EBOLA in Sierra Leone
Lessons learnt
Dr Marta Lado
Infectious Diseases coordinator
Kings Sierra Leone partnership, KSLP.
Kings Global Health partners.
Kings College London
CONNAUGHT HOSPITAL
Freetown, Sierra Leone

UNIVERSITY OF SIERRA LEONE
TEACHING HOSPITALS COMPLEX

King’s Sierra Leone Partnership (KSLP)

<table>
<thead>
<tr>
<th>CONNAUGHT GOVERNMENT HOSPITAL</th>
<th>COLLEGE OF MEDICINE &amp; ALLIED HEALTH SCIENCES</th>
<th>MINISTRY OF HEALTH AND SANITATION</th>
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</thead>
</table>

Connaught is the main government referral and teaching hospital, providing general adult and paediatric surgical care.

COMAHS is Sierra Leone’s only medical and pharmacy school and main institution for basic and specialist nursing.

KSLP works closely with MOHS to ensure that all activities are aligned with government priorities and plans, and support work on policy.
EBOLA NATIONAL TASKFORCE at MoHS
CASE MANAGEMENT PILLAR

CREATION GUIDELINES AND SOP

EBOLA PREPAREDNESS ASSESSMENT

NATIONAL MEETINGS

OPERATIONAL PLAN FOR MANAGING EBOLA FEVER

Sierra Leone Government
Ministry of Health and Sanitation

The Operational Plan for managing Ebola Fever has been developed to ensure the country is prepared and able to respond effectively to any outbreak of Ebola. The plan includes measures to prevent the spread of the disease, ensure early detection and prompt treatment of cases, and provide appropriate care for those affected. It also outlines the roles and responsibilities of different stakeholders involved in the response.

The plan comprises:
- Case classification and staging
- Surveillance procedures
- Clinical management of suspected cases
- Exercises and drills

CASE ISOLATION

- Having had contact with a clinical case AND
- Presenting with symptoms

CASE

- Having had contact with a clinical case (suspect, probable, or confirmed) AND
- Presenting with 3 or more of the symptoms below:
- FEVER
- Headache
- Muscle pain
- Joint pain
- Vomiting
- Diarrhea
- Bruising
- Abnormal bleeding

DEFINITION OF CONTACT

Contact is any person who came into contact with a case by:
1. Sleeping in the same household with the case
2. Direct physical contact with the case (dead or alive)
3. Touching or handling bodily fluids
4. Attendance at a funeral of a confirmed or suspected case of Ebola

Facility name: Connaught Provincial Hospital
Facility code: CPH
Contact person: Dr. R. Quie
Contact number: 076 297 60
Location: Freetown

Facility name: Kindu Hospital
Facility code: KHD
Contact person: Dr. M. Massaquoi
Contact number: 076 297 60
Location: Kindu

Facility name: New Amsterdam Provincial Hospital
Facility code: NAP
Contact person: Dr. A. Johnson
Contact number: 076 297 60
Location: New Amsterdam

Facility name: Nkonde Hospital
Facility code: NKD
Contact person: Dr. J. Johnson
Contact number: 076 297 60
Location: Nkonde
EBOLA OUTBREAK AWARENESS
MANUALS EBOLA

March 2014
TRAINING EVD for Health Care Workers
COMMAND CENTER WESTERN AREA

BED CAPACITY

AMBULANCE SERVICE

BURIAL TEAM

If you have fever, diarrhoea and vomiting, with or without bleeding, go to the nearest health facility.

For more information call FREE 117.
CONNAUGHT HOSPITAL ISOLATION UNIT
Clinical features of patients isolated for suspected Ebola virus disease at Connaught Hospital, Freetown, Sierra Leone: a retrospective cohort study


Symptom pattern similar in EVD cases and non-EVD cases

- Fever (84.1%)
- Intense fatigue (72.8%)
- Vomiting (54.5%)
- Diarrhoea (44.0%)
- Anorexia (36.9%)
- Abdominal pain (31.7%)
LABORATORY DIAGNOSIS IN EBOLA

1. **RT-PCR**: rapid, more sensitive than antigen detection ELISA, and provides specific identification of genetic fragments of the virus

2. **ELISA**: allows the detection of the viral antigen or antibody on inactivated specimens, such as blood, serum, or tissue suspensions

3. **Virus isolation**: requires a Biosafety Level-4 laboratory and can take several days

