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REVIEW ARTICLE

THERAPEUTIC ASPECTS OF LASSA FEVER; A REVIEW

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Abstract

Lassa fever is a viral hemorrhagic, Rodent-borne disease caused by the Lassa virus. It is mainly endemic in the Sub-regions of West Africa, including Nigeria due to the predominance of the zoonotic host in the region. Treatment options in Nigeria presently are limited and mortality rate is also high, due to lack of an approved preventive Vaccine, with Ribavirin being the major therapy for now. Our analytical findings unveiled that the genetic diversity among the different strains of Lassa fever has the ability to circumvent the immune system and this poses a critical challenge to the development of therapeutics for the disease. Hence understanding the biochemical mechanism of host immune invasion by the virus and its genetic polymorphism is key in the development of more effective therapeutics to combat this deadly virus, especially now that recent reviews have identified the Lassa fever Nucleoprotein (which functions in several aspects of the viral life cycle) as a novel target for therapeutics. Moving forward, Lassa fever Nucleoproteins inhibitors inhibitors can be employed as effective therapeutics to potentially inhibit the disease replication. Effective preventive measures, vaccine development, Repurposing of existing drugs using activity or in silico-based and computational bioinformatics, would be critical in the development of novel therapeutics for Lassa fever treatment.

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Introduction:-

Lassa fever (LF) is a life-threatening haemorrhagic, rodent-borne disease caused by the Lassa virus. It affects 2–3 million people in Africa annually with approximately 5,000 deaths (Ilesanmiet al., 2015; Hassan et al., 2022; Nwovu et al., 2018; Vincent et al., 2021). Lassa fever is predominant in most West African sub-regions with its incidence more prominent in Guinea, Liberia, Nigeria, and Sierra Leone because, Zoonotic host, Mastomysnatalensis, which serves as Lassa fever reservoir and vector is more abundantly seen in these regions (Danny et al ; 2019) The virus that causes lassa fever is a single strangled RNA virus belonging to the Family Arenaviridae (Adefisan, 2022). Several studies have confirmed that the primary mode of spread of the disease is from rodents(Zoonotic host) to man through consumption of food and water contaminatedwith the virus from excreta of these rats (Mbuk, 2018).

Presently, there is no approved therapeutic approach or prophylactic vaccine for Lassa fever in Nigeria. Ribavirin, a nucleoside analog has been reported to be efficacious at the onset of infection, although the drug is linked with severe side effects (McCormick et al ; 1986).

Several studies have confirmed that supportive care remains the primary method for treating and managing the disease condition, therefore finding a definitive treatment guideline will not only reduce the death rate accompanied with the disease but will also shorten the course of the infection as well (Alliet al., 2021).

Pathogenesis / Pathphysiology

Several studies have shown that the virus chiefly target the antigen presenting cells which are mainly the dendritic and endothelial cells (Hensley et al., 2011). According to Flatzet al., (2010)following an infection, the virus gains entry into the host cell via endocytosis using the cell-surface receptor (alpha-dystroglycan). The alpha-dystroglycan (alpha-DG) is a versatile receptor for protein of the extracellular matrix (Yun and Walker, 2012).

Once the virus attaches to the host cell receptor, they are rapidly delivered to the endosomes. Lassa virus resists degradation in the endosomes using envelope glycoproteins.

The antigen-presenting cells are the focal points of the virus immediately after it gets into the host cells. The virus infects most tissues in humans culminating in multi-systemic malfunction, immunosuppression of host's innate interferon (IFN) response via halting of interferon regulatory factor-3 (IRF-3) translocation (Hastieet al ; 2012, Rojek et al ; 2008). Reports have shown that Lassa virus has exonuclease activity only targeted at double-stranded RNAs, which mostly inhibits the responses of IFN. This is achievable via assimilation of pathogen-associated molecular patterns (PAMP), which helps the Lassa virus to circumvent the immune response of the host (Azeez-Akande, 2016). The blood vessels are the tissues mostly afflicted and the Lassa virus replicates in the cells of the reticuloendothelial system culminating in capillary injury. Bleeding might be observed in the following organs such as hepatocyte, intestine, myocardium, lungs and the brain (Günther et al ; 2001)

According to Ne and Walker, (2012) the Lassa fever virus evades the host immune system by production of nucleocapsid protein (NP) proteins which helps in the inhibition of the host immune response resulting in endothelial dysfunction, which in turns results in the release of pro-inflammatory cytokines and cell mediators.

The pro-inflammatory cytokines and cell mediator causes platelet dysfunction, cardiac function suppression, hepatic necrosis, facial edema and hypovolemic shock, (Ne and Walker, 2012). If the host fails to mountand/or resuscitate its immune response through the production of neutralizing antibodies to fight the spread of the virus replicationwithin the tissues, death may occur.

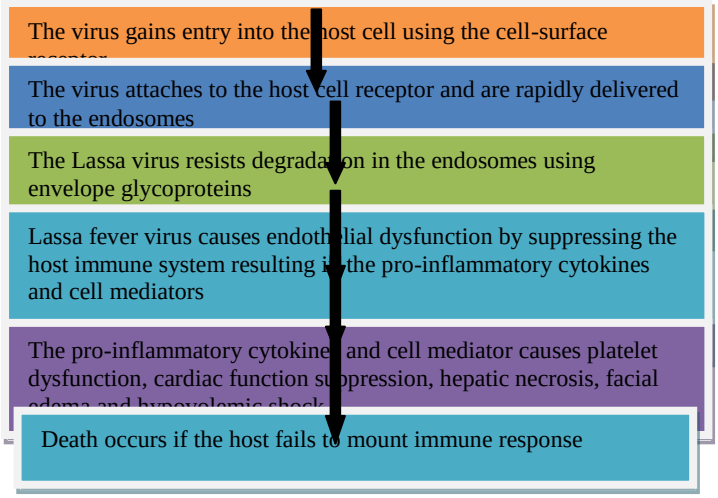

Figure 1:- Pathogenesis of Lassa fever (Hensley et al., 2011).

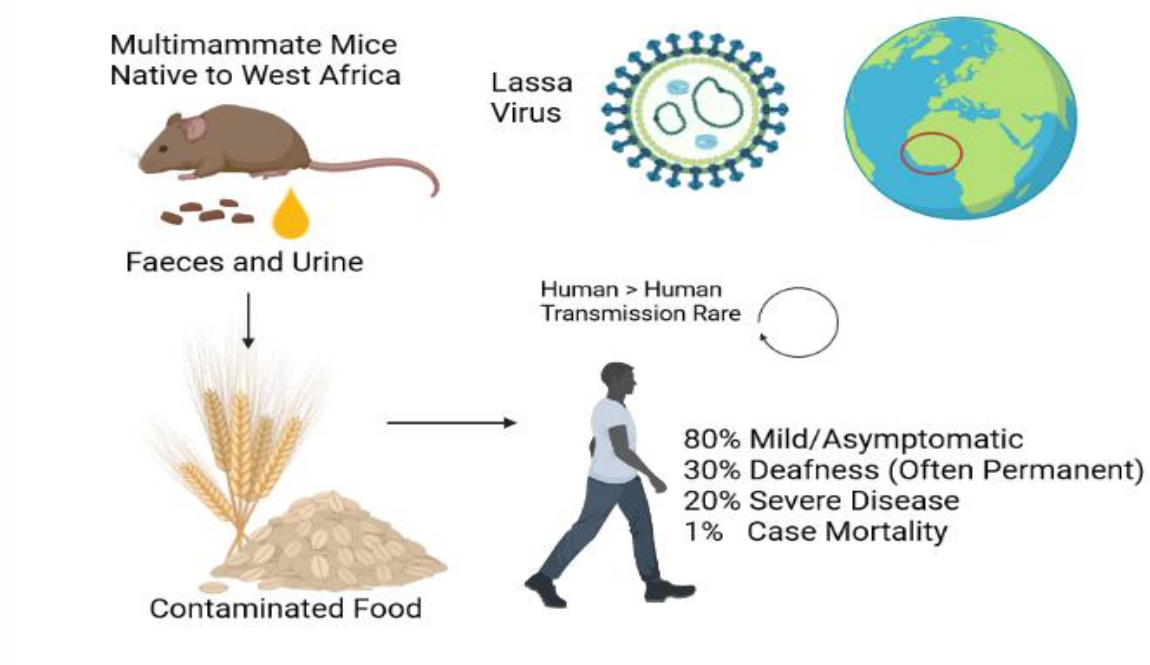

Figure 2:- Lassa fever Transmission and Pathogenesis(Yun and Walker, 2012).

