Update on Clinical Protocols and Standards for Ebola Virus Disease

Nikki Shindo, MD
Team Lead
Clinical Standards
WHO
WHO integrated, clinically compatible guidelines/tools for limited-resource countries

Second-level learning programme: District clinicians at small hospitals in limited-resource countries

Larger than child pocket book - adults have more diverse problems
- Sex, drugs
- Mental health
- More chronic problems etc

First-level learning programme: Health centres/outpatients

Usually nurse or clinical officer led teams

IMCI
IMAI
IMAI-IMCI-IMPAC
IMAI-STB
IMAI-IMCI

CHWs, community/family caregivers, peer support
Home-based care, treatment support; palliative care tools
Uganda - December 2013 - printed Feb 2014

Ebola/Marburg, CCHF

WHO- interim emergency guidelines
- Generic draft for West African adaptation
- 30 March 2014
- printed April 2014

Ebola/Marburg, CCHF, Lassa fever

Sierra Leone adaptation - printed December 2014
Focused on Ebola;
includes Marburg, CCHF, Lassa fever

WHO- second generic version - based on Sierra Leone version, removes SL specifics; some updates.
Sections to be reviewed
The Meeting: Logistics

- “Clinical Aspects of the Ebola Virus Disease: Advancing Standards of Clinical Care”
- January 26-27, 2015, Geneva, Switzerland
- Co-hosted by Hôpital Université de Genève, led by Professor Laurent Kaiser, and supported by the Swiss Federal Office
- Participants: clinicians caring for EVD on the front lines in West Africa, U.S. and Europe representing African Union Member States, NGOs, and national and international agencies.
- Joined by experts in filovirus laboratory science, animal models, clinical trials, database and information management, and WHO Secretariat
Meeting Objectives

• Share information and build consensus regarding clinical standards for EVD
• Review clinical aspects, including clinical manifestations, disease evolution and complications, and case management experiences
• Improve clinical outcomes
• Provide standardized protocols to facilitate comparisons between different experimental therapies
Meeting Participants

- Primarily clinicians caring for EVD patients on the front lines in West Africa as well as United States and Europe
- Representing African Union Member States, NGOs, and national and international agencies
- Joined by experts in filovirus laboratory science, animal models, as well as those involved in clinical trials, and database and information management
- WHO Staff from Essential Medical Devices and Medicines, Infection Prevention and Control, Pregnancy and Child Health, Foreign Medical Teams, Clinical Management Team
Animal models are useful in understanding many aspects of disease pathogenesis, but all of the available models have limitations. Duodenal oedema and haemorrhage in NHPs—could explain GI symptoms seen in humans. CT scans in NHPs show abdominal compartment syndrome and cerebral parenchymal ischemic lesions compatible with severe abdominal pain and encephalopathy in human EVD.
Key messages: EVD pathogenesis

- Asymptomatic persons thought not infectious
  - PCR negative into early disease
  - More virus studies are needed for pre-symptomatic period

- No laboratory tests can currently diagnose during incubation period.

- No evidence of major mutations in virus with progression of epidemic
The classic pattern of fever, viremia and antibody production in persons infected with and surviving Ebola virus disease.
Preliminary data

Significantly higher average viral RNA load in Sierra Leonean patients with EVD, despite no difference in the interval between symptom onset and collection of blood samples.

Suggests that virus replication kinetics may differ at the two sites possibly due to differences in the infecting virus strain and/or host factors like presence of co-morbidities or genetic differences.
Serial data: EVD patients in Kailahun, Sierra Leone, from July to December 2014

- Average admission viral load diminished as the epidemic progressed, despite no differences in time to presentation.
- Has potential implications on severity of illness and case fatality ratio (CFR); indicate need for caution when using historical cohorts as a control group in clinical trials.
- Further research is needed to confirm these findings.
- May relate to both virus and host factors; different routes of infection or inoculum size; rapid access and earlier implementation of supportive care in ETUs.
Genetic evolution of the virus

- Continues to be assessed as the outbreak progresses
- Sequence comparison from two patients evacuated to the United Kingdom from Sierra Leone in August and December indicate no major variation.
Key Messages: Challenges to Triage

