LASSA FEVER: A Review of Clinical Features, Diagnosis and Treatment

ABSTRACT

Lassa virus (LASV) is an enveloped single stranded RNA virus that results in Lassa fever (LF). The causative organism belongs to the Arenavirus genus. Since it's initial diagnosis in 1969 in Lassa town Nigeria, numerous endemic outbreaks have occurred with spread to other regions in Africa and beyond. LF is transmitted via rodent to human and human-to-human transmissions with rodents being the reservoir of infection. Risk factors for the disease include residing in an endemic area with poor sanitation and overcrowding, close contact with infected individuals and being a health care worker. About 80% of infected patients do not develop symptoms but the remaining develop a multisystem disease, where up to 15% die in-hospital care with is hallmark symptom being bleeding especially from body orifices. This review will introduce a general overview of Lassa fever and describe the epidemiology, clinical features, diagnosis and treatment of Lassa fever patients. It will also provide a means to raise awareness among healthcare workers. Furthermore, our review focuses on the most up-to-date clinical information for the effective management, prevention and counseling of Lassa fever patients.

INTRODUCTION AND BACKGROUND

Lassa fever (LF) is a viral hemorrhagic fever caused by the Lassa virus of the family Arenaviridae, genus Mammarenaviridae, order Bunyavirales, and phylum Negarnaviricota (1). Arenaviridae family comprises a diverse group of enveloped, negative-sense single-stranded RNA viruses (2). Arenaviruses are grouped into two: based on genetic differences and geographic distribution. The first group, New World viruses are found in the Western Hemisphere—North and South America while the second group, Old World viruses are found in the Eastern Hemisphere—Africa, Europe, and Asia (3). LASV is an RNA virus enveloped in a lipid membrane. The RNA genome of the virus is bi-segmented and its coding strategy is in the ambisense form (3). The disease originated in 1969 when a nurse in Lassa, a town in Borno Nigeria, got infected and died from it (4). The primary reservoir host is a rodent, Mastomys nataliensis, which is responsible for most of its spread was identified in 1974 in Sierra Leone (4,5). The Lassa virus is currently endemic in various regions of West Africa with the incidence of LF more prominent in Guinea, Liberia, Nigeria, and Sierra Leone because Mastomys natalensis, the animal which serves as LASV reservoir and vector is more abundantly seen in these regions (3,4). Current literatures have shown the disease endemicity in neighboring countries such

as Mali, Ivory Coast, Togo, Cameroon, Benin, and Ghana, indicating a continuous geographical expansion of the virus and human disease (6).

It has been reported to have affected over 2 million people (3). LF has the second highest global burdens among all known viral hemorrhagic fevers, second only to Dengue fever which has an estimated 390 million infections per year (1). Studies have shown that about 300,000 to 500,000 cases are diagnosed, and 5000 mortalities are recorded annually, orchestrating significant hardship in the economy of these countries and posing a worldwide clinical challenge for the public officials owing to the danger of importation of LF patients (3). LF cases are categorised as suspected, confirmed and probable (7).

As a result of its high case fatality rate (approximately 20%), potential to spread easily via human-human contact, severity of infectivity (suppresses immune cells so that they do not secrete pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-6, and IL-8β, contrary to what is seen in other hemorrhagic fevers), lack of effective vaccines and therapeutics, and spread via aerosol, LASV is classified as category A, Biosafety Level 4 agent. The World Health Organization (WHO) in 2015 reported LF as one of the priority ailments needing urgent attention for research and development (2,3,8).

Nigeria has been a major target of this deadly disease, with annual outbreaks and continues to report the greatest number of cases in the region with peak incidence of LF cases reported in January to March (4,9). Owing to the foregoing and the public health impact of this deadly disease, we aim to undertake a mini-review the clinical features, diagnosis and treatment options available as well as equipping healthcare practitioners to with a view to self-protection and limiting disease spread.

REVIEW

Etiology.

Lassa fever is an epidemiologically significant zoonotic disease with the potential of culminating into severe hemorrhage that is caused by Lassa virus, belonging to the Arenaviridae family (11). Structurally, the Lassa virus has a bi-segmented RNA genome that is encapsulated in a helical nucleocapsid with a surrounding lipid bilayer and glycoprotein spikes (12). Like other viruses belonging to the genus, mammarenavirus, viral entry into cells is via glycoprotein-receptor mediated interaction. In the case of Lassa virus,this interaction involves alpha-dystroglycan on

the cell membrane of host cells leading to subsequent internalization of virus and the beginning of its life cycle (12).

Based on phylogenetic and genome sequence analyses of Lassa isolates ,there are currently seven different lineages (I-VII),with each lineage having remarkable preponderance in certain geographic locations or countries (13).The lineage diversity has been shown to be a reflection of the variation in the sequence of viral Glycoprotein and Nucleoprotein (14).

TRANSMISSION OF LASSA FEVER.

Most cases of Lassa fever are due to rodent to human transmissions of the Lassa virus via direct contact with infected animals or their excreta. However, a probable 20% has been attributed to human-to-human transmissions (15.) The multimammate rodent, mastomys natalensis, is the paramount vector of the Lassa virus. Additionally, other mastomys rodents viz Mastomys huberti and Mastomys erythroleucus and non-Mastomys small mammals including Rattus rattus, Hylomyscus pamfi, Praomys daltoni, Mus minutoides and Crocidura spp,has been shown to be reservoirs of the Lassa virus (16).

Most of the transmission occurs through ingestion or inhalation of contaminated air. This can happen in myriads of ways such as direct consumption as a source of food(a common practice in west Africa) especially in communities with poor sanitation or crowded living conditions, handling of contaminated items or infected wounds as well as during cleaning activities where aerosolized infected particles can become inhaled. While incidental touch or skin to skin contact without exchange of body fluids with another infected individual has not been shown to result in infection, human to human transmission has been documented to occur in other ways.This is particularly seen in Hospital settings where nosocomial infection can occur due to unavailability of personal protective equipment or use of contaminated medical equipments (17, 24, 27, 28).

CLINICAL FEATURES OF LASSA FEVER

The period of incubation of Lassa fever ranges from 6–21 days (25). Vascular permeability is increased after the entry of the Lassa virus in the host body (18). As a result, fluid and immune cell accumulation occur at the site of the infection. Some Lassa fever patients have clinical signs of lesions in their adrenal glands, liver, and spleen (18). Bronchial oedema, ascites, pleural, pericardial effusions, and

hemorrhagic gastrointestinal symptoms are also prevalent (18). The most frequent abnormalities of the liver are hepatocytes localized cytoplasmic degradation, multifocal hepatic necrosis, monocytic response to necrosis, and hepatocellular mitosis (18). Among the survivors, memory loss, neuromuscular pain, sensorineural hearing loss, and ataxia are all common neurological sequelae (18). Fever, headache, sore throat, general body fatigue, cough, nausea, vomiting, diarrhoea, muscular aches, chest discomfort, and, in extreme cases, bleeding from the mouth, nose, ears, eyes, and other body openings are its symptoms. About 80% of infected patients do not develop symptoms, but the remaining develop multisystem diseases, where up to 15% of patients died in hospital care (20). Poor outcomes are more common among some individuals, including pregnant women and their fetuses (26).

DIAGNOSIS

One significant challenge in diagnosis of LF is differentiating between etiologies of febrile illness with similar initial clinical presentations, including malaria, influenza, dengue and yellow fever as laboratory facility and reagents are limited (21). Laboratory diagnosis of LASV infection is made by detection of the virus (culture), LASV RNA, LASV-specific IgG or IgM antibody response or LASV antigens shed during replication (21,22).

Viral isolation in cell culture remains the "gold standard" for the diagnosis of Lassa fever (21). Real-time RT-PCR is a commonly used diagnostic approach for infectious diseases due to the high specificity and sensitivity of the method and has become a clinical standard for Lassa fever diagnosis detecting LASV RNA. Antibodies and antigens can be detected by indirect immunofluorescence assay test (IFA or IIFT), western blot (WB), ELISA or rapid diagnostic test (RDT) formats. Generally, the LASV antigens(nucleoproteins) are positive in the first week of infection with the LASV antibodies(IgM and IgG) being positive in the second and third week (21,22).

TEST	DESCRIPTION	SAMPLE USED
Viral culture	Gold standard. Not routinely done	Blood, urine, throat swab,csf and organ biopsy
PCR	Based on NAAT to detect LASV RNA. Real time PCR is most commonly used	Blood Specimen
LASV specific IgG or IgM	Detect antibody titre rise as a result of infection.	Blood Specimen

antibody	Starts to rise in second and third week	
LASV antigen	Detects antibodies to viral antigens especially nucleoprotein. Usually detected in the first week	Blood Specimen

TABLE 1: Showing the diagnostic modalities for Lassa Virus

MANAGEMENT

While there are no guidelines to approach patients with LF, management of the disease is mainly supportive including fluid replacement for hemodynamic stability, treating electrolyte imbalance, monitoring coagulation factors, dialysis in case of declining renal function and prophylactic antibiotics (1,4,8). Ribavirin has been traditionally used for the treatment of Lassa fever (4). Ribavirin, a broad spectrum guanosine analogue, is the recommended treatment for LF and for post-exposure prophylaxis using both intravenous and oral administration respectively. Initiating early treatment is vital to improve the rate of survival (7). Oral ribavirin is indicated in the dose of 500 to 600 mg every 6 h for 7 to 10 days while intravenous dosing begins with a loading dose of 2.4 g, followed by 1 g every 6 h for 10 days based on adult weight and has been shown to reduce the case fatality (1,7). There is no adequate data supporting the use of oral ribavirin for therapy, but it has been shown to be effective for post exposure prophylaxis (1). Interestingly, patients with aspartate aminotransferase (AST) values > 150 U/lL show greater efficacy (1). Ribavirin is ineffective when administered late in the course of disease after viraemia has peaked and physiological dysregulation has progressed into severe and often irreversible stages (10).

Favipiravir, a nucleoside analog designed to inhibit RNA-dependent RNA polymerase in influenza viruses has shown activity against LASV as it decreased viremia in animal studies. Also, its use combined with ribavirin on two patients who contracted secondary LF further buttressed this (8).

Other drugs has also shown activity against LASV in animal/invitro studies such as Stampidine(a nucleoside derivative of d4T, a retroviral reverse transcriptase inhibitor), amodiaquine, Small interfering RNAs (siRNAs), 5-ethynyl-1-b-D-ribofuranosylimidazole-4-carboxamide (EICAR), mycophenolic acid (MPA), isavuconazole, apilimod, niclosamide, and zoniporide (1,8). In vitro analysis showed

that arbitol (a membrane fusion inhibitor) combined with aripiprazole (a cellular micropinocytosis inhibitor) or combined with sertraline (a membrane fusion inhibitor) can synergistically inhibit the Lassa virus (1). None of this drugs have gone through clinical trials for LASV and is not approved for clinical use. Convalescent plasma has shown some promising results when given to patients early in the disease course (1). More so human monoclonal antibodies (humAbs) derived from B cells of convalescent donors have also been studied in animals and showed promising results. Recently, a combination of three broadly neutralizing human monoclonal antibodies known as Arevirumab-3 (8.9F, 12.1F, 37.2D) demonstrated marked efficacy in preclinical studies protecting cynomolgus macaques against various strains of LASV (23). Therefore, humAbs have a significant potential as a LF treatment modality in humans (1,23). Extensive research is still ongoing to generate effective therapeutic interventions for treatment and prophylaxis for LASV (4).

PREVENTION OF LASSA FEVER

The World Health Organization highlights preventive measures in communities as one of the key considerations for LF control. Studies have shown that community initiatives play a significant role as critical enablers in the control of communicable diseases in low and middle-income countries (LMIC) (19). Prevention of Lassa fever relies on promoting good "community hygiene" to discourage rodents from entering homes. Effective measures include storing grain and other foodstuffs in rodent-proof containers, disposing of garbage far from the home, maintaining clean households and keeping cats. Family members should always be careful to avoid contact with blood and body fluids while caring for sick persons (19). In health-care settings, staff should always apply standard infection prevention and control precautions when caring for patients, regardless of their presumed diagnosis. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe burial practices (19).

Vaccines. There are currently no Lassa virus vaccines approved for use. However, several vaccine platforms have been developed that show efficacy in animal models, and some of these have recently entered phase I human clinical trials. Among platforms that have been evaluated as potential Lassa virus vaccines are a ML29 MOPV/Lassa virus live reassortant (a DNA vaccine and recombinant vesicular stomatitis virus), rabies virus, measles virus, vaccinia virus and adenovirus vectored vaccines. Additional vaccine candidates include LASV virus-like particles and a virus replicon particle vaccine (10).

CONCLUSION

Lassa fever caused by LASV is a deadly disease and remain a public health threat. While it is endemic in some parts of West Africa, it's spread to other areas and recent outbreaks in endemic areas compound the issue. More research is needed in this field as there are no vaccines till date and effective treatment for it. Health care workers at the frontline must be armed with knowledge of this disease to ensure smooth delivery of their duties.

REFERENCES

1. Murphy HL, Ly H. Pathogenicity and virulence mechanisms of Lassa virus and its animal modeling, diagnostic, prophylactic, and therapeutic developments. Virulence. 2021 Dec;12(1):2989-3014. doi: 10.1080/21505594.2021.2000290. PMID: 34747339; PMCID: PMC8923068.

2. Pennington HN, Lee J. Lassa virus glycoprotein complex review: insights into its unique fusion machinery. Biosci Rep. 2022 Feb 25;42(2):BSR20211930. doi: 10.1042/BSR20211930. PMID: 35088070; PMCID: PMC8844875.

3. Aloke C, Obasi NA, Aja PM, Emelike CU, Egwu CO, Jeje O, Edeogu CO, Onisuru OO, Orji OU, Achilonu I. Combating Lassa Fever in West African Sub-Region: Progress, Challenges, and Future Perspectives. Viruses. 2023 Jan 3;15(1):146. doi: 10.3390/v15010146. PMID: 36680186; PMCID: PMC9864412.

4. Naeem A, Zahid S, Hafeez MH, Bibi A, Tabassum S, Akilimali A. Re-emergence of Lassa fever in Nigeria: A new challenge for public health authorities. Health Sci Rep. 2023 Oct 24;6(10):e1628. doi: 10.1002/hsr2.1628. PMID: 37885466; PMCID: PMC10598329.

5.Olayemi A, Fichet-Calvet E. Systematics, Ecology, and Host Switching: Attributes Affecting Emergence of the Lassa Virus in Rodents across Western Africa. Viruses. 2020 Mar 14;12(3):312. doi: 10.3390/v12030312. PMID: 32183319; PMCID: PMC7150792.

6. Opara NU, Nwagbara UI, Hlongwana KW. The COVID-19 Impact on the Trends in Yellow Fever and Lassa Fever Infections in Nigeria. Infect Dis Rep. 2022 Nov 21;14(6):932-941. doi: 10.3390/idr14060091. PMID: 36412749; PMCID: PMC9680345.

7. Grace JA, Egoh IJ, Udensi N. Epidemiological trends of Lassa fever in Nigeria from 2015-2021: A review. Ther Adv Infect Dis. 2021 Nov 29;8:20499361211058252. doi: 10.1177/20499361211058252. PMID: 34868582; PMCID: PMC8637796.

8. Alli A, Ortiz JF, Fabara SP, Patel A, Halan T. Management of Lassa Fever: A Current Update. Cureus. 2021 May 2;13(5):e14797. doi: 10.7759/cureus.14797. PMID: 34094756; PMCID: PMC8167379.

9. Arruda LB, Haider N, Olayemi A, Simons D, Ehichioya D, Yinka-Ogunleye A, Ansumana R, Thomason MJ, Asogun D, Ihekweazu C, Fichet-Calvet E, Kock RA. The niche of One Health approaches in Lassa fever surveillance and control. Ann Clin Microbiol Antimicrob. 2021 Apr 24;20(1):29. doi: 10.1186/s12941-021-00431-0. PMID: 33894784; PMCID: PMC8067790.

10. Garry RF. Lassa fever - the road ahead. Nat Rev Microbiol. 2023 Feb;21(2):87-96. doi: 10.1038/s41579-022-00789-8. Epub 2022 Sep 12. PMID: 36097163; PMCID: PMC9466315

11)Hallam HJ, Hallam S, Rodriguez SE, Barrett ADT, Beasley DWC, Chua A, Ksiazek TG, Milligan GN, Sathiyamoorthy V, Reece LM. Baseline mapping of Lassa fever virology, epidemiology and vaccine research and development. NPJ Vaccines. 2018 Mar 20;3:11. doi: 10.1038/s41541-018-0049-5. PMID: 29581897; PMCID: PMC5861057.

12) Ehichioya DU, Dellicour S, Pahlmann M, Rieger T, Oestereich L, Becker-Ziaja B, Cadar D, Ighodalo Y, Olokor T, Omomoh E, Oyakhilome J, Omiunu R, Agbukor J, Ebo B, Aiyepada J, Ebhodaghe P, Osiemi B, Ehikhametalor S, Akhilomen P, Airende M, Esumeh R, Muoebonam E, Giwa R, Ekanem A, Igenegbale G, Odigie G, Okonofua G, Enigbe R, Omonegho Yerumoh E, Pallasch E, Bockholt S, Kafetzopoulou LE, Duraffour S, Okokhere PO, Akpede GO, Okogbenin SA, Odia I, Aire C, Akpede N, Tobin E, Ogbaini-Emovon E, Lemey P, Adomeh DI, Asogun DA, Günther S. Phylogeography of Lassa Virus in Nigeria. J Virol. 2019 Oct 15;93(21):e00929-19. doi: 10.1128/JVI.00929-19. PMID: 31413134; PMCID: PMC6803284.

13) Ibukun FI. Inter-Lineage Variation of Lassa Virus Glycoprotein Epitopes: A Challenge to Lassa Virus Vaccine Development. Viruses. 2020 Mar 31;12(4):386. doi: 10.3390/v12040386. PMID: 32244402; PMCID: PMC7232328.

14)Cao W, Henry MD, Borrow P, Yamada H, Elder JH, Ravkov EV, Nichol ST, Compans RW, Campbell KP, Oldstone MB. Identification of alpha-dystroglycan as a receptor for lymphocytic choriomeningitis virus and Lassa fever virus. Science. 1998 Dec 11;282(5396):2079-81. doi: 10.1126/science.282.5396.2079. PMID: 9851928.

15)Lo Iacono G, Cunningham AA, Fichