Clinical Care of the PUI or Confirmed Patient with Ebola: Lessons Learned
Outline

- Background on Ebola Virus Disease
- Clinical Care in high level isolation
- Clinical Pearls from patients with EVD
- Critical illness in EVD
- Renal support in EVD
- Nutritional support
Care of the Person Under Investigation (PUI) or Confirmed Case of Ebola Virus Disease
Case Definition

- Person Under Investigation (PUI)
  - A person who has both consistent signs or symptoms and risk factors as follows should be considered a PUI:
    - Elevated body temperature or subjective fever or symptoms, including severe headache, fatigue, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage; AND
    - An epidemiologic risk factor within the 21 days before the onset of symptoms.

- Confirmed Case
  - Laboratory-confirmed diagnostic evidence of Ebola virus infection.

**Note: Algorithms are helpful, but do not replace good clinical judgment!**

http://www.cdc.gov/vhf/ebola/hcp/case-definition.html
http://www.cdc.gov/vhf/ebola/hcp/international/case-definitions.html
Identifying Patients of Interest

- Identify the exposure history
  - Travel to Sierra Leone or Guinea
  - Any contact with an individual with confirmed Ebola Virus Disease

- Identify the signs and symptoms
  - Fever ≥ 38°C or 100.4°F
  - Diarrhea, nausea, vomiting, abdominal pain, weakness, joint or muscle aches
Isolation of Patients of Interest

- Identify isolation room and how the patient will be transported to the isolation room
- Determine who will transport the patient
- Develop process flowcharts for each entry point
Early Clinical Presentation

- **Acute onset**
  - typically 8–10 days after exposure (range 2–21 days)

- **Signs and symptoms**
  - Initial: Fever, chills, myalgia, malaise, anorexia
  - After 5 days: GI symptoms, such as nausea, vomiting, diarrhea, abdominal pain
  - Other: Headache, conjunctivitis, hiccups, rash, chest pain, shortness of breath, confusion, seizures
  - Hemorrhagic symptoms in 18% of cases (usually occur late)

- **Other possible infectious causes of symptoms**
  - Malaria, typhoid fever, meningococcemia, dengue, influenza, Lassa fever and other bacterial infections (e.g., pneumonia) – all very common in Africa
  - PCR testing may be negative early in the course of illness
  - Prepare to care for patients for up to 72 hours prior to confirmation (or refutation) of EVD
Initial Signs and Symptoms of Ebola Are Non-Specific

- Acute infection starts as a non-specific febrile illness
  - Fever, myalgia, malaise
  - Usually rapid progression of intensity
- Significant overlap with other common syndromes and diagnoses
- Some more unique features:
  - Asthenia
  - Anorexia
  - Right upper quadrant pain, hiccups
  - Conjunctivitis
  - Rash
  - Oozing blood from gums, injections site

Courtesy of Pierre Rollin, CDC
Clinical Features

- Nonspecific early symptoms may progress to:
  - Hypovolemic shock and multi-organ failure
  - Hemorrhagic disease
  - Death

- Non-fatal cases
  - Typically improve 6–11 days after symptom onset if supportive care is provided promptly

- Fatal disease associated with more severe early symptoms
  - Fatality rates of 70% have been reported in rural Africa
  - Intensive care, especially early intravenous and electrolyte management, may increase the survival rate
Ebola Virus Pathogenesis

- Direct infection of tissues
- Immune dysregulation
- Hypovolemia and vascular collapse
  - Electrolyte abnormalities
  - Multi-organ failure, septic shock
- Disseminated intravascular coagulation and coagulopathy
- Vascular leak / cytokine effect
Clinical Characteristics of Ebola

- Small vessel involvement
  Increased permeability due to cellular damage

- Multisystem Compromise

- Hemorrhage may develop in the second week

- Poor prognosis associated with Shock, encephalopathy, extensive hemorrhage
Opportunities for human-to-human transmission:

