Care of Patients with Emerging Infectious Diseases

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NETEC
Conflict of Interest

- Research Support through institution
  - Astellas
Federal Select Agents - 1\textsuperscript{st} Tier

- Botulinum toxin
- Ebola virus
- Marburg virus
- \textit{Francisella tularensis}
- Variola major
- Variola minor
- \textit{Yersinia pestis}

- \textit{Bacillus anthracis}
- \textit{Burkholderia mallei}
- \textit{Burkholderia pseudomallei}
- Several toxins
Other Select Agents

- *Coxiella burnetii*
- Eastern Equine Encephalitis
- Crimean-Congo HF
- Lassa fever virus
- Monkey Pox
- *Rickettsia prowazekii*
- SARS-CoV
- S. American HF
  - Junin
  - Machupó
  - Guanarito
  - Sabia
- Tick-borne encephalitis
- Kyasanur Forest disease
- *Yersinia pestis*
Recently Emerged Viruses

- Chikungunya
- Zika
- MERS-CoV
The Unit at Emory
SCDU Team

- Nineteen Emory Healthcare critical care nurses
- Five Infectious Diseases physicians
- Emory Biosafety Office
- Laboratory personnel
- Materials Management
- Designated Environmental Services personnel
- Occupational Health
- Spiritual Health
Assumptions

- Only direct care providers in the patient room
- No person enters room without mandatory training and demonstrated competency
- Autonomous practice (supported by experts)
  - Ventilator management
  - Continuous renal replacement therapy (CRRT)
  - Physical and occupational therapy
  - Environmental decontamination
Culture of Safety

- Shared accountability for safety
- Effective and assertive communication is central to the safety of the team
- Communication is so important, the team uses rules to govern
  - Direct patient care communication
  - Daily team huddles
Daily Family Huddles

- Held everyday at 0715 when a patient was in the SCDU
- Agenda items included:
  - Clinical update
  - Unit updates
  - Schedule updates
  - Family Rules
Family Rules

- Follow all standard operating procedures to the best of our ability
- Ensure that others follow the standard operating procedures.
- Report all accidents and near misses.
- Report any symptoms which match the pathogen.
- Report any new medical conditions.
Daily Schedules

• It was important to have a schedule in order to maintain a safe, structured environment.
• Staff reported to the unit 15-30 minutes prior to scheduled shift, depending on level of PPE required.
• Discussion of daily schedule took place during the family huddle.
Standard Operating Procedures in the Serious Communicable Disease Unit

- Provide consistency in how procedures are performed in the unit
- Allows staff to identify possible deviations when performing the procedure
- Gave staff confidence knowing they were performing procedures consistently
SCDU SOPs

• The care team train and validate competency in the following areas:
  • Donning and doffing of PPE
  • Utilization of the “Buddy System”
  • Waste management protocols
  • Decontamination and containment protocols
  • Specimen handling for diagnostic testing
Standard Operating Procedures

- Donning—patient room and anteroom
- Doffing—patient room and anteroom
- Toileting—ambulatory and non-ambulatory patient
- Waste management
- Spill clean up
- Needle stick/exposure
- Creating chemical mats
- Obtaining and handling lab specimens
- X-ray process
- Transferring equipment between patient rooms
- Cleaning durable medical equipment
The Critical Role of Nursing

• The ability to provide high-level nursing care and supportive care made a significant impact
• 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
Patient Evaluation
Physical Examination

• Palpation
  • Slightly diminished by extra gloves

• Inspection
  • Can be diminished by face shield or goggles
    • Especially if eye protection becomes foggy
    • Plastic can occasionally distort vision

• Auscultation
  • No skin exposed means layer of Tyvek or Tychem between stethoscope and ear drum
Clinical Signs and Symptoms
Clinical Characteristics of EVD

- Acute infection starts as a non-specific febrile illness
- Fever, severe headache, muscle pain, malaise
- Progression to include GI symptoms
- diarhhea and vomiting
- May appear 2-21 days after exposure
- 8-10 days most common

Courtesy of Pierre Rollin, CDC
Signs and Symptoms on Presentation

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>% Patients</th>
<th>IDSA 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>*Asthenia</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Headache</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>*Anorexia</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Chest pain</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Cough</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Arthralgia/Myalgia</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>*Sore throat</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>*Right upper quadrant tenderness</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Back pain</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>*Conjunctival injection</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rales/rhonchi</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bloody stool</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>*Rash</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>*Gum bleeding</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>*Bleeding-injection sites</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hiccups</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anuria</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemothysis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Convulsion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Ebola
- Non-Ebola

N = 906
<table>
<thead>
<tr>
<th>Clinical Symptoms and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Myalgias</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Decreased urine</td>
</tr>
<tr>
<td>MOF/Death</td>
</tr>
</tbody>
</table>
Clinical Care = Supportive Care

• No proven therapeutics
• Unclear availability of any experimental agents
• Limited safety or efficacy data in humans
• BUT, we received SIGNIFICANT support and advice from CDC, FDA, and medical and scientific colleagues throughout the world
Medical Management
• Supportive Care
  • Fluid management
  • Electrolyte replacement
  • Life support
Designated Consulting Physicians

- Critical Care
- Anesthesiology
  - Airway management
- Nephrology
- Pathology
- Others
Fluid Balance

Intake and Output (mL)

- Intake and output data for the period from 8/4/2014 to 8/18/2014.
- Graph shows daily intake and output with specific markers for medications, continuous infusion, platelets, oral intake, output, stool volume, and urine voided.
- Note the daily net balance, showing positive and negative values.
Fluid Balance

Intake and Output (mL)