Clinical Features

There have been several reports that the symptoms associated with Lassa fever is non-specific, but may include fever, diarrhea, malaise, headache, sore throat, cough, abdominal pain, nausea, vomiting, and myalgia (Port et al., 2020). In cases of severe illness complication by abnormal bleeding, generalized edema, respiratory distress, hypotension, proteinuria, transaminitis, deafness and encephalopathy have been reported to develop (WHO, 2016).

Table 1:- The Classical Clinical Course of Lassa fever(Port et al., 2020).

Stage	Symptoms
(days 1-3)	General weakness and malaise
(days 4-7)	Sore throat, abdominal pain, nausea, diarrhea and vomiting
(after 7 days)	Convulsion, mucosal bleeding, facial oedema and internal bleeding
(after 14 days)	Coma and death

Prevention

Lassa fever can be prevented and controlled by regulating the zoonotic host by the avoidance of bush burning, use of snares in and within homes to curtail their numbers, obstruction of rodents' hiding place, and shunning rat hunting for human consumption.

In addition, sensitization/health education of both health workers and the general public on the disease dynamics, transmissibility, symptoms, and preventive measures (Dimie et al ;

Other preventive measures include good and healthy personal hygiene, good environmental sanitation, food-items storage in rat-proof containers. Contaminated individuals are quarantined and usage of personal protective devices including face masks and other PPIs.

Treatment

Ribavirin is an antiviral drug that acts by causing the inhibition of the replication of RNA viruses, several studies have been shown that the drug acts as a competitive inhibitor of the guanylation step in the 5' capping of messenger RNA, thus its effect on virus replication occurs during translation (Alliet al., 2021).

Multiple studies carried out in Nigeria have confirmed the use of Ribavirin as the standard for treating Lassa fever,ribavirin lowers the mortality risk to less than 5% if only the patients commences treatment with the drug

during the first 6 days of illness, but studies carried out by Hallamet al., (2018) have it that the beneficial effect of drug diminishes if it is started later in the course of illness. According to a study carried out Alliet al., (2021), Ribavirin showed a high level of efficacy in the treatment of Lassa fever and have also shown protective role as it have been confirmed by numerous studies to increase the survival rate of patients infected with the virus with mild to no drug reaction.

Convalescent plasma have been shown by several studies to have beneficial effect in improving the health condition of patients suffering from Lassa fever. A clinical trial carried out by Horbyet al., (2021)in Nigeria reported that 75% of patients suffering from Lassa fever that were treated with convalescent plasma recovered, whileEberhardtet al., (2019) reported that a combination of ribavirin and convalescent plasma played an important role as a prophylaxis therapy and that use of convalescent plasma alone did not significantly reduce the mortality rate among treated patients.

Emerging Therapy

There have been recent updates on the development of therapeutic drugs that can be use to combat Lassa fever, one of such drugs is Favipiravir. The drug have been shown to be effective by several studies, but there have been reported cases of nausea, vomiting, and transaminitisHorbyet al., 2021)

Arbidol is a new drug that have potential efficacy against Lassa fever, one of the beneficial property of the drug is that it can be administered orally (Alliet al., 2021).
5-ethynyl-1-b-D-ribofuranosylimidazole-4-carboxamide (EICAR) and mycophenolic acid (MPA) have been shown by several studies to be effective in the treatment of Lassa fever, but the drug is required at low concentration to bring about desired effect (Alliet al., 2021).

Thou, there is no vaccine for Lassa fever in Nigeria yet, in 2017 the WHO released a target profile for the development of vaccine against Lassa fever.

Table 2:- Fatality rates of the different treatments for Lassa fever (Alliet al., 2021).

Type of Treatment	Viremia Levels More Than $10^{3.6}$ TCID50 (Fatality rate)
No treatment	76%
Favipiravir	20%
IV ribavirin	32%
Oral ribavirin	30%
Convalescent plasma	57%

Conclusion:-

Lassa fever is disease of public health importance because of its challenging threat to the global healthcare system. Several studies have supported the use of Ribavirin as the gold standard for treatment of Lassa fever in Nigeria.Favipiravirhasrecently been tried and also proved to be efficacious in the treatment of Lassa fever.Many studies have also stated favorable findings on the use of convalescent plasma.Besides, effective preventive control measures, vaccine development, as well as repurposing of the existing drug like ribavirin using in silico-based approach have been suggested as plausible means of curtailing the dreaded disease.

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