymph nodes and spleen resulting in immune invasion and widespread inflammation leading to organ failure and hemorrhage

Clinical Presentation

- *Less than ⅓ of patients with EVD will present with bleeding![1]*

Table 1. Clinical features of EVD.

Early Clinical Features	**Late Clinical Features**
● Fatigue ● Fever	● Diarrhea - watery or bloody stools ● Vomiting

• Headache • Myalgias • Arthralgias • Nausea and loss of appetite • Sore throat and difficulty swallowing • Abdominal pain (mainly epigastric) • Diarrhea - watery or bloody stool • Conjunctivitis	• Confusion and irritability • Shock - septic or hypovolemic • Internal and or external bleeding • Oozing from puncture sites bleeding from gums • Skin rash • Seizures • Chest pain • Miscarriage in pregnant women • Respiratory distress • Hiccups

Table 2. Clinical stages of EVD.

Early Phase		**Gastrointestinal phase (days 4-9)**	**Terminal recovery phase (days 10-12)**
1-2 days	**3-4 days**		
• Mild fever, decreased appetite, headache • Usually can eat and drink • Ambulatory	• Fever, headache decreased appetite nausea • Onset of diarrhea (2-3 bowel motions per day) • Epigastric pain and hiccups • Still ambulating but may experience onset of lethargy/lassitude	• Fever, headache, myalgias, arthralgias • Diarrhea and vomiting - up to 10 L/day, which may be bloody • Pulses are weak and fast • Decreasing urine output • Little to no ambulation • Delirium and wide-eyed stare	• Fever • GI symptoms subside • Confusion and delirium worsen • Renal failure - may be anuric or oliguric • Multiorgan failure and DIC[2] are possible • Death versus recovery

DIC = disseminated intravascular coagulation, GI = gastrointestinal

Table 3. Screening, triage, and isolation for EVD and other viral hemorrhagic fevers.

Screening	**Triage**	**Isolation**
• Commonly performed at the entrance of health facilities. Everyone entering the facility including	• Involves assessment of patients to determine those who are critically ill and prioritize care	• Involves separating patients from others to prevent the spread of the disease and transferring patients

healthcare workers should be screened ● Consists of observing patients, taking non contact temperature, asking questions about travel, looking for risk factors/signs/symptoms ● Can be done without coming into physical contact with the patient, maintaining at least 1 meter ● Screening areas should be set up with red and green zones	● Likely requires physical contact - therefore healthcare workers should put on full and appropriate PPE ○ Eye protection ○ Respirator mask ○ Face shield ○ Gloves (up to the elbows) ○ Gown or coverall ○ Head covering ○ Apron ○ Rubber boots[1]	for testing and treatment ● Requires physical contact - appropriate PPE required

PPE = personal protective equipment

- **AIRWAY**: Look for signs of secretions, vomitus (usually bloody), petechiae
- **BREATHING**: Tachypnea, respiratory distress
- **CIRCULATION**: May be normotensive or hypotensive. Look for signs of shock: tachycardia, pallor, cold extremities, changes in capillary refill (likely > 3 seconds in patients with hypovolemic/hemorrhagic shock)
- **DISABILITY**: Altered mental status, hypoglycemia
- **EXPOSURE**: Fever. Look for signs of blood loss/discharge from orifices such as mouth, ears, nose, vagina, or rectum. Skin changes may include petechiae, ecchymosis, or maculopapular rash.[2] Look for signs of dehydration

Differentials

- Anthrax
- Cholera
- Dengue fever
- Hepatitis
- Influenza
- Leptospirosis
- Malaria
- Meningitis
- Relapsing fever
- Rickettsioses
- Typhoid
- Sepsis
- Shigellosis[1,2]

Diagnostic Workup

- Reverse Transcription Polymerase Chain Reaction (RT-PCR) is the *gold standard* for the detection of viral RNA due to its high sensitivity and specificity
    - Has a fast turnaround time
    - If < 3 days of symptoms, a second specimen is required after 72 hours to rule out EVD
    - RT-PCR may be conducted on blood, saliva, urine, or tissue samples
    - Blood samples are collected in EDTA purple top. Always use plastic collection tubes that don't contain heparin. Keep cold
    - *Avoid oral swabs in live patients*
- Rapid immunoassay screening tests exist but are NOT adequate unless RT-PCR is unavailable[2]
- Viral isolation and culture may be done but requires specialized facilities, is, time-consuming, and resource-intensive
    - Commonly used for research and confirmation purposes
- EVD IgG and IgM serology tests are used to detect early or past infection
    - Commonly applied in epidemiological studies and vaccine trials
    - *Should not be used to test and confirm for active EVD*

