Advances in management of filovirus disease
AFIRM 30th March

Dr Janet Diaz
Clinical Management and Operations Unit
Country Readiness Strengthening, Health Care Readiness
Learning from 2014-2016 EVD Outbreak: Disparities in case fatality rate and care received

<table>
<thead>
<tr>
<th>Sub-Saharan African outbreaks</th>
<th>US/EUROPE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled case-fatality rate of 60% (95%CI: 47-73%)</strong> in outbreaks from 2010-2020.</td>
<td>EVD cases treated in US and Europe: 27 cases, <strong>case-fatality rate 5/27 (18.5%)</strong></td>
</tr>
</tbody>
</table>

Only at the end of the west Africa outbreak (2014-016) ventilation and renal replacement therapy were available, and only in Sierra Leone in one treatment unit.

Nine (33%) of these patients received non-invasive or invasive mechanical ventilation and five (19%) received renal replacement therapy for between 2 and 28 days.
A new strategy to manage EVD patients that saves lives: Three core interventions!

**Design and Biosecurity of ETC**
Beyond a simple isolation unit.
A facility centered around patients, staff, families and communities.
A facility where patients can receive, quality care with all biosecurity and IPC standards in place.

**Optimized supportive care**
Systematic evaluation and monitoring patients.
- Resuscitation with oral and IV fluids
- Availability of point of care testing (biochemistry, electrolytes, hemoglobin) and use of oxygen and blood products
- Prevention and care of complications

**EBOV specific Therapeutics**
Strong recommendation for two neutralising monoclonal antibody therapeutics:
- Ansvirimab (mAb114, Ebanga)
- Atoltivimab, maftivimab, odesivimab (REGN-EB3, INMAZEB)
Treatment Centres (ALIMA, Beni) DRC 2018
“The Cubes”
Treatment Centres (MSF, Butembo) DRC 2018
Optimized supportive care (oSOC)


Evidence-based guidelines for supportive care of patients with Ebola virus disease

Developed by clinical experts representing major stakeholders in EVD care with experience in EVD management in DRC using investigational therapeutics, point of care laboratory testing and close patient monitoring
<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress</td>
<td>Protect airway</td>
</tr>
<tr>
<td>In-efficient respiratory effort</td>
<td>Bag-mask ventilation &amp; Oxygen</td>
</tr>
<tr>
<td>If severe dehydration/shock +/-</td>
<td>Insert peripheral IV/ IO</td>
</tr>
<tr>
<td>Anemia</td>
<td>Start fluid therapy; Transfusion if needed</td>
</tr>
<tr>
<td>If patient in coma or has seizure</td>
<td>Manage “ABC”; Control Hypoglycemia; Anti- seizure medication if needed</td>
</tr>
<tr>
<td>Treat possible co-infections</td>
<td>Give antimalarials (artesunate IV or artesunate-amodiaquine oral) and broad- spectrum antibiotics ( + source control)</td>
</tr>
<tr>
<td>Obtain supportive care diagnostic tests</td>
<td>POC glucose, malaria test, biochemistry and electrolyte testing</td>
</tr>
</tbody>
</table>
EVD-specific THERAPY
Hallmark randomized clinical trial (PALM) conducted in DRC

- Patients receiving these investigational therapeutics as part of the RCT also received optimized supportive care that included clinical and laboratory monitoring.
- The PALM trial was conducted at 4 sites, in DRC from November 2018 to August 2019, when the data safety and monitoring board determined that two of the therapeutics (mAb114, REG-EB3) were safe and more effective than the standard of care which included Zmapp and Remdesivir.

Atoltivimab, maftivimab, odesivimab (Inmazeb, REGN-EB3)

Ansuvimab (mAB114, Ebanga)

CRR 64-85% despite EBOV-specific therapeutic, even the most effective ones!

Mab114 and REGN-EB3 improved 28 day mortality rates (versus the Zmapp control arm) and were well-tolerated

We need to combine early effective therapeutics with early and effective supportive care to improve patient outcomes!

CFR was improved to approximately 10% in patients with CT-NP>22

We need to diagnose EVD EARLY!

Mulangu et al, NEJM (2019)
RESEARCH AGENDA

CROSS CUTTING

Increase uptake and use of standardized Case reporting forms (CRFs): WHO hosting clinical platform (i.e. COVID-19)

Develop core outcome set (COS) for EVD/VHF prioritized from a patient perspective

- Can a bundle of optimized supportive care and therapeutics reduce mortality in the highest risk patients? What is the optimal composition of bundled care for EVD?
- How can we implement optimized supportive care for all EVD patients, especially at the beginning of an outbreak?
- What renal replacement interventions are most effective and feasible for patients with EVD?
- What is the influence of co-existing or super infection with endemic pathogens (for example, malaria, HIV), on disease course and outcomes?

- Novel therapeutics, including pan ebolavirus neutralizing monoclonal antibodies
- Trials of combination therapy
- Ensure continued inclusion of vulnerable populations (pregnant women, neonates, children, older people)
- Therapeutics for post-exposure prophylaxis

- Develop understanding of natural history of the disease
- Pathophysiology, pathogenesis of end organ failure (eg. mechanism of acute kidney injury).
- Post-Ebola syndrome (Characterization, prevention and management, long term sequelae)
- Viral persistence, relapse and potentiality for onward transmission
SPECIFIC THERAPEUTICS RESEARCH QUESTIONS

In the PALM study 40% of patients presented at admission with Ebola virus RT-PCR CT NP of 22 or less, Case Fatality Ratio was 70% with mAb114 and 64% with REGN-EB3. Therefore:

MORE EFFECTIVE STRATEGIES NEEDED FOR INDIVIDUALS WITH SEVERE DISEASE

• What is the optimal dosage of mAb114 and REGN-EB3?
• Are fractionated doses of neutralizing monoclonal antibodies more efficacious?
• Does combination therapy with a neutralising monoclonal antibody plus another agent reduce mortality compared to the use of single monoclonal antibody therapy?
• Are there significant interactions between neutralizing monoclonal antibodies and EVD vaccines when administered concurrently?
• Is there a potential risk of viral resistance caused by selective pressure of neutralising monoclonal antibodies?

Currently recommended neutralising monoclonal antibodies are only active against Zaire species of EBOV. Therefore:

THERAPEUTIC BREADTH
-PAN EBOLA VIRUS ACTIVITY

Post Ebola syndrome and viral persistence- sexual transmission of Ebola virus has been proven or strongly suspected eight times, with the first molecular evidence shown in 2016. Therefore:

THERAPEUTIC PENETRATION INTO IMMUNE-PRIVILEGED SITES

Do neutralizing monoclonal antibodies prevent or reduce clinical sequelae and viral persistence?

This could be achieved through observational cross-sectional study of PALM participants
COMING SOON

• WHO therapeutics for EVD guideline estimated publication date: May 2022
  strong recommendations for two monoclonal antibodies

• new EVD holistic case management training package in development
Thank you for your attention