- Direct contact (through broken skin or unprotected mucous membranes) with an Ebola-infected patient’s blood or body fluids
- Sharps injury with Ebola virus-contaminated needle or other sharp
- Direct contact with the remains of a person who died of Ebola
- Indirect contact with an infected patient’s blood or body fluids via a contaminated object (soiled linens)
- Possibly from contact with semen from a man who has recovered from Ebola
Human-to-Human Transmission

- Infectiousness of Ebola Virus Disease
  - Infected persons are not contagious until onset of symptoms
  - Infectiousness of body fluids increases as patients become more ill
  - Remains from deceased infected persons are highly infectious

- Human-to-human transmission of Ebola virus via inhalation has not been demonstrated
  - However, respiratory protection (e.g. N-95, PAPR) are recommended in case there is an unexpected need to perform an aerosol-generating procedure (e.g. emergency intubation)
Practical Considerations for Evaluating Patients for Ebola in the United States

- **Key points:** Identify, Isolate, Inform

- CDC encourages all U.S. healthcare providers to
  - Ask patients about travel or contact with individuals within previous 21 days
  - Know signs and symptoms of Ebola
  - Know initial steps to take if a diagnosis of Ebola is suspected

- CDC has developed documents to facilitate these evaluations

PUIs may present with a range of severity of illness

- Some have presented relatively well with fever, prodromal symptoms
- Some have presented critically ill with multi-organ system failure
  - Need for emergent dialysis, intubation and mechanical ventilation
- Preparations should include plans for handling this range of illness until diagnosis of EVD is either confirmed or ruled out
  - Additional considerations for range of ages possible from infants to older adults
Clinical Care in High Level Isolation

- Relatively limited diagnostic testing
  - Laboratory tests
  - Imaging tests
    - Portable x-rays require advance planning/protocols
    - Use of point of care ultrasound for diagnostic imaging and procedure guidance

- Invasive procedures in PPE
  - Threshold may be different – response time to deteriorating patient longer in isolation than in regular ICU due to PPE donning
  - Consider simulation exercises of procedures – central line placement, endotracheal intubation

- Consider telemedicine based consultations when possible
  - Limit the number of providers who need to enter the patient room
Airway Management

- Prepare dedicated airway equipment/bundle
  - Standard blades/tubes/airway adjuncts
  - Induction/Emergency medications
  - Video laryngoscope

- Canadian EVD guidelines recommend video laryngoscopy
  - Increase distance from the patient
  - Consideration of rapid sequence induction (RSI) to reduce cough and possible aerosolization
    - [www.canadiancriticalcare.org](http://www.canadiancriticalcare.org)

- Practice using simulation
Central Line Placement

- Central vascular access often required
- Consider early placement
  - Viral load may be lower earlier in course
- Planning/Simulation in PPE
- Ultrasound guidance
  - Consider ultrasound confirmation of placement
- Safety and PPE considerations
  - Safety needles and catheters to replace any non-safety devices in the kit
Care of the Patient with Ebola Virus Disease

Clinical Course
Clinical Course of EVD

Prodromal phase – day 1-3
- Fever, malaise/fatigue, headache, myalgias
- Leukopenia (esp lymphopenia) & thrombocytopenia
- Limited viral shedding

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**Clinical Course of EVD**

- Fever + Gastroenteritis/hepatitis – day 3-4 to 8-12
  - Vomiting, diarrhea → volume depletion, electrolyte loss
  - Metabolic acidosis
  - Elevated AST > ALT but minimal hyperbilirubinemia

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Later Clinical Course of EVD

- RUQ Tenderness +/- hepatomegaly
- Profuse Diarrhea
- Severe Vomiting
- Confusion, delirium, seizures, coma
- Icterus/jaundice
- Miscarriage in pregnant women

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### Critical Illness in EVD

- Respiratory distress/failure
- Renal Failure
- Encephalopathy
- Severe Shock
- Severe Hemorrhage

#### Symptom Chart

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## Predictors of Clinical Outcomes in EVD

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<td>(10^7) viral genome copies/ml serum</td>
<td>(10^{10}) viral genome copies/ml serum</td>
</tr>
<tr>
<td>Detectable antibodies in blood at onset of symptoms</td>
<td>No detectable antibodies in blood at onset of symptoms</td>
</tr>
<tr>
<td>Low Nitric Oxide</td>
<td>High Nitric Oxide levels</td>
</tr>
<tr>
<td>High sCD40L levels</td>
<td>Low sCD40L levels</td>
</tr>
</tbody>
</table>

Predictors of Clinical Outcomes in EVD

LESSONS LEARNED
The Critical Role of Nursing

- Ability to provide high-level nursing care and supportive care is essential
- 24/7 one-on-one nurses allowed for rapid response to changes and adjustment of care
- Ability to support patients in nutrition, physical therapy, and self care
- Emotional support
- Family support

- Patient- and Family-Centered Model of Care
Clinical Pearls

- Patients will be hypovolemic even while their body weight increases (15-20 kg)
  - low albumin
  - vascular damage
- May not be a factor in underdeveloped healthcare systems due to inability to match fluid losses
- Large volume losses: 5-10 liters/day
Impact of Nutrition and Electrolytes

- Patients may have marked electrolyte abnormalities and nutritional deficiencies
  - Hypokalemia, hypocalcemia and hyponatremia
  - Both intravenous and oral replacement
  - Used oral nutritional supplements including nutritional drinks high in easily absorbed proteins, minerals and vitamins
- Laboratory testing for chemistries was critical to provide supportive care (to be covered in another session)
Monitoring Virologic Status

- CDC assistance in monitoring EBOV viral loads in blood by PCR and antibody titers
  - Increased IgG levels correlated with decreased viral loads
  - Progressive decline in viral load correlated with improvements in clinical condition
  - May have very low level of nucleic acid detection for several days despite resolution of symptoms
Example: Longitudinal Trends in EBOV PCR, Antibodies and Symptoms
No proven therapeutics

- Unclear availability of any experimental agents
- Limited safety or efficacy data in humans
- Significant support and advice from CDC, FDA, and medical and scientific colleagues throughout the world
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convalescent plasma</td>
<td>Provide anti-EBOV antibodies</td>
<td>• Studies have not shown a clear benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Has been used in multiple evacuated patients in this outbreak</td>
</tr>
<tr>
<td>Hyperimmune globulin from immunized animals or previously infected humans</td>
<td>Concentrated plasma to provide high titers of neutralizing antibody</td>
<td>• Not currently available.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Work in horses and cattle are underway</td>
</tr>
<tr>
<td>ZMapp (Mapp Biopharmaceutical Inc.)</td>
<td>Cocktail of three chimeric mouse human monoclonal antibodies targeting the GP envelope protein</td>
<td>• Very promising data in macaques</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No human trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Very limited supply</td>
</tr>
<tr>
<td>TKM-100802 Lipid (TKM-Ebola; Tekmira)</td>
<td>Nanoparticle Small interfering Ribonucleic acid (siRNA) Targets two essential viral genes to stop the virus from replicating</td>
<td>• single-dose phase 1 study in healthy volunteers found side effects including headache, dizziness, chest tightness and raised heart rate at high doses.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A limited number of treatment courses</td>
</tr>
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## Experimental Interventions

