Overview

- Review Ebola Virus Disease (EVD) and the 2014 West African Outbreak
- Examine the evidence for the role of convalescent plasma in treating EVD
- Highlight ongoing trials in West Africa of convalescent plasma
- Describe the work of Academic Consortium Combating Ebola in Liberia (ACCEL)
Ebola Facts

- Ebola Virus Disease (EVD) is severe, often fatal zoonotic disease
  - Fatality rate is ~50%, range 15-90%
  - Family of filoviruses (Ebola Zaire)
  - Recognized since 1976
- Incubation period (asymptomatic) for 2-21 days (no transmission until symptoms)
- **Poorly transmitted disease Reproductive Number (R₀) = 1-2,**
  - 1.96 in Liberia at height of transmission

- Community practices modification is key to control
  - Massive change of behavior in Liberia in terms of physical contact and central cultural practices

Feldmann 2014 371:1375–1378
Common Nonspecific Symptoms

- FEVER (87%)
- LOSS OF APPETITE (65%)
- FATIGUE (77%)
- VOMITING (68%)
- DIARRHEA (66%)
- Abdominal Pain (44%)
- Conjunctivitis (20%)
- Rash (6%)
- bloody diarrhea (6%)
- bloody Nose (2%)

Muscle Pain (38%)

Bleeding is not a major consequence

Images: CDC
Ebola Pathogenesis

- Direct contact with infected body fluids
  - Initial size of viral inoculation correlates with morality
- Invades Dendritic cells and macrophages
  - Hepatocytes, renal epithelial, endothelial cells
- Cytokine storm
- Coagulation Defects and Thrombocytopenia
  - Massive release of tissue factor from damage cells and by macrophage secretion
- Immune Dysregulation
  - Antibody mediated endocytosis uptake via C1q
  - Inhibition of interferon type 1 innate immune response (eVP24, eVP30)
  - Inhibition of macrophage maturation and antigen presentation
  - In vitro bystander apoptosis of T cells and Macrophages
- Survivors show robust T and B cell responses with viral specificity during acute infection (McElroy 2015 PNAS 112:4719–4724)
2014 West Africa Ebola Outbreak

- Greatest Outbreak on Record

Total (5/5/15): 26,536 cases (14,913 confirmed) 10,980 fatalities

WHO situation reports
Early Recommendations

- Use of convalescent whole blood collected from patients recovered from Ebola (WHO Recommendations and Guidelines, Sept 2014)
  - Potential evidence, rational, and effectiveness in other related diseases
  - Proposed basic guidelines for the collection and provision of units.
    (WHO Publication: WHO/HIS/SDS/2014.8)

  - WHO has stated that convalescent blood or plasma is an option in the treatment of Ebola. In 1999, transfusion of locally collected convalescent blood helped decrease Ebola mortality. WHO recommends collection of convalescent plasma to treat patients in the fight against the Ebola outbreak. As there is an estimated 70% mortality, a randomised clinical evaluation involving 50 patients, receiving convalescent and control normal plasma, would be sufficient to confirm the usefulness of this approach in treatment strategies.
    (Burnouf 2014 October, Lancet 384:1347-8)
What is the available evidence?

- Human Epidemiology
- Human Antibodies in animal studies
- Animal Studies (Monkey Trials)
Human Studies

- Isolated case reports
- Kikwit Outbreak (Zaire 1995)
  - Outbreak had average morality rate of 80%

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>No. of days between onset of symptoms and transfusion</th>
<th>Blood volume (cm³)</th>
<th>Received blood from donor no.</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>7</td>
<td>400</td>
<td>1</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>11</td>
<td>150</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>13</td>
<td>150</td>
<td>3</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>9</td>
<td>250</td>
<td>2</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>15</td>
<td>250</td>
<td>4</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>13</td>
<td>250</td>
<td>4</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>11</td>
<td>450</td>
<td>5</td>
<td>Survived</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>4</td>
<td>400</td>
<td>2</td>
<td>Died</td>
</tr>
</tbody>
</table>

Mupapa K. J Infect Dis. 1999;179: S18–S23
However...