Other Diagnostics

1. Complete blood count (CBC) - monitor platelets, white blood cell counts, and hemoglobin levels
2. Coagulation profile (PT/INR, aPTT) - to assess bleeding risk
3. Liver function tests and renal function tests - to rule out multiorgan failure
4. Electrolytes and blood chemistry - to monitor electrolytes given that these patients are at high risk from volume losses
5. Arterial blood gas (ABG) - to assess for acidosis

    *Remember that venous blood gas (VBG) can be substituted in most circumstances. ABG is painful for the patient - https://www.emdocs.net/abg-versus-vbg-in-the-emergency-department/#:~:text=ABG%20and%20VBG%20Correlation&text=In%20general%2C%20VBG%20pH%20is,value%20is%20needed%20(7).

Potential laboratory findings may include:

- Increased hemoglobin and thrombocytopenia on CBC[2]
- Increased creatinine and blood urea nitrogen (BUN) due to volume losses
- Metabolic acidosis and lactic acidemia due to loss of bicarbonate in diarrhea
- Hyper- or hyponatremia associated with dehydration
- Hyperkalemia with severe renal dysfunction due to volume losses
- Hypoglycemia due to low food intake
- Malaria co-infection - should especially be considered in patients with altered mental status

NOTE: Remember to ensure proper disposal of used materials, PPE, and laboratory samples, adhering to safety protocols and guidelines. Decontaminate work surfaces and environment. Document and store test results in compliance with regulatory guidelines for biohazardous waste