- Daily Net
- Medications
- Continuous Infusion
- Oral/Tube Medications
- Oral Intake
- Urine Voided mL
- Stool Volume

* Partial Day
The Impact of Electrolytes

- Our patients had MARKED electrolyte abnormalities and nutritional deficiencies
  - Hypokalemia, hypocalcemia and hyponatremia
  - Required 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
Monitoring Virologic Status

• With the help of the CDC, we monitored ebola in blood
  • Progressive declines in viral loads that correlated with improvements in clinical condition
  • Had very low level of nucleic acid detection for several days despite resolution of symptoms
A graph showing antibody titer (1:x) over the course of illness. The x-axis represents the day of illness, ranging from 12 to 28. The y-axis represents the antibody titer, with values ranging from 0 to 7200. The graph includes bars for IgM, IgG, NP IgG, and PCR CT, and a line graph for the antibody titer. The graph also shows temperature (C) and diarrhea over the course of the illness.
# Experimental Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Convalescent plasma</strong></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><strong>Hyperimmune globulin from immunized animals or</strong></td>
<td>Concentrated plasma to provide high titers of neutralizing antibody</td>
<td>• Not currently available.</td>
</tr>
<tr>
<td><strong>previously infected humans</strong></td>
<td></td>
<td>• Work in horses and cattle are underway</td>
</tr>
<tr>
<td><strong>ZMapp (Mapp Biopharmaceutical Inc.)</strong></td>
<td>Cocktail of three chimeric mouse human monoclonal antibodies targeting the</td>
<td>• Very promising data in macaques</td>
</tr>
<tr>
<td></td>
<td>GP envelope protein</td>
<td>• No human trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Very limited supply</td>
</tr>
<tr>
<td><strong>TKM-100802 Lipid (TKM-Ebola; Tekmira)</strong></td>
<td>Nanoparticle Small interfering Ribonucleic acid (siRNA) Targets two</td>
<td>• single-dose phase 1 study in healthy volunteers found side effects</td>
</tr>
<tr>
<td></td>
<td>essential viral genes to stop the virus from replicating</td>
<td>including headache, dizziness, chest tightness and raised heart rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>at high doses.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A limited number of treatment courses</td>
</tr>
<tr>
<td>Therapy</td>
<td>Mechanism</td>
<td>Status</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</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 (Toyama Chemical/ Fuji Film) | 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 available |
| BCX4430 (Biocryst)            |                                                                             | • 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) (Chimerix) | 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 |
## Experimental Therapies

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<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chimpanzee adenovirus serotype 3 (ChAd3) vaccine</td>
<td>Uses a chimpanzee adenovirus that does not grow</td>
<td>• 16/16 monkeys were protected from a lethal dose by a single dose of the vaccine</td>
</tr>
<tr>
<td></td>
<td>Contains the gene for EVD surface protein</td>
<td>• Trials in humans ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Approximately 15 000 doses might be available by the end of 2014</td>
</tr>
<tr>
<td>Recombinant Vesicular Stomatitis Virus (rVSV) vaccine</td>
<td>Recombinant VSV vector expressing ebola GP protein to induce EBOV-specific immune responses</td>
<td>• 20/ 20 monkeys protected from a lethal dose of EVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Animals with weakened immunity were not harmed by rVSV-EVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Unknown if rVSV-EVD will grow in humans, which would affect immunogenicity and safety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Phase 1 trials underway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ~800 doses available</td>
</tr>
</tbody>
</table>
Conclusions from our experience

• Patients with Ebola can be safely cared for in our healthcare system

• We do expect a lower mortality rate than in under-developed healthcare systems

• Much can be learned about patient management that can be fed back to facilities with lesser levels of infrastructure

• Communication is critical

• Comprehensive, multidisciplinary patient- and family-centered models of care can be delivered even in extreme circumstances
Other agents
Chemoprophylaxis and Vaccination Post Exposure

- Friedlander et al. JID 1993;176:1239-43
- Following exposure to a lethal inhaled dose of *B. anthracis*, 10 rhesus monkeys in each of 6 groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Survival after 1st challenge</th>
<th>Survival after rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>7/10</td>
<td>0/7</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>8/9</td>
<td>0/8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>9/10</td>
<td>0/9</td>
</tr>
<tr>
<td>Doxycycline+vaccine(2)</td>
<td>9/9</td>
<td>8/9</td>
</tr>
<tr>
<td>Vaccine(2)</td>
<td>2/10</td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>1/10</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Options

- **Penicillin**
  - resistance occurs naturally

- **Doxycycline**
  - resistance has been engineered

- **Ciprofloxacin**
  - Other fluoroquinolones likely active
  - May be combined with rifampin, vancomycin, imipenem, chloramphenicol, penicillin and ampicillin, clindamycin, or clarithromycin in severe disease

- **Experimental treatment: anthrax IG**
Botulism: Treatment/Prophylaxis

- Ventilatory assistance and supportive care
- Botulinum antitoxin
  - Trivalent equine product against types A, B, and E available from CDC
  - Most effective if given early
- Antibiotics for wound botulism
  - Penicillin
- Vaccine investigational
- Infection Control - human-to-human transmission does not occur
Plague: Medical Management

- Antibiotic therapy
  - Gentamicin or Streptomycin
  - Tetracyclines
  - Sulfonamides
  - Chloramphenicol (meningitis/pleuritis)
Unknown or Emerging Pathogens

- Most likely to be viral
  - Probably won’t have an effective vaccine for years,
    - If ever (HIV)
  - May have effective antivirals
    - Pre-existing antivirals but testing will need to be done
    - Lamivudine for EVD

- Probably won’t create zombies
Thank you

Questions?