4. **Immuno-histochemical staining and histopathology**: On collected tissue or dead animals; localizes viral antigen
MANAGEMENT OF LABORATORY SAMPLES

Decontamination at the collection point

SPRAY 0.5% Chlorine

1. Labeled sample
2. 50 ml-sampe
3. ziplock

4. (several samples)

LAB CLOSE BY

LABORATORY IN SITE
ReEBOV Antigen Rapid Test kit for point-of-care and laboratory-based testing for Ebola virus disease: a field validation study

Mara Jana Broadhurst, MD, John Daniel Kelly, MD, Ann Miller, PhD, Amanda Semper, DPhil, Daniel Bailey, PhD, Elisabetta Gropelli, PhD, Andrew Simpson, FRCPath, Tim Brooks, FRCPath, Susan Hula, MSc, Wilfred Nyoni, MSc, Alhaji B Sankoh, DLT, Santigi Kanu, DLT, Alhaji Jalloh, Quy Ton, MD, Nicholas Sarchet, RN, Peter George, MD, Mark D Perkins, MD, Betsy Wonderly, BSc, Prof Megan Murray, MD, Dr Nira R Pollock, MD

Published Online: 25 June 2015

DOI: http://dx.doi.org/10.1016/S0140-6736(15)61042-X | CrossMark
RAPID TEST EBOLA

Defence Science and Technology Laboratory (DSTL)

Evaluation of a point-of-care blood test for identification of Ebola virus disease at Ebola holding units, Western Area, Sierra Leone, January to February 2015

24 RDT positives:
15 EVD PCR positive
9 EVD PCR negative

Diagnostic accuracy of DSTL rapid diagnostic antigen test for Ebola virus disease compared with gold standard PCR, by CT score, Sierra Leone, January–February 2015 (n = 131)
EVD Progression

Symptom Stages

1 - ‘Bodi wam’
- Intermittent fever, no pattern, not very high
- Headache, LOA
- Back pain, joint pain, myalgia
- Intense fatigue, severe progressive weakness
- Malarial symptoms – late presentation

2 - ‘De kaka fast fast’
- Vomiting, diarrhoea, abdominal & chest pain
- Liver tenderness
- Hiccups? paralytic ileum

3 - ‘De torment’
- Conjunctivitis
- Cognitive slowing – ‘Ebola stare’, startled, disorientation, confusion, falling over, lying on floor

Photos: Michael Duff/KSLP
Clinical presentation, biochemical, and haematological parameters and their association with outcome in patients with Ebola virus disease: an observational cohort study


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<thead>
<tr>
<th>Clinical features</th>
<th>Typical patient</th>
<th>Standard treatment</th>
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<tr>
<td>Stage 1: early or mild</td>
<td>Non-specific features: pyrexia, weakness, lethargy, myalgia, and arthritis</td>
<td>Ambulatory, able to compensate for fluid losses via oral intake</td>
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<tr>
<td>Stage 2: gastrointestinal involvement</td>
<td>As above plus: diarrhoea, vomiting or abdominal pain, or both</td>
<td>Unable to compensate for fluid losses via oral intake due to emesis or loss of large volumes</td>
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<tr>
<td>Stage 3: complicated</td>
<td>As above plus: haemorrhage, shock, neurological involvement, or signs of organ failure</td>
<td>Critically ill, usually hypovolaemic, often with confusion or seizures, bleeding</td>
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</table>

A typical patient is a patient most representative of that specific disease stage. * Sodium, potassium, magnesium, calcium, and phosphate replaced according to biochemistry results. † Ceftriaxone (2 g once per day for adults) was given as an empirical 5 day course in all stage 2 and 3 patients. It was continued for longer or given to stage 1 patients if clinically indicated. ‡ Fresh frozen plasma was given when haemorrhage continued despite vitamin K and when available.

Table 1: Clinical staging system for Ebola virus disease used at Kerry Town Ebola treatment centre and subsequent standard clinical management
Severe Ebola virus disease with vascular leakage and multiorgan failure: treatment of a patient in intensive care

T Wolf, Gerrit Kopp, Christoph Stephan, Hans-Reinhardt Brodt, Philipp de Leuwe, Thomas Gernswald, Thomas Vogl, Volkhard A J Kempf, Oliver T Keppeler, Kai Zacharowski

DOI: http://dx.doi.org/10.1016/S0140-6736(14)62384-9
Clinical Illness and Outcomes in Patients with Ebola in Sierra Leone


Figure 4. Comparison of Metabolic Measures in Patients with Fatal and Nonfatal EVD.

