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EBOLA HEMORRHAGIC FEVER-RECENT OUTBREAK

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ABSTRACT

ABSTRACT: Ebola Hemorrhagic Fever (EHF) is a deadly infection which has no cure till today. Treating the symptoms and supportive care are the main stay in the management of the disease. There are some treatments and vaccines in initial stage of development but, they are never tested on humans. BACKGROUND:According to New York Times recent outbreak of Ebola Hemorrhagic fever (EHF) or Ebola virus disease (EVD) traced back to two year boy in a small village of Guinea. The child died on December 6th and one week later his mother, grandmother and 3 year old sister died. Since then disease has spread to Nigeria, Liberia, Sierra Leone and Guinea. More than 1000 people have died so far.

Ebola Burden in West Africa

Country	Suspected cases	Deaths
Nigeria	4	1
Liberia	468	255
Sierra Leone	646	273
Guinea	485	358

Source: World Health Organization

HISTORY

Ebola virus first appeared in 1972 in Congo and Sudan. It named "Ebola" after the river which runs near the village of Congo, where it was first appeared. Since then there are several outbreak has been reported.

CLASSIFICATION:

Ebola virus is a single stranded, negative sense RNA virus and belongs to a family Filoviridae. It has five subspecies.

1 Bundibugyo (BDBV)

2 Zaire (EBOV)

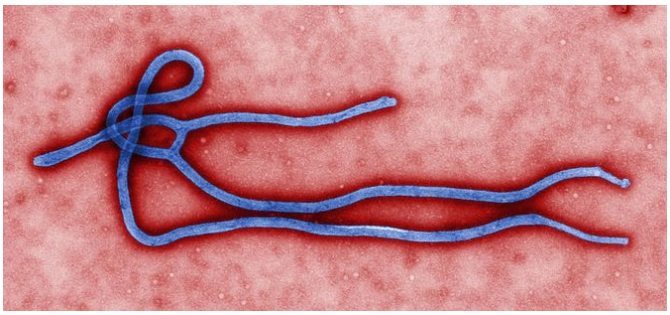
3 Reston (RESTV)

4 Sudan (SUDV)

5 Taï Forest (TAFV)

BDBV, EBOV and SUDV are associated with outbreak in Africa. RESTV and TAFV are not associated any breakout so far (2). Recent outbreak in West Africa is associated with a strain closely related to Zaire, which is the most virulent subspecies.

Ebola virus is a zoonotic virus which infects primates like chimpanzee, monkeys, gorillas, and humans. Fruit eating bat is the natural reservoir host (CDC).



A colorized transmission electron micrograph of the Ebola virus virion, created by CDC microbiologist Cynthia Goldsmith. Credit: CDC Public Health Image Library

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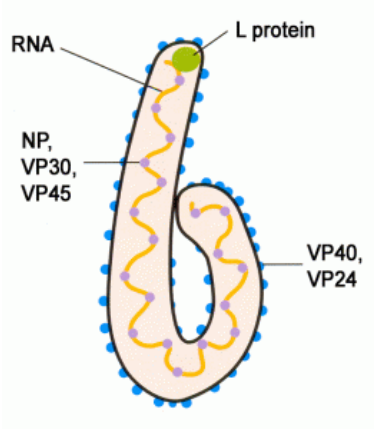
VIRALOGY



Source: BlogSpot. Ebola Virus

Ebola virus is generally 80nm in diameter and 800nm long. It carries genome which carries a code for 7 structural and one none-structural protein. 3′ – leader – NP – VP35 – VP40 – GP/sGP – VP30 – VP24 – L – trailer – 5 (4).

TRANSMISSION:

Ebola virus can be transmitted from animal to human and human to human. The major route of transmissions is through direct contact, broken skin, mucus membrane, body fluid and blood. So far no airborne infection is reported. It has also been noted that men who recovers from the disease can still transmit the disease through their semen for up to 7 weeks (2).

Signs and Symptoms:

Initial signs and symptoms of EHF or EVD are very nonspecific. They resemble to acute viral illness and can easily be misdiagnosed. It starts with sudden onset of fever, myalgia, chill, anorexia, and weakness in 2-21 days after exposure. In about 5-7 days patient may develop diffuse erythematous macupapular rash on face, neck, trunk or in arms. May have abdominal pain, watery diarrhea, vomiting, conjunctival injection, and hiccups. As the disease progress patient may develop signs of internal bleeding, multi-organ failure, and septic shock and typically die in 6-16 days after the infection.

Diagnosis:

If a patient is presented with initial symptoms and there is a strong reason to believe that patient is infected with Ebola virus then He/she should be isolated immediately and public health authorities should be notified. Following laboratory test can be performed to confirm the diagnosis.

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Timeline of Infection	Diagnostic tests available
+Within a few days after symptoms	Antigen-capture enzyme-linked immunosorbent assay (ELISA) IgM ELISA
Later in disease course or after recovery	Polymerase chain reaction (PCR) Virus isolation
Retrospectively in deceased patients	IgM and IgG antibodies Immunohistochemistry testing PCR Virus isolation

Adapted: CDC

Table: Chronology of previous Ebola virus disease outbreaks

Year	Country	Ebola virus species	Cases	Deaths	Case fatality
2012	Democratic Republic of Congo	Bundibugyo	57	29	51%
2012	Uganda	Sudan	7	4	57%
2012	Uganda	Sudan	24	17	71%
2011	Uganda	Sudan	1	1	100%
2008	Democratic Republic of Congo	Zaire	32	14	44%
2007	Uganda	Bundibugyo	149	37	25%
2007	Democratic Republic of Congo	Zaire	264	187	71%
2005	Congo	Zaire	12	10	83%
2004	Sudan	Sudan	17	7	41%
2003 (Nov-Dec)	Congo	Zaire	35	29	83%
2003 (Jan-Apr)	Congo	Zaire	143	128	90%
2001-2002	Congo	Zaire	59	44	75%
2001-2002	Gabon	Zaire	65	53	82%
2000	Uganda	Sudan	425	224	53%
1996	South Africa (ex-Gabon)	Zaire	1	1	100%
1996 (Jul-Dec)	Gabon	Zaire	60	45	75%
1996 (Jan-Apr)	Gabon	Zaire	31	21	68%
1995	Democratic Republic of Congo	Zaire	315	254	81%
1994	Cote d'Ivoire	Taï Forest	1	0	0%
	EBOLA HEMORRHAGIC FEVER-RECENT OUTBREAK				
1994	Gabon	Zaire	52	31	60%
1979	Sudan	Sudan	34	22	65%
1977	Democratic Republic of Congo	Zaire	1	1	100%
1976	Sudan	Sudan	284	151	53%
1976	Democratic Republic of Congo	Zaire	318	280	88%

Adapted: WHO Facts Sheet*103. Update April 2014

Treatments:

There is no effective treatment for EHF or EVD. Treating the symptoms and supportive care with balancing fluid and electrolyte, maintaining oxygen and blood pressure and treating any co infections if they appear, are the main stay for the management of the disease.

There are some treatments under investigation but, they have never been tested in humans, so it is very difficult to say how effective they are.

ZMAPP:

It is a cocktail of three human monoclonal antibodies (mAb) (2 from ZMab and 1 from MB-003) (4). These mAb attach to virus glycoprotein and prevent the virus to attach itself with normal human cell. Also, tagging the virus with these mAb help the immune system to recognize and destroy them.

Development Process:

Mouse was injected with Ebola virus glycoprotein (GP). The mouse produced antibodies against virus GP. These antibodies producing B-cell were isolated and fused with cancer cell to produce single line of cell, and then mouse component was replaced with human component and transfected in tobacco plants. Antibodies extracted and purified (2, 6).

Does it really work?

It is not known that it really works in human. No clinical trial on human has been done. Limited trial of MB-003 done on monkeys and approximately there were 43% survival rate (7). In a preclinical trial published in Science Translational Medicine on June 13, 2012, shows that four macaques who were treated with this cocktail survived. Then a study published in the same journal on Oct 16, 2013, with new formulation of ZMapp, was injected to eight monkeys after 72 hours of infection and 7 out of 8 monkeys survived (9). This cocktail was also given to two Americans health workers, who are recovering and a Spanish priest named Miguel Pajares, who has just passed away. It is very difficult to tell that two Americans who are recovering, because of the effect of the drug or they are among those 40% people who do recover of their own after infection.

AVI-7537:

It is in Phase 1 trial and is a Phosphorodiamidate morpholine oligomer (PMO plus) which binds to viral VP24. VP24 protein is involved in inhibiting type 1 interferon response. Thus inhibition of VP24 results in more efficient host immune response. It is postulated that VP24 binds to VP35 and NP and play a role in switching from viral replication to viral transcription, which is crucial for viral life cycle. (3). Manufacturer is Sarepta Therapeutics. According to company site, in a preclinical trials on non-primate animals it shows 80% survival rate when they are exposed to Ebola virus and treated with AVI-7537.

TKM-Ebola:

It is also in Phase 1 trial and is manufactured by Takmira bio pharmaceuticals. It is RNA interfering (siRNA) drugs, it target 3 out of 7 genes that produce structural proteins that are necessary for viral survival. In preclinical trials by Geisbert, 2 of 3 rhesus monkeys survived when given post exposure dose of TKM-Ebola, while all macaques survived from ZEBOV challenge with treatment (8, 9). TKM-Ebola program's pre-clinical cohort study demonstrated 83% survival rate when treated 24 to 48 hours post exposure and 67% survival rate when treatment started 72 hours later after the exposure, as compared to 0% survival rate in placebo group.

BXC 4430:

BXC 4430 is structurally similar to adenosine. Its mechanism of action is that it is taken up by viral RNA polymers and halts the RNA replication. In vitro studies it showed promising results against Ebola Virus. It is in phase 1 trial and Biocrst Pharma is the manufacturer.

Favipravir:

Late stage of development for the treatment of influenza virus. It has shown activity against Ebola virus and it has decrease the severity and mortality in Ebola virus infected mouse. In a study, Favipravir (T-705) which is a pyrazinecarbomaxide derivative showed suppressive activity against Ebola virus in vitro and vivo. The drug was injected to mice 6 days after post exposure, and results were very promising, 100% of the animals survived (10). It inhibits viral RNA polymerase, which is RNA dependent, and it has no effects on mammalian cell.

Ebola Vaccine:

There are about 4-5 companies who are working to develop vaccine and according to the recent news first vaccine would be in the market as early as next year. Vaccine called VSV-EBOV by National Microbiology laboratory and licensed by Ames has also shown effectiveness in animal models after they exposed to virus. The exact mechanism is not known. GlaxoSmithKline is developing a vaccine which deliver attenuated form of Ebola genes into the body to stimulate immune systems, it protect from future infection.

SUMMARY:

There are several treatments and vaccines are under initial stage of development or in trials. If everything goes all right we will see big changes in the management of EVD or EVHF within couple of years. FDA has given fast track status to most of these drugs and we are hoping to see some results soon.

Ebola virus first appears in1972, since then there is no treatment or vaccine has developed. The reason is social and economical. The disease affecting few thousand peoples in the poorest region of the world. Pharmaceutical companies have no economical gain for spending millions of dollars for research and have no return. The only research that has been done, are by the companies who are given grants from US or Canadian governments as a research on bio-terrorism. Hopefully, recent outbreak of EVD bring some breakthrough in the treatment of EVD, otherwise, we are looking pandemic which would be hard to control.

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