23

Rift Valley Fever

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INTRODUCTION

Rift Valley Fever (RVF) is an acute viral infection which is spread by arthropods mainly mosquitoes. The disease is of zoonotic importance as it can spread in domestic animals as well as in humans (Sissoko et al. 2009). The RVF virus can also spread through the direct contact with the infected organisms, but it is very rare that this virus spread directly from humans to humans (Seufi and Galal 2010). It can spread through exposure from tissues of infected animals, body fluids and viremic blood or by biting of the mosquitoes (Hassan et al. 2011). Signs and symptoms include fever, muscle aches, headaches, loss of vision, liver problems and encephalitis and may also cause abortions in females. People who work with butchers, deals with the raw meat having rift valley fever or infection have a greater chance to get the infection and the people who sleep outdoor or spend the night-time outside their homes are more exposed to the mosquitoes which may be infected with RVF virus, so more chance to cause infection. Lab workers, farmers, herdsmen, abattoir workers and veterinarians are also at risk (Hassan et al. 2011, Seufi and Galal 2010). It is considered among the transboundary animal diseases (Sindato et al. 2011). Initially, it was only present in Africa, but now it has spread to most of the world (Bell et al. 2018, Himeidan et al. 2014).

History and Background

RVFV was first observed in rift valley in Kenya in 1930 from sheep and then spread to other regions of the world through animal movement from one place to another place (Bashir and Hassan 2019, Hassan et al. 2011) like African countries, Republic of Comoros, Arabian Peninsula, Madagascar, Saudi Arabia, Yemen, Egypt (Sissoko et al. 2009). In the rift valley numerous newborn deaths of lambs and abortion in pregnant sheep was happened in 1930. High mortalities of sheep on the farm occurred that led to its investigation. Blood from the ill lamb was taken and to check for bacterial or viral infection, it passed through a porcelain filter and was then inoculated in the healthy lamb, the same clinical signs and symptoms were observed. Investigators came to the point that outbreak occurred during high mosquito activity, so to confirm this, they isolated the healthy sheep at high altitude under mosquito nets. This approach confirmed the mosquito involvement in the disease transmission that was later confirmed by the isolation of RVFV from different species of mosquitoes involving *Aedes* and *Culex* (Wright et al. 2019).

Importance

Host Spectrum

The susceptibility of host depends upon age and species (Sindato et al. 2011). The major amplifying hosts of RVFV include cattle, sheep, and goat, although it causes disease in many other species, including buffaloes, camels, and many mammals (Borrego et al. 2016). Humans are dead-end RVFV hosts (Borrego et al. 2016, Bird et al. 2009).

Epidemiology

The severe epidemics occurred due to climatic conditions including huge greenery and floods (Kwaśnik et al. 2021). Frequently, epidemics have occurred in Africa and other countries. Major epizootics of RVFV occurred in many countries, including Africa and Asia (Kimani et al. 2016; Métras et al. 2011).

Mortalities

RVF-infected patients have a greater risk of mortality in case of hemorrhagic fever, jaundice and neurologic disease (Atkins and Freiberg 2017). Naive communities are at greater risk of inducing large mortalities and morbidities (Grossi-Soyster and Labeaud 2020).

Status of Virulence

The major factors of virulence are viral NSs proteins that suppress the innate immune status of the host (Boshra et al. 2011).

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No	Region	Epidemic year	Disease burden	References
1:	Kenya and south Africa	1950-1951	100000 sheep died and abortions up to half million	(Wright et al. 2019)
2:	Horn of Africa	1961-1962		(Martin et al. 2008)
3:	Horn of Africa	1982-1983		(Martin et al. 2008)
4:	Horn of Africa	1989		(Martin et al. 2008)
5:	Horn of Africa	1997-1998		(Martin et al. 2008)
6:	Horn of Africa	2006-2007		(Martin et al. 2008)
7:	Sudan	1973		(Martin et al. 2008)
8:	South Africa	1974-1975	110 human cases and 7 deaths	(Martin et al. 2008)
9:	Egypt	1977-1979	200000 human cases and 598 deaths	(Wright et al. 2019)
10:	Mauritania	1987	Considerable human cases and 220 deaths	(Wright et al. 2019)
11:	West Africa	1987-1988		(Martin et al. 2008)
12:	Egypt	1993		(Martin et al. 2008)
13:	East Africa	1997-1998	89000 human cases and 478 deaths	(Martin et al. 2008, Wright et al. 2019)
	Saudi Arabia	2000	880 human cases and 123 deaths	(Wright et al. 2019)
14:	Kenya	2006-2007	US$66M losses, 684 cases and 155 deaths	(Martin et al. 2008)
15:	Somalia	2006-2007	US$471M losses	(Labeaud et al. 2010)
16:	Tanzania	2007	50000 mortalities in livestock	(Labeaud et al. 2010)
17:	Sudan	2007-2008	747 human cases and 230 deaths	(Labeaud et al. 2010, Baba et al. 2016)
18:	Mayotte	2007-2008		(Labeaud et al. 2010)
19:	Madagascar	2008		(Labeaud et al. 2010)
20:	Swaziland	2008		(Labeaud et al. 2010)
21:	South Africa	2008,2009,2010		(Labeaud et al. 2010)

Economic Effect

RVF poses severe economic effects and food insecurity (Bashir and Hassan 2019). It is a potential bioterrorism weapon. Due to deaths in livestock, losses in revenue generated. Quarantine procedures and disease burden on the animal cause less production of animal products. Moreover, continuous abortions in pregnant animals, result in the loss of progeny that induces financial burden (Grossi-Soyster and Labeaud 2020). It ~~is~~ greatly affects the agro industries and the worldwide trade (Muga et al. 2015; Peyre 2015).

Zoonosis

Most of the emerging infectious illnesses cause zoonosis. There is an increasingly high zoonosis in endemic areas (Seetah et al. 2020). It is declared as one of the threats by the US center for disease control, to the livestock industry (Seetah et al. 2020). Slaughterhouse workers, farmers, herders and veterinarians are at greater risk of acquiring infection (Paweska 2014).

Etiology

Whole Family

The etiological agent of rift valley fever is a virus named as RVFV or arbovirus, family; *bunyaviridae*, genus; *phlebovirus* (Flick and Bouloy 2005). RVFV is a single-stranded negative-sense, tripartite RNA virus. It can survive in both biotic and abiotic environment (Meegan and Bailey 2019).

Topographic Spread (genus, species)

The vectors of the RVFV are the mosquito species belonging to the genus *Culex*, *Aedes* and *Manzoni* (Atkins and Freiberg 2017).

Life Cycle

Basically, the genome of RVFV consists of three segments. These three segments are termed as S, M and L segments and these segments are RNA segments. Among the three, L and M have negative polarity (Paweska 2014). These three segments encode different genes. S segment encodes genes; N, NSs, M; Gn, Gc and NSm genes and the last segment L, encodes RNA polymerase L gene. The pH dependent RVFV virions bind primarily through endocytic pathway to cellular receptors. After entry into the cell, uncoating takes place and ribonucleocapsid principally comprised of genomic RNA segments and proteins, is released in cytoplasm. Within 40 minutes after viral infection, viral m RNA synthesis takes place by viral polymerase through transcription (Ikegami et al. 2009). After transcription, replication of viral RNA takes place within 1 to 2 hours then viral RNP and RNA segments packaging starts. Finally, RNP packaging leads to viral virions formation. The surface of RVFV virions is symmetrical icosahedral lattice. Nucleoproteins have no pathogenic significance (Boshra et al. 2011).

Animals

Pantropic hemorrhage and hepatic necrosis cause high mortalities in young animals and abortion in pregnant animals (Martin et al. 2008).

Sheep

The incubation period ranges between 24-36 hours including listlessness, bloody diarrhea and loss of appetite. Postmortem findings reveal mild splenomegaly and liver necrosis of multifocal nature (Faburay et al. 2016). In acute cases sheep have 100% mortality rate.

Goat

The pathogenesis of the disease is less severe in lambs of the same age. It does not result in febrile illness. In disease condition, necrotic hepatitis is followed by necrotic lesions that is focal in nature in adults (Wright et al. 2019).

Cattle

These are less susceptible as compared to goats and sheep. These develop an acute disease with a 0-5% mortality rate, but calves have 10% mortality rate. Viraemia and liver pathology can be seen (Wilson et al. 2016)

Camel

Camels are less susceptible than others; this includes foot lesions, hemorrhages, and abortions during epidemics (El Mamy et al. 2011).

Monkey

African green monkeys acquire the neurological disease that is similar to humans (Wonderlich et al. 2018).

Humans

Commonly RVFV cause hepatitis, hemorrhagic complications, and encephalitis (Martin et al. 2008).

Pathological Findings

Hepatitis/hemorrhagic Disease

Liver is the organ which effects severely and bear burden of RVFV in almost all species. Hemorrhagic disease and jaundice develop because of enlargement of the liver, which is the major site of replication of RVFV. The level of liver enzymes, including alanine transaminase and aspartate transaminase, increases (McElroy and Nichol 2012). Platelet count and hemoglobin level decrease, that ultimately increase clotting time. Thrombosis, scleral icterus and delirium may also be present. There is a high fatality rate among hemorrhagic fever patients (Ikegami and Makino 2011).

Ocular Disease

In 2 to 5% of patients, ocular manifestations are observed, that develop within 3 weeks after the start of the symptoms (Al-Hazmi et al. 2005). It causes uveitis, retinal hemorrhage, retinitis, and blind spots (McMillen and Hartman 2018).

Neurologic Disease

It includes encephalitis, hemiparesis, excessive salivation, vertigo, weakness, decerebrate posturing and pleocytosis (Ikegami and Makino 2011).

Abortions/Miscarriage

In 2006, there was a significant increase in abortion frequency, but more in animals than humans (Baudin et al. 2016).

Clinical Sign and Symptoms

Humans

In humans, diverse symptoms scale from headaches and photophobia to encephalitis and retinitis (Boshra et al. 2011; Flick and Bouloy 2005). The symptoms vary according to the severity to disease; likewise, the flu may be accompanied by nausea, headache, arthralgia, joint aching and myalgia. Moreover, diarrhea, fever, oliguria or anuria can also be seen. Some patients may have the symptoms like vomiting, loss of appetite, light sensitivity and stiffness of neck. Hemorrhagic or encephalitic disease conditions account for less than 1%. Meningoencephalitis state in humans develop within 1 to 4 weeks after the onset of the disease, its clinical features include memory loss, headache, confusions, hallucinations, vertigo, disorientation, lethargy, convulsions, and coma. After 2 to 4 days of the illness, hemorrhagic sign and symptoms appear that is evidenced by the bleeding from gums or nose, or from GIT, ecchymosis, petechiae, venipuncture sites, purpura, or menorrhagia. In this case, the fatality rate is up to 50%. Usually, death happens after 3 to 6 days of the symptoms. Further, in some patients, ocular lesions cause a severe form of disease. In this case, scotomas and central vision loss were observed, which lead to blindness in one or both eyes (Paweska 2014).

Animals

Severe clinical signs and symptoms are present in sheep, which include fever, abdominal pain, and disinclination to move (Martin et al. 2008). Goats develop less severe signs and symptoms than sheep. In cattle, the adults are mostly asymptomatic, although fever-like symptoms may be present. The signs and symptoms appear in camels include hemorrhages, ocular discharge, and foot lesions (Martin et al. 2008).

Treatment in Practice

Currently, we provide supportive care to cure RVF (Atkins and Freiberg 2017). For chemotherapy, kinase inhibitors alone or in combination can be used (Bell et al. 2018).

Vaccines

Treatment by vaccines started soon after the isolation of RVFV in 1931 (Bird et al. 2008). No vaccine schedule is present for humans and animals in non-endemic regions (Borrego and Brun 2021). Smithburn vaccine is commonly used in Africa, and it was established by Smithburn in 1949 and cause immunity for lifetime in vaccinated animals (Sindato et al. 2011). The soldiers of the United Nations who are staying in infected countries were administered by a vaccine that is formalin-inactivated mosquito-derived (Lancelot et al. 2019). MP-12 is conditionally approved by the FDA for administration in the USA (Lancelot et al. 2019); it was developed by the Egyptian virulent strain ZH548 but still has teratogenic effects in sheep (Boshra et al. 2011). Several inoculations are required in the case of DNA vaccines, as they are less immunogenic (Lancelot et al. 2019). Clone 13 does not cause abortion in ewes (Boshra et al. 2011). A human infected with 74HB59 is the source of collection of clone 13 vaccine (Wright et al. 2019).