Laboratory measurements at presentation that were associated with a fatal outcome included elevated levels of blood urea nitrogen, creatinine, and aspartate aminotransferase (AST). Blue shading indicates normal ranges for the various measures. Results for sodium, potassium, chloride, glucose, calcium, albumin, total protein, and total bilirubin are provided in Table 5 (in the Supplementary Appendix). The t bars indicate standard errors. ALT denotes alanine aminotransferase. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
Monitoring the severely ill patient

• **Regular monitoring of vital signs** (temp, HR, RR, BP, O2 sats) and other clinical signs and symptoms
• Use Quick Check or other **severity indicators** for triage
• Record results of **input and output** at patient bedside (vomit, diarrhea and urine)
• Priority **lab tests** (for those moderate and severe):
  • Electrolytes especially **potassium, sodium, glucose**
  • Renal function: creatinine
  • Haemoglobin / Haematocrit
Clinical management of Ebola:
Supportive, but aggressive

1. GI fluid loss from diarrhea and vomiting: administer fluids aggressively to keep up with losses
2. Electrolyte abnormalities Monitoring – Point of Care monitoring devices (e.g., I-STAT®)
   • Oral or IV replacement
   • K+, glucose, HCO3-
   • May be proximate cause of death (arrhythmia, cardiac arrest, seizure)
3. Septic shock physiology:
   • Aggressive fluids (but monitor for vascular leak/pulmonary edema)
4. Symptomatic management of nausea, vomiting, diarrhoea, seizures, myalgia & abdominal pain
5. Prophylactic antibiotic use for possible gut translocation of bacteria and sepsis
6. Transfusion of fresh whole blood or red blood cell components or plasma may be considered

Clinical management of patients with viral haemorrhagic fever
A pocket guide for front-line health workers

Interim emergency guidance for country adaptation

World Health Organization
Consideration of co-infections during the management of EVD, cont.

• If malaria:
  • **Option 1:** Test everybody for malaria (RDT)
  • **Option 2:** If not available, then treat for malaria according to the treatment guidelines:
    • Uncomplicated malaria – **ACT** (Artesunate/amodiaquine)
    • Complicated/Severe malaria – **IV/IM Artesunate**

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**Effect of Artesunate–Amodiaquine on Mortality Related to Ebola Virus Disease**

Etienne Cibasus, M.P.H., Andrew S. Azman, Ph.D., Martin de Smet, M.D., Philippe Azama, M.D., Moses Massaguio, M.D., Dorian Jia, M.D., Amanda Tiffany, M.P.H., Roberti Petrucci, M.D., Esther Sterk, M.D., M.I.H., Julien Poter, M.Sc., Motoi Suzuki, M.D., Andreas Kruh, Ph.D., Angela Cmam, Ph.D., Anne Bocquin, M.Sc., Thomas Strecker, Ph.D., Christopher Logue, Ph.D., Thomas Pottage, B.Sc., Constanze Yue, Ph.D., Jean-Clement Cabrol, M.D., Micaela Serafini, M.D., M.P.H., and Iza Ciglenecki, M.D.

A total of 125 of the 194 patients in the artemether–lumefantrine group (64.4%) died, as compared with 36 of the 71 patients in the amodiaquine group (50.7%). In adjusted analyses, the artemether–lumefantrine group had a 31% lower risk of death than the artemether–lumefantrine group (risk ratio, 0.69; 95% confidence interval, 0.54 to 0.89), with a stronger effect observed among patients without malaria.
The New York Times
Ebola Doctors Are Divided on IV Therapy in Africa

...the restriction of use of intravenous fluid resuscitation and the electrolyte supplement is not medically justified.

Even two of the most admired medical charities have squinted off over the issue. Partners in Health, which has worked in Haiti and Rwanda, but is just beginning to treat Ebola patients in West Africa, supports the aggressive treatment. Its officials say the more measured approach taken by MSF is overly cautious.

By DONALD G. WISON JR. JUNE 5, 2015

Caring for Critically Ill Patients with Ebola Virus Disease
Perspectives from West Africa

Clinical Presentation and Management of Severe Ebola Virus Disease

Colin Brown, Benno Kreuels, Peter Baker, Tim Baker, Tom Boyles, Marta Lado, Oliver Johnson

Ebola treatment facility, Goderich, Sierra Leone—February 2015

Ebola treatment facility, Royal Free Hospital, London, UK—September 2014

Emory University Hospital special isolation unit.

  11 US
  3 SPAIN
  3 UK
  3 GERMANY
  2 FRANCE
  1 NORWAY
  2 ITALY
  1 SWITZERLAND
  1 NETHERLANDS

14/27 got infected in Sierra Leone
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CRRT continuous renal replacement therapy, F female, IHD intermittent hemodialysis, LOS length of stay, M male, MV invasive mechanical ventilation, N/A not available, NIV non-invasive ventilation, TKM TRM-E small interfering ribonucleic acids (siRNA) produced by Tekmira.
Clinical Management of Ebola Virus Disease in the United States and Europe


ABSTRACT

CONCLUSIONS

Among the patients with EVD who were cared for in the United States or Europe, close monitoring and aggressive supportive care that included intravenous fluid hydration, correction of electrolyte abnormalities, nutritional support, and critical care management for respiratory and renal failure were needed. 81.5% of these patients who received this care survived.
Medical treatment of an Ebola-infected doctor—ethics over costs?

*Kai Zacharowski, Hans-Reinhardt Brodt, Timo Wolf
kai.zacharowski@kgu.de


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<tr>
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<td>46 352.54</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Other costs (not classified)</td>
<td>18 475.00</td>
</tr>
<tr>
<td>Overall total</td>
<td>106 278.93</td>
</tr>
</tbody>
</table>

ICU=intensive care unit.

Table: Hospital costs to treat one patient with Ebola
NEW THERAPIES

- **FAVIPIRAVIR**: Guinea
  *Sierra Leona: prophylaxis POST EXPOSURE (KSLP)- 14 dias.

  **INITIAL**: 6,000 mg (2,400 mg 0h y 8h)
  **LATER**: 1,200 mg (16h).
  **MAINTENANCE**: 1,200mg/12h

- **BRINCIDOFOVIR**: Liberia (MSF)
- **AMIODARONE**: 79 patients Sierra Leona
  – CRF: 42% vs 52%
- **ZMAPP Monoclonal**: Western Area y Lunsar.
- **FX06**: 2 expatriated
- **Zmab**: 4 expatriated
- **EVD SURVIVOR CONVALENCENT PLASMA**
Brincidofovir – Chimerix

CMX001 a broad-spectrum antiviral for the prevention and treatment of clinically significant infections caused by DNA viruses. Brincidofovir is an oral nucleotide analogue that has shown in vitro antiviral activity against all five families of DNA viruses that affect humans, including cytomegalovirus (CMV), adenovirus (AdV), BK virus and herpes simplex viruses.

Favipiravir – Toyama

T-705 selected as a clinical candidate based on its remarkable therapeutic efficacy demonstrated in mice infected with influenza virus. T-705 possesses potent and broad spectrum antiviral activity against multiple strains of influenza virus infection in vitro and in vivo. Directly inhibits RNA dependent RNA polymerase.

TKM-Ebola – Tekmira

TKM-Ebola, an experimental antiviral drug for EVD, is a combination of small interfering RNAs targeting three of the seven proteins in Ebola virus: Zaire Ebola L polymerase, Zaire Ebola membrane-associated protein (VP24), and Zaire Ebola polymerase complex protein (VP35). The drug was effective in rhesus monkeys infected with Ebola.

ZMapp™ – Mapp Bio

ZMapp™ is composed of three “humanized” monoclonal antibodies manufactured in plants, specifically Nicotiana. Antibody genes are infiltrated into tobacco plants to transiently manufacture the ZMapp™ antibodies. It is an optimized cocktail combining the best components of MB-003 (Mapp) and ZMAb (Defyrus/PHAC).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>M</th>
<th>Patients</th>
<th>Enrolment</th>
<th>Endpoint reached</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brincidofovir</td>
<td>Single-arm phase 2 trial</td>
<td>1</td>
<td>4</td>
<td>01/01/15-31/01/15</td>
<td>No – trial terminated</td>
<td>All 4 died</td>
</tr>
<tr>
<td>Favipiravir - JIKI</td>
<td>Single-arm phase 1 trial</td>
<td>4</td>
<td>126 (540 historic controls)</td>
<td>17/12/14-08/04/15</td>
<td>No – reported differently</td>
<td>Nuanced conclusions – limited tolerability</td>
</tr>
<tr>
<td>Favipiravir – Jui</td>
<td>Single-arm phase 2 trial</td>
<td>1</td>
<td>39 (85 historic controls)</td>
<td>01/11/14-10/11/14</td>
<td>N/A</td>
<td>Survival rate (56% [22/39] vs 35% [30/85]; p= 0.027).</td>
</tr>
<tr>
<td>TKM-Ebola</td>
<td>Single-arm phase 2 trial</td>
<td>1</td>
<td>14 (3 cohort, observational)</td>
<td>11/03/15-15/06/15</td>
<td>No</td>
<td>No survival benefit</td>
</tr>
<tr>
<td>ZMapp</td>
<td>RCT (non-blinded)</td>
<td>11</td>
<td>36 (35 controls), Guineans had FVP, unclear if matched</td>
<td>01/03/15-01/11/15</td>
<td>No – stopped early, low EVD numbers</td>
<td>Mortality rate (37% [13/35] vs 22% [8/36]; 91.2% posterior probability).</td>
</tr>
<tr>
<td>Plasma</td>
<td>Non-random comparative study</td>
<td>1</td>
<td>99 (507 controls)</td>
<td>17/02/15-03/08/15</td>
<td>No – ? if any neutralizing antibody</td>
<td>Mortality rate (31% [26/84] vs 38% [158/418]; p=0.92 after age/CT adjustment</td>
</tr>
</tbody>
</table>

OTHER THERAPIES

AVI-7537
BCX4430
JK-05
FGI-106
U18666A
Clomiphene
Toremiphene

Amiodarone
Chloroquine
Lamivudine
Imipramine
Statins
Artemisinin
FTY720
Ebola vaccines bring hope to victims

Two vaccines are being tested on patients, including VSV-ZEBOV, developed in Canada.

1. Ebola virus (Zaire type)
   - Gene: GP protein
   - RNA
   - GP protein: The virus attacks human cells by locking on to them with the aid of this protein, which covers the virus.

2. VSV (Vesicular stomatitis virus, affects cattle)
   - This virus is weakened and will act as a vector for the vaccine.

3. The vaccine therefore contains the modified VSV, but no other molecule belonging to the Ebola virus.
   - The GP protein's gene is taken from the Ebola virus then transferred into the VSV virus.

   - Thereby replacing the VSV surface protein gene.

   - Anti-GP antibodies
   - If all goes to plan, the vaccinated individual will produce antibodies neutralising GP proteins, thus ensuring protection against Ebola.

Sources: HUG, Geneva University, WHO
Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

Ana Maria Henao-Restrepo, Ina M Longini, Matthias Egger, Natalie E Dean, W John Edmunds, Anton Camacho, Miles W Carroll, Alhousseynou Diatta, Bertrand Dragne, Sophie Dufourg, Godwin Enwere, Rebecca Greis, Stephan Gunther, Stefania Hossmann, Mandy Kader Koné, Souleymane Koné, Ewa Kuzma, Myron M Levine, Semu Mandé, Gunnarstein Norheim, Ximena Rivera, Alhoubcar Soumoh, Sven Trefle, Andrea S Viscari, Conal D Watson, Sakoba Kita, Marie Paule Kreisy, John-Arne Ratténgen*


Immediate (48 - 4123) 21 days (42 - 3528)

0 16

infections infections

Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

Ana Maria Henao-Restrepo, Anton Camacho, Ina M Longini, Conal D Watson, W John Edmunds, Matthias Egger, Natalie E Dean, Ibrahim Diatta, Maria Soumoh, Bertrand Dragne, Sophie Dufourg, Godwin Enwere, Rebecca Greis, Stephan Gunther, Pierre-Stéphane Guell, Stefania Hossmann, Sara Viksømo Wüstlé, Mandy Kader Koné, Sakoba Kita, Souleymane Koné, Ewa Kuzma, Myron M Levine, Semu Mandé, Thomas Maugé, Gunnarstein Norheim, Ximena Rivera, Alhoubcar Soumoh, Sven Trefle, Andrea S Viscari, John-Arne Ratténgen*, Marie Paule Kreisy

Lancet December 22, 2016 http://dx.doi.org/10.1016/ S0140-6736(16)32621-6

vaccine efficacy of 100% (95% CI 74.7–100.0; p=0.0036)

cluster vaccine efficacy of 75% (95% CI -7.1–95.1; p=0.1791)