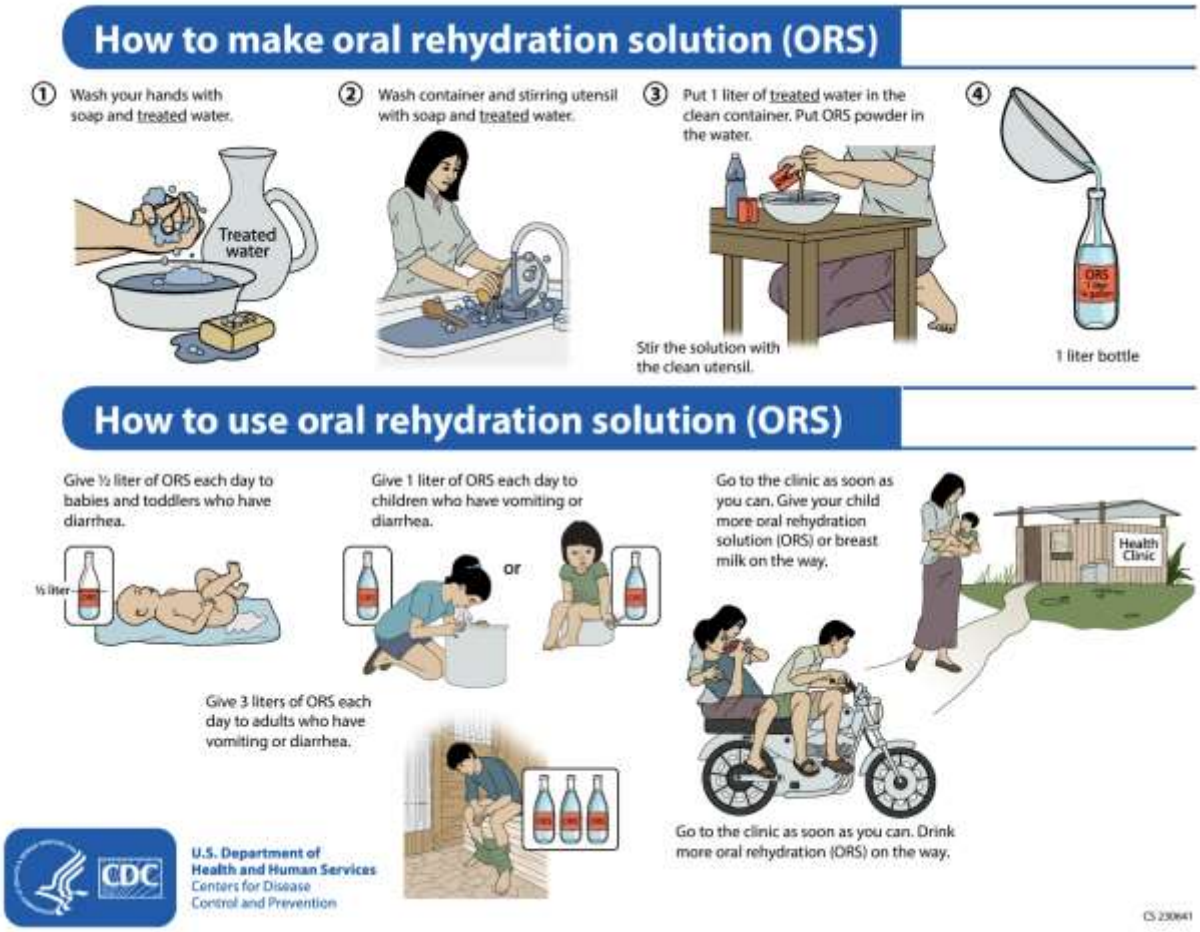
Treatment

- Aggressive supportive management
    - Fever - paracetamol oral, per rectum, or intravenous (IV)*
    - Pain - paracetamol, opioids*
    - Nausea and vomiting - antiemetics such as ondansetron, metoclopramide, promethazine
    - Dyspepsia- chlorpromazine, haloperidol
    - Hiccups - chlorpromazine, haloperidol
    - Anxiety, confusion - reassurance, haloperidol
        - Benzodiazepines can increase the risk for transient delirium, so risks and benefits should be weighed - https://dam.upmc.com/-/media/upmc/services/palliative-and-supportive-institute/for-professionals-and-students/the-tablet/2022/the-tablet-v2n8-benzodiazepine-use-in-delirium.pdf?la=en&rev=735be28c388c4315925deab18adeef02&hash=E222236ECE24F41B68A9928E30765CFC#:~:text=Benzodiazepines%20have%20been%20shown%20to,delirium%20related%20to%20alcohol%20withdrawal.
    - Seizures - diazepam, phenobarbital

    *Non-steroidal anti-inflammatory drugs (NSAIDS should be avoided for fever and pain control due to the risk of renal failure.[2]

- Fluid management: ALL patients are given oral rehydration solution (ORS) to drink and require constant reassessment

Figure 1. How to make ORS if you do not have access to pre-made packets. Source: https://www.cdc.gov/global-water-sanitation-hygiene/media/pdfs/ors_seasia_508.pdf



- Must use IV fluids if the patient is too sick to drink
  - The preferred IV fluid is ringers lactate 1-1.5 liter bolus (for adults) over 30 mins or faster and reassess for ongoing dehydration or fluid overload after the bolus is finished. For children, 10-20 cc/kg boluses are reasonable, followed by reassessment
    - Signs of volume overload include crackles on lung examination, difficulty breathing, peripheral edema, and jugular venous distension
    - Fluid status to determine the need for ongoing IV fluid rehydration can be evaluated using capillary refill, point-of-care ultrasound, orthostatic vital signs, and passive leg raise - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9994306/
- Anemia - transfuse for hemoglobin < 7 g/dL[2]
- Metabolic acidosis - if severe (pH < 7), consider sodium bicarbonate 1-2 ampoules (each ampule contains 50 mEq of bicarbonate)
  - Remember that bicarbonate will be converted to carbon dioxide and must be exhaled by the patient. If they are already maximally tachypneic (i.e. exhibiting

Kussmaul respirations), they may not be able to “blow off” additional carbon dioxide - https://www.ncbi.nlm.nih.gov/books/NBK559139/