Antiviral Therapeutics

Ribavirin is used against ZH501 strain, inhibit replication of virus (Atkins and Freiberg 2017). It enhances survival rate up to 100% at dose rate 18.8 mg/kg, subcutaneously. Ribavirin at the dose rate of 75 mg/kg can treat the peracute state of RVF disease in animals (Kimani et al. 2016). Favipiravir/ T-705/Avigan is a broad-spectrum antiviral agent. Its efficiency has been evaluated in hamsters against RVFV ZH501 strain. It is effective against different genera of bunyaviruses (Scharton et al. 2014). In mouse model, rapamycin, an FDA-approved drug, is used to control the pathogenesis of RVFV by decreasing N protein production (Bell et al. 2018).

Type 1 interferon α/β holds the key significance in treating RVFV as have great antiviral potential (Borrego et al. 2016). Argovit is a silver nanoparticle with 35 nm size approximately, is the commercial preparation used to treat RVFV in humans and animals (Borrego et al. 2016). Eryl methylidene, a Rhodanine derivative, is an effective drug against the rift valley fever virus as it has broad-spectrum activity and inhibits virus cell merging (Labeaud et al. 2010, Wolf et al. 2010). Bavituximab is another broad-spectrum antiviral agent; it shows its antiviral activity by targeting phosphatidylserine, which is visible on the plasma membranes of the infected cell and also of enveloped viruses (Labeaud et al. 2010, Soares et al. 2008). Other antiviral therapeutics include suramin, sorafanib and bortezomib etc. (Atkins and Freiberg 2017).

Insecticide Treatment

At mosquito breeding sites, larvicide treatment is useful; some of the common larvicides include Bacillus thuringiensis israeliensis and pyroxyprofene or methoprene (Lancelot et al. 2019). In the live bait trap technique, cattle are treated with remnant insecticide, which kills mosquitoes during feeding and stops transmission of RVFV (Lancelot et al. 2019, Poché et al. 2015).

Treatment Being Searched

Several vaccines against rift valley fever virus are in clinical trials (Grossi-Soyster and Labeaud 2020). ChAdOx1 is a human vaccine that is under processing (Stylianou et al. 2015). To fight with the RVFV, the kinases are being studied in translational pathway (Bell et al. 2018). For effective medication, we are searching for host-based therapeutics (Bell et al. 2018).

Control Measures

The proper prevention and control need well collaboration between entomologists, health and veterinary authorities, biologists and environmental specialists (Hassan et al. 2011). This one health approach will help us to eradicate RVFV from the world. Various control measures include larvicides for vectors, vaccines for animals, control of animal trade and proper training sessions for the awareness of public (Meegan and Bailey 2019). Vaccination is the best method in animals for the protection of human health. To control RVFV, the best way is to vaccinate both humans and animals (Atkins and Freiberg 2017).

Avoiding direct contact with the infected body tissues, fluids; mosquito evading, proper bed nets and proper use of mosquito repellent sprays, moreover restrict themselves to the houses during peak feeding hours of mosquitoes (dawn and dusk) (Grossi-Soyster and Labeaud 2020). Instant precaution includes the use of personnel repellents. We should be careful in dealing with the infected animals for examination, milking or during other nursing approaches and use personnel protection equipment (Lancelot et al. 2019).

In order to stop the outbreaks, we should use meat and milk after proper cooking and boiling and stop the consumption of non-inspected meat (Sindato et al. 2011). In endemic areas proper care can control RVFV that include proper pasteurization of the food; light color clothes that comprise of long-sleeved shirts and trousers are preferred (Paweska 2014).

Conclusion

Rift Valley fever (RVF) is an arthropod-borne viral disease of ruminants, camels, and humans. It is considered as a

significant zoonotic issue causing uncomplicated influenza-like illness but may also lead to hemorrhagic illness with liver involvement. The ocular or neurological lesions may also be present. In animals, RVF may be inapparent in non-pregnant adults, but outbreaks are characterized by the onset of abortions and high neonatal mortality. Jaundice hepatitis and death are seen in the older animals. Outbreaks are generally linked with heavy rainfall, producing high population of mosquitoes which act as a main vector. After virus amplification in vertebrates, mosquitoes act as secondary vectors to sustain the epidemic. The above discussion and the relationship of disease between animals and humans ensure the concept of one health triad and needs appropriate control measures to limit the spread of disease.

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