- Fever not present in all EVD at presentation, especially pregnant women
- Common complications of pregnancy (e.g. vaginal bleeding, miscarriage) also the same as those seen in pregnant women with EVD
- In children, significant overlap between case definition for EVD and other common treatable childhood illnesses, such ARI and ADI
- EVD co-infection with other endemic diseases (e.g. malaria, typhoid fever).
Key Messages: Laboratory Diagnostics

- Initial decisions currently based on triage algorithms, with significant potential for misclassification
- Laboratory diagnostic capacity improved considerably since the epidemic onset but,
- Better diagnostics needed at the point-of-care
  - For EVD: virus or RNA detection
  - For electrolytes and clinical parameters
- Several point-of-care diagnostic studies planned
Key Messages: Healthcare Worker Infections

- 844 healthcare workers with EVD, including ~25 expatriates
- CFR ~60%
- Sources of infection in expatriates-most acquired outside ETUs, including:
  - exposure to sick colleagues (some of whom did not declare their illness)
  - during doffing of PPE
  - uncontrolled environments (e.g. triage areas) where EVD diagnosis not yet established
- Limited number of HCWs with sharps injuries did not result in infection
Key Messages: Treatment

- Observed CFRs vary considerably between ETUs
- Different standards of care?
- Centres with proper fluid resuscitation strategies often report lower CFRs of 25-40%
- HCW infections can be avoided with adequate IPC measures, so ‘no touch’ policy practiced in some treatment centres not indicated
  - Undermines community engagement and confidence in control and treatment measures
Difficulties measuring vital signs and fluid inputs/outputs and in supporting oral intake in ETUs acknowledged

↑ risk of disease progression in absence of adequate oral fluid intake

ORS for initial phases of disease and mild cases

Low threshold to initiate IV fluids (i.e. vomiting, diarrhea, any sign of dehydration, inadequate oral intake)

Ringer lactate preferred
Key Messages: Electrolyte Monitoring

- Electrolyte correction ideally based on monitoring of laboratory values with set administration protocol
- Hypokalemia frequently noted in expatriates but MSF data showed potassium levels to often be normal
- When electrolyte monitoring not possible, consideration should be given to routine empiric oral potassium supplementation.
Key Messages: Symptomatic Treatment

- **Pain**: Paracetamol, then morphine. Tramadol (but WHO Essential Medicines list)
- **Nausea and vomiting**: Odansetron preferred
  - May also improve oral feeding and gut healing
- **Delirium and agitation**: Haloperidol, diazepam
- **Diarrhoea**: Debate regarding efficacy and safety of antimotility agents in EVD
Key Messages: Antibiotics

- Empiric Abx frequently given but no data on risk-benefit
- EVD symptoms often mimic bacterial sepsis or ADI, especially in children (~50% of children with suspected EVD test negative)
- Bacterial infections may coexist with EVD and early Abx in sepsis can be lifesaving
- Translocation of gut bacteria in EVD?
  - Some evidence but blood culture systems rarely available/feasible to confirm
- Indiscriminate antibiotic use should be avoided
- When to stop as important as when to start (usually ≤ 10 days)
Key Messages: Malaria Treatment

• All patients with fever in malaria endemic areas should be treated with antimalarials following national program guidance.
• Rapid diagnostic tests for malaria can be used if available and reliable.
Key Messages: Helminths and other Parasites

- Antihelminthics added at physician’s discretion
- Use knowledge of the prevalence of helminth infection in the area
- Overwhelming strongyloides most likely to mimic EVD
- Metronidazole for patients with bloody diarrhoea if amoebiasis suspected
Key Messages: EVD in Children

- In current outbreak ~20% of EVD patients ≤ 18 years
- Elevated CFRs: 80% in < 1 yr, 60% in < 5 yrs
- Special challenges to safely isolate and not infect or become infected and to keep hydrated
- Psychological trauma: need for grouping children together and/or for nearby adult at all times
- Children rarely weighed on ETU admission, leading to under- or over-dosing of fluids and medicines
- Some need vitamin A supplementation
- Need early administration of IV fluids if not taking orally
Key Messages: EVD and Pregnancy (I)

- CFR of pregnant women and offspring over 90%
- Rare cases of mothers who survive with baby still in utero
- Healthcare workers should check for foetal heart tones in these women
- In 1 case, amniotic fluid PCR+ with high viral load several days after the mother’s blood PCR-. Virus isolation result pending
- Intrauterine contents considered infectious and thus proper IPC precautions for delivery of children born to mothers recovering from EVD
Key Messages: EVD and Pregnancy (II)

- Need for induction?
- Invasive procedures such as C-section do not appear to improve chances of survival
- Oral misoprostol preferred treatment to prevent PPH
- Ebola virus isolated from breast milk
  - Recommended to stop breast feeding
- More data are needed to fully understand the pathogenesis and risks of EVD in pregnancy
Ebola virus shedding in body fluids. Colors=PCR positive. Bars=culture positive. Source: Pierre Rollin/CDC
Key Messages: Discharge Policy

- Present Criteria:
  - Clinically stable and “dry” (i.e. without vomiting, diarrhea, or bleeding) for 2-3 days
  - 1-2 negative PCR laboratory results
  - Criteria driven more by prevailing laboratory capacities and political concerns (e.g. “abundance of caution”) than by evidence-based assessment of risk?
  - Epidemiologic data + years of field observation have yielded no documented cases of transmission from a convalescence patient
  - More research on virus shedding needed
Key Messages: Sexual Transmission

- Male-to-female sexual transmission suspected but never definitely documented for EVD but,
- Ebola virus isolated from semen of survivors up to 82 days post disease onset
- Abstinence or condom use advised for 3 months after disease onset.
- PCR results on vaginal secretions in one patient were positive on day 33 after disease onset, although virus not isolated
Symptoms After suffering from Ebola (%)

Others include: palpitations(7), Mental confusion(2), Erectile dysfunction(1), Deafness(1), Amenorrhea(1), Neurological(1), Deafness(1), Numbness(1), Amenorrhoe(1)
1) Establish framework for the provision of:
   - General Medicine and Pediatric care
   - Psychiatric/Mental Health Support
   - Ophthalmic Services
   - Obstetric Services
   - Social Services
2) Contribute re-establishment and strengthening of healthcare services
3) Provide platform for systematic data collection and better understanding of post-EVD sequelae and associated social problems, enabling improved management
4) Basis for prospective research on best practices for management
EDCARN: 
Emerging Disease Clinical Assessment and Response Network

Clinical & Infection Control
Pandemic & Epidemic Diseases
WHO-HQ, Geneva

World Health Organization
EDCARN: Emerging Disease Clinical Assessment and Response Network

**Vision**
The mortality due to emerging pathogens is reduced through improved clinical management, even in absence of vaccine or specific treatment. Enhance/empower the role of clinical care / clinicians

**Mission**
In the Global Health Security context,
To strengthen global collaboration between clinicians, researchers, WHO, medical NGO's, national health authorities and other stakeholders in order to improve clinical management of patients during outbreaks of emerging diseases.

Catalyst of new dynamics of PED control – bench to bed and beyond
Basic science>animal models>regulatory mechanism>clinical trials>improved patient care>public health>policy
EDCARN: Emerging Disease Clinical Assessment and Response Network

Aim

• To assist national health authorities in coping with outbreaks of emerging pathogens through the provision of advice, guidance, training and other technical support to countries as well as implementing partners and practicing clinicians in order to improve the diagnosis, clinical management, and prevention of emerging infectious diseases;

• To accelerate production of scientific knowledge on these diseases.
EDCARN Partner mapping

WHO Secretariat

WHO ERC

Disease / initiatives Specific Advisory Panel

Network (ISARIC)

Network (InFact)

Network (SCC)

Network (WFICCS)

WHO CC Clinical trials

WHO CC Preclinical research

WHO CC Training of EID Clinical management and clinical research

WHO CC Systematic reviews

Ministry of Health

Working Groups

Institutions, clinicians, researchers

World Health Organization

Network (ISARIC)

Network (InFact)

Network (SCC)

Network (WFICCS)

WHO CC Clinical trials

WHO CC Preclinical research

WHO CC Training of EID Clinical management and clinical research

WHO CC Systematic reviews

Ministry of Health

Working Groups

Institutions, clinicians, researchers

World Health Organization