- Hypoglycemia - oral feeding is the ideal method to resolve this, but for patients who are too ill to take food and fluids by mouth, use IV dextrose bolus followed by maintenance IV fluid infusion
- Hyponatremia - improves with ringer's lactate fluid infusion
    - Normal saline can cause hyperchloremic metabolic acidosis - https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1778-428X.2003.tb00184.x
- Hypokalemia - give oral potassium chloride or IV potassium chloride (30-40 meq/hr). Every 1 mmol drop in potassium requires 80-100mEq of potassium supplementation. Monitor with repeat electrolytes
    - Consider co-repletion of magnesium with magnesium sulfate 2-4 g IV over 1 hour
        - Avoid rapid administration of magnesium, as this can lead to hypotension and respiratory depression
- Consider co-infections like malaria and treat per national guidelines
- Compassionate use approval of monoclonal antibodies MBP134 and remdesivir for EVD
    - This was applied in only about 17.5% of patients managed at the ETU in the last Sudan outbreak and was most effective in early phase of the disease
- If the patient is in shock, consider empiric antibiotics to treat for sepsis due to coinfection from a bacterial source
    - Ceftriaxone is first-line, with ciprofloxacin second-line
    - Consider metronidazole for patients with gastrointestinal symptoms if there is suspected co-infection due to amoebiasis
- Respiratory support - respiratory failure is uncommon in these patients but can occur secondary to septic shock, hypervolemia, or transfusions given for severe anemia. Provide supportive care with supplemental oxygen and invasive airway management as needed[2]
- Nutrition with a balanced and protein-rich food
- Manage comorbidities per national guidelines (i.e. HIV, TB)
- Psychosocial support

For more details on supportive care in EVD, click here: https://www.who.int/publications/i/item/9789241515894

NOTE: There are no specific unique guidelines for children with viral hemorrhagic fevers

Factors associated with higher mortality
● Age - very young (< 10) or > 40 years ● High viral load ● Organ failure ● Delayed presentation to healthcare* ● Pregnancy ● Comorbid conditions (i.e. diabetes, immune suppression)

*55% mortality rate for patients who present after 10 days compared to 23% fatality rate for those that present 0-2 days after onset of symptoms - this information was presented in the ECHO session by Dr. Kobba

Complications

- Multi-organ failure

Disposition and Ongoing Care

- Admit under isolation
- All patients with suspected EVD should be sent to the regional referral hospital[1]
- For patients who die from EVD
    - Healthcare workers should avoid handling the body
    - No funeral permitted
    - Body should be buried by a designated team[1]
- Key education for patients/families
    - Potential long-term sequelae of infection can include chronic arthralgias and myalgias, fatigue, abdominal pain, deafness, visual complaints[2]
    - Belongings of infected individuals must be disinfected or destroyed
    - No breastfeeding - EVD can be transmitted for up to 26 days after symptom onset
    - Isolation of mother from infant should take place for a minimum of 3 weeks if mother is suspected to have EVD[2]
    - The World Health Organization recommends using condoms/protected sex until an individual's semen has tested negative for EVD twice[2,3]

Prevention

- Depending on the type of viral hemorrhagic fever, patients need to be isolated
- Avoid eating raw, undercooked bush meat or having contact with blood, meat, or body fluids of animals/persons showing signs of viral hemorrhagic fever
- Use of appropriate PPE and public health measures to curb the spread of the disease
- Hand hygiene is key - soap and water or alcohol-based hand sanitizers
- Anything an EVD patient or their body fluids touched should be cleaned with 0.5% chlorine solutions
- Vaccines exist for EVD[4] but do not cover the Sudanese strain, which was implicated in the last Ugandan outbreak[5]
    - Clinical trials are ongoing in Uganda[6] - stay tuned!

Figure 2. Appropriate hand hygiene for preventing EVD transmission.

Washing
with soap & water

Disinfecting with alcohol-based hand rub

With weak (0.05%) chlorine
ONLY if water and soap or alcohol NOT available

Figure 3. Levels of control needed for EVD prevention.

Special Notes

- Initial clinical manifestations are nonspecific and mimic many common infections, therefore making early diagnosis difficult
- Hemorrhage is seen in less than 30% of patients with EVD; therefore, it is important to have a high index of suspicion and know the other signs and symptoms of EVD
- Education and frequent training are essential to ensure effective infection control practices
- Always assess the risk of exposure and correctly wear and dispose of PPE to prevent self-contamination

Collaborating Partners

1. Ministry of Health of the Republic of Uganda
2. Seed Global Health

3. Techies Without Borders

References

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