<table>
<thead>
<tr>
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</tr>
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</table>
| **AVI 7537 (Sarepta)**              | Phosphorodiamidate oligonucleotide                                                          | • Monkey studies showed 60-80% when given at the time of infection  
• Tolerability has been demonstrated in early studies.  
• No human grade availability until late October |
| **Favipiravir/T-705**               | Selective inhibition of viral RNA-dependent RNA polymerase  
Does not inhibit RNA or DNA synthesis in mammalian cells | • Effective against EVD in mice, but in animal monkey study only 1/6 survived  
• Approved in Japan for influenza treatment under special circumstances.  
• ~10,000 treatment courses may be available |
| **BCX4430**                         |                                                                                             | • 83-100% survival in rodents with EVD  
• Effective in animals 48 hours after infection with the lethal Marburg virus  
• Testing for EVD in monkeys is underway |
| **Brincidofovir (CMX001)**          | lipid conjugate of the nucleotide analog, cidofovir (CDV)  
uses endogenous lipid uptake pathways to achieve high intracellular concentrations | • In vitro data at CDC showing good anti-EBOV activity  
• Has been used in 4 patients |
<table>
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</tr>
</thead>
</table>
| Chimpanzee adenovirus serotype 3 (ChAd3) vaccine | Uses a chimpanzee adenovirus that does not grow                              | • 16/16 monkeys were protected from a lethal dose by a single dose of the vaccine  
• Trials in humans ongoing  
• Approximately 15,000 doses might be available by the end of 2014 |
| Recombinant Vesicular Stomatitis Virus (rVSV) vaccine | Recombinant VSV vector expressing ebola GP protein to induce EBOV-specific immune responses | • 20/20 monkeys protected from a lethal dose of EVD  
• Animals with weakened immunity were not harmed by rVSV-EVD  
• Unknown if rVSV-EVD will grow in humans, which would affect immunogenicity and safety  
• Phase 1 trials underway  
• ~800 doses available |
Blood Product Support

- Packed red blood cells as needed
  - May need to use O- blood if blood typing not available
- Consider platelet transfusion if platelets < 50,000
- Correction of Coagulopathy
  - FFP if INR > 2 with serious bleeding
  - Cryo if fibrinogen low with serious bleeding
Clinical Management of Ebola: Supportive but Aggressive

- **Hypovolemia and sepsis pathophysiology**
  - Aggressive intravenous fluid resuscitation
  - Hemodynamic support and critical care management if necessary

- **Electrolyte and acid-base abnormalities**
  - Aggressive electrolyte repletion
  - Correction of acid-base derangements

Symptomatic management of fever and gastrointestinal symptoms

- Avoid NSAIDs, aspirin
- Anti-emetics and antidiarrheal agents may be needed

Multisystem organ failure can develop and may require

- Oxygenation and mechanical ventilation
- Correction of severe coagulopathy
- Continuous renal replacement therapy

Care of the Patient with Ebola Virus Disease

CRITICAL CARE
Emerging Critical Illness Phenotype

- Day 8-11
- Gastroenteritis/hepatitis & febrile phases may be improving
- Pulmonary
  - Progressive hypoxemia + multifocal/diffuse interstitial infiltrates
  - Respiratory distress → respiratory failure
- Renal
  - Acute kidney injury – rapid loss of small solute clearance
  - Oliguria → anuria
  - Metabolic acidosis
- Encephalopathy
  - Often severe & may develop earlier in course of illness

Courtesy of Michael Connor
Emerging Critical Illness Phenotype

- Consider secondary infections
- Nosocomial infections
- Malaria
  - Co-infection up to 30-50% in current EVD outbreak
  - Check 2-3 rapid malaria screens
  - Always complete malaria prophylaxis
Emerging Critical Illness Phenotype

- No proven EVD-specific organ support beyond established CCM “best” practices
- Lung protective ventilation & minimizing sedation as possible
- Target euvolemia
- Nutrition support – early & aggressive
- Delivery of critical care requires special consideration/planning
CRRT generates less spent effluent than conventional
- 48-96 L/day CRRT vs 192 L/4h IHD session

All RRT effluent should be non-infectious (for Ebola virus)
- Virus/RNA too big to fit through membrane
- Tested effluent multiple days by PCR to confirm

Disposed in same manner as local guidelines required for stool/urine

Courtesy of Harold Franch and Michael Connor
Table 2: Proposed clinical practice guidelines for RRT in acute phase of EVD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modality</td>
<td>CRRT recommended for initial treatment. Consider transition to PIRRT (using same CRRT equipment) for continued RRT until patient either a) recovers renal function OR b) is capable of leaving biocontainment isolation (i.e. negative viral PCR studies in blood).</td>
</tr>
<tr>
<td>Staff</td>
<td>If possible at the institution, all patients should receive RRT using CRRT equipment by extensively trained ICU nurses as primary clinical nurses at bedside. Minimize additional staff entry in biocontainment environment (i.e. specialty dialysis nurses).</td>
</tr>
<tr>
<td>Access</td>
<td>Temporary non-tunneled dialysis catheter placed at bedside under direct ultrasound visualization. Extra precautions should be taken to contain bloody waste from this procedure.</td>
</tr>
<tr>
<td></td>
<td>Right internal jugular (IJ) vein is the preferred access site (with left internal jugular IJ as backup site) given these present lowest bleeding risk as EVD patients may experience bleeding diatheses. Recommended that subclavian insertion sites be avoided.</td>
</tr>
<tr>
<td></td>
<td>Unless portable chest imaging following access insertion is unavailable, femoral access sites should be avoided secondary to bleeding risks (retroperitoneal bleeding).</td>
</tr>
<tr>
<td></td>
<td>Consider use of non-reflux dialysis grade caps for dialysis vascular access</td>
</tr>
<tr>
<td>CRRT Dosing</td>
<td>No EVD-specific dosing needs. Consistent with KDIGO statements, support target CRRT dose to deliver a total effluent dose of 20-25 ml/kg/hr\textsuperscript{10} unless higher dosing needed to augment small solute &amp; electrolyte clearance or correction of acidemia.</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Regional citrate anticoagulation is preferred and recommended on all patients to extend filter life and reduce potential staff exposures with filter exchanges.</td>
</tr>
<tr>
<td>Effluent disposal</td>
<td>CRRT effluent has a low infectious risk, but as it is handled in an Ebola positive area and a small dialyzer leak may be undetected, recommend effluent be treated as hazardous and disposed in similar manner as individual institution/local guidelines require for disposal of other bodily fluids in EVD\textsuperscript{11}</td>
</tr>
<tr>
<td>Nutrition support during CRRT</td>
<td>Ensure patients receive appropriate augmented nutrition support while receiving CRRT as recommended by clinical guidelines (total daily protein intake of approximately 2 g/kg/day)\textsuperscript{24, 25}</td>
</tr>
</tbody>
</table>

\textsuperscript{10} Connor MJ Jr, Franch H, et al. JASN. 2014

\textsuperscript{11} Serious Communicable Diseases Unit
LESSONS LEARNED
Lessons Learned

- Patients with Ebola can be safely cared for in our healthcare system with good preparation
- We do expect a lower mortality rate than in under-developed healthcare systems
- Communication is critical
- Critical and advanced care can be delivered if appropriately planned
- Comprehensive, multidisciplinary patient- and family-centered models of care can be delivered even in extreme circumstances
Patient Recovery

- Case-fatality rate between 50%-70% in the 2014 Ebola outbreak
  - Case-fatality rate is likely much lower with access to intensive care

- Patients who survive often have signs of clinical improvement by the second week of illness
  - Associated with the development of virus-specific antibodies
  - Antibody with neutralizing activity against Ebola persists greater than 12 years after infection

Patient Recovery

 Prolonged convalescence
   Includes arthralgia, myalgia, uveitis, abdominal pain, extreme fatigue, and anorexia; many symptoms resolve by 21 months
   Significant arthralgia and myalgia may persist for >21 months
   Depression, headache, skin sloughing, and hair, vision, and hearing loss have also been reported

Slit-Lamp Photograph of the Left Eye 14 Weeks after the Onset of Ebola Virus Disease (Varkey et al, NEJM 2015)

Questions?