- Patients received better care later in outbreak: fluids, nutrition, etc.

- Additional patients in outbreak treated with plasma at other sites during outbreak:
  - 5 patients presenting with bleeding received blood only 1 survived.

- Authors' Discussion:

  Transfusions are probably useful for the treatment or prevention of shock and may provide coagulation factors to stop or to prevent bleeding. However, because of the small number of patients studied and the lack of control subjects, we cannot conclude that the neutralizing antibodies in transfused convalescent blood improves the outcome for EHF patients”

HOWEVER...

- Companion Paper Statistically Investigating “Determinants of Survival”
  - 4 phases: mortality: 93.2%, 80%, 78.1%, and 69%
  - After symptoms: 7 days: 70% morality; 14 days: 25% mortality
  - Transfused patients received blood on average 10 days after symptoms
  - Controlling for age, sex, time from first symptoms at treatment, phase of outbreak
    - Expected mortality rate was 24% vs 12.5% \((P=0.171)\).

Sadek RF et al. 1999  J Infect Dis. 179: S24–S2
Best Human Data is Monoclonals

- Monoclonal antibodies isolated from humans and applied in NHP models showed efficacy in preventing disease and mortality
  (Maruyama. 1999; J Virol. 73:6024–6030)
- MB-003 and ZMab: represent human and mouse derived monoclonals that show protection as well
## Non-Human Primate Studies

### Table 2. Historic postexposure treatments for filoviruses and outcome

<table>
<thead>
<tr>
<th>Virus</th>
<th>Treatment</th>
<th>Macaque species</th>
<th>Initiation of treatment</th>
<th>Outcome, % survival</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBOV</td>
<td>Equine IgG</td>
<td>Cynomolgus</td>
<td>Day 0</td>
<td>0, 0</td>
<td>9, 13</td>
</tr>
<tr>
<td>EBOV</td>
<td>Whole-blood transfusions</td>
<td>Rhesus</td>
<td>Day 0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>EBOV</td>
<td>hMAb</td>
<td>Rhesus</td>
<td>Day –1</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>EBOV</td>
<td>rIFN</td>
<td>Cynomolgus</td>
<td>Day 0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>EBOV</td>
<td>rNAPc2</td>
<td>Rhesus</td>
<td>10 min</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBOV</td>
<td>rVSV vaccine</td>
<td>Rhesus</td>
<td>20–30 min</td>
<td>50</td>
<td>22</td>
</tr>
<tr>
<td>EBOV</td>
<td>rhAPC</td>
<td>Rhesus</td>
<td>30–60 min</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>EBOV</td>
<td>siRNA-SNALPs</td>
<td>Rhesus</td>
<td>30 min</td>
<td>67–100</td>
<td>26</td>
</tr>
<tr>
<td>EBOV</td>
<td>PMOplus</td>
<td>Rhesus</td>
<td>30–60 min</td>
<td>63</td>
<td>27</td>
</tr>
<tr>
<td>EBOV</td>
<td>Rhesus IgG</td>
<td>Rhesus</td>
<td>48 h</td>
<td>100</td>
<td>Present study</td>
</tr>
</tbody>
</table>

hMAb, EBOV-specific human monoclonal IgG1 monoclonal antibody vaccine; PMOplus, phosphorodiamidate morpholino oligomers; rhAPC, recombinant human activated protein C vaccine; rhesus IgG, fractionated IgG from convalescent serum from rhesus macaques; rIFN, recombinant IFN vaccine; rNAPc2, recombinant nematode anticoagulant protein C2 vaccine; rVSV, recombinant vesicular stomatitis virus vectored vaccine; siRNA-SNALPs, siRNAs in stable nucleic acid-lipid particles.
Replicating Kikwit Whole Blood in Non-Human Primates

- Study: 4 monkeys received a single “human-unit” equivalent of whole blood (6 mL/kg of CPDA) from immune monkeys at time of inoculation
  - High-titer donors (1:100,000): hyperimmune monkeys that had been re-challenged to boost antibodies titers prior to collection
  - Provided titers of ~1:2000 on par with titers observed in convalescent human patients
- Result: All 4 transfused monkeys died as well as the control.

IV Ig Trial in Rhesus macaque

- Post exposure hyperimmune prophylaxis protects non-human primates from filovirus disease

- IV Ig dosing
  - Donors: viral challenge post vaccination (titre 1:1,000,000)
  - 80mg dose at 2, 4, and 8 days

- Signs and Symptoms:

Study 3: Macaques challenged with 1,000 pfu EBOV; treatment initiated 48 h after challenge

<table>
<thead>
<tr>
<th>Animal 7</th>
<th>Thrombocytopenia (day 6), no viremia</th>
<th>Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal 8</td>
<td>Fever (day 6, 8, 10), thrombocytopenia (day 6), lymphopenia (day 12), no viremia, two- to threefold increase in AST (day 12, 14, 16)</td>
<td>Survived</td>
</tr>
<tr>
<td>Animal 9</td>
<td>Thrombocytopenia (day 6), no viremia</td>
<td>Survived</td>
</tr>
<tr>
<td>Control 5</td>
<td>Fever (day 4, 6), anorexia (day 6–8), depression (day 6–8), thrombocytopenia (day 6, 8), lymphopenia (day 5, 8), viremia (day 4, 5, 8), more than fivefold increase in ALT/AST (day 5, 8), mild rash (day 8)</td>
<td>Died, day 8</td>
</tr>
</tbody>
</table>

Dye JM 2012 PNAS 109 5034–5039
Summary of Evidence

- Human data truly provides no significant evidence
  - Kikwit 7/8 survivors has been over interpreted
  - Human monoclonals protection in NHP best support
  - No evaluation of the role of normal plasma in terms of replacement of normal factors or volume expansion

- Results non-human primate suggests that a single unit may not be sufficient, and/or dosing schedule may be important.
  - One whole blood unit equivalent at time 0 (~60 mg Ig) ineffective
  - 3 x 80 mg IV Ig effective – ~3-4 units of plasma

Likely human antibodies are effective but sufficient dosage is key!
Current Situation in West Africa

Today: “Ebola-free”

Source: Situation Report WHO
Ongoing Trials in Current Outbreak

- **Clinical Trial to Evaluate the Efficacy and Safety of Convalescent Plasma for Ebola Treatment (EVD001) [NCT02333578] [Phase I/II nonrandomized]**
  - Sponsor: Clinical Research Management, Inc. (Gates, Duke, UNC)
  - Planned enrollment: 70
  - Dosing: convalescent FP24, 200mL, up to 3 times over 48 hours
  - Outcome: change in viral load before and after transfusion and relative to non-transfused

- **Emergency Evaluation of Convalescent Plasma for Ebola Viral Disease (EVD) in Guinea (Ebola-Tx) [NCT02342171] [Phase II/III nonrandomized]**
  - Sponsor: Institute of Tropical Medicine, Belgium (Oxford, LSTMH)
  - Trial of Convalescent Plasma versus Standard Supportive Care only
  - Planned enrollment: 200
  - Dosing: 200-250 mL x 2 (adults); 10 mL/kg children/small adults
  - Outcomes: 14 day survival (primary), 30 day survival (secondary), viral load (secondary), severe transfusion reactions (secondary)
Sierra Leone

- **Convalescent plasma for early Ebola virus disease in Sierra Leone (Ebola_CP) [ISRCTN13990511 nonrandomized]**
  - Sponsor: University of Liverpool / Wellcome Trust
  - Dosing: Single unit of CP vs. equivalent volume of Lactate Ringer's –non-randomized
  - Subjects: 200 in CP arm and 100 in LR arm
  - Outcomes: 14 day survival (primary)

- **Unregistered study reported in February (Col. Foday Sahr):**
  - 35 Ebola patients transfused with plasma
  - 80% survival in recipients versus ???% controls (unanalyzed).
  - Case example
    - December 4 (day 1), 2014: Kadiatu Fofanah feels weak.
    - December 5 (day 2): Fofanah begins to vomit and have diarrhea.
    - December 10 (day 6): Fofanah feels extremely sick, checks into the 34th Military Hospital in Freetown, Sierra Leone, and learns she is Ebola positive.
    - December 12 (day 8): A military doctor offers Fofanah an infusion of Ebola survivor blood as part of a study, and she accepts. (Kikwit >60% survival)
    - January 20 (day 17): Fofanah is discharged from the hospital as an Ebola survivor.


Data sharing and cross study support and funding.
Will we get an answer?

- Current studies are limited both in terms of practical limitations as well as study design:
  - Adequate power?
    - Presumes Kikwit levels of protection
  - Adequate controls?
    - Non-randomized
    - Historical matching
  - Adequate dosing?
    - Units needed?
      - patient titers of Ebola IgG of 1:2000 versus Rhesus hyperimmune macaque studies of 1:1,000,000?
Liberia

- Population of 4.3 million
- Human Development Index: 175 of 187
- Civil War (1989-2003) destroyed the little infrastructure that existed
- UMass Med School and Academic Consortium
  - Helping Rebuild undergraduate and graduate medical education
- Still severely resource constrained
  - Lack of efficient supply chains
  - Minimal laboratory and transfusion support
  - 51 physicians practicing
  - 22 registered technologists
• Consortium of UMass, Boston Children's, MIT, and other previous partners.
  – Concern for our friends & colleagues as healthcare workers lacking access to protective health equipment
    • *Health care workers disproportionately affected*
    • *The capital city of Monrovia with a population of 1.5 million people had NO open hospital for the entire month of September*
  – Work to support Ebola relief and reopen normal health care where we had worked before
Comprehensive Infection Prevention and Control at all 24 government hospitals in partnership with CDC, WHO: MOH “Keep Safe, Keep Serving”
Partners
MIT Humanitarian Logistics Lab
Avenir Analytics

Support: Airlink, UNMEER
Ebola Diagnostics
Jackson F Doe
Hospital

WELCOMES YOU TO TAPPITA

OUR THEMATIC AREAS:
- Educational Support to Adolescent Girls
- Access to Justice
- Adult Literacy
- Economic Empowerment:
  - Skills Training
  - Agriculture

MOTTO: "TOGETHER WE CAN MAKE A DIFFERENCE"

THOMAS HILL, TAPPITA, NIMBA COUNTY, LIBERIA
Cell: +231886611979, +231777511979 Email: advanga2015@gmail.com
Ebola Diagnostics
(maintaining vigilance)

Testing ~8 samples per day since Feb 28
Using 2 BioFire FilmArrays

Collaboration with CDC and Liberian MOH
Transfusion Support

- Build long-term capacity for convalescent plasma
- Provide equipment for the production of blood components (plasma, red blood cells and platelets) and infectious disease testing.
- Provide support and training by stationing experienced blood bank technologists from US academic institutions within the Regional Blood Donations
- Support blood safety training within hospitals for both collection of whole blood and transfusion of whole blood and blood products.
- National Donor facilities restarting after diversion of staff and infrastructure
Montserrado Regional Blood Center #1

- Approximately 700 whole blood units collected per year, prior to Ebola crisis.
- Majority of units are collected from community outreach drives – schools, organizations, government offices.
- Working to relocate and start component manufacture.
Regional Blood Center #2 in Phebe

- Approximately 200 whole blood units collected per year, prior to Ebola crisis.
- Currently non-operational.
- Moving to component production.
Grifols Plasma Donor Center

- Four bed plasmapheresis center to collect convalescent plasma for transfusion
  - Initial goal for treatment and support of trials
- Potential for manufacturing to immunoglobulin
- Partnership with Liberia – plasma and any plasma products would be Liberian products
- Long-term potential for research into other regional products such as convalescent plasma / Ig for Lassa Fever
Conclusions

● Maintaining Momentum
  – Defining efficacy of convalescent plasma
  – Rebuilding and improving health care in West Africa
● Providing for sustainability
● Foster research capacity
● Providing surveillance to avoid future outbreaks of Ebola or any other deadly communicable disease.
Acknowledgements

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• Liberian health care workers and MOH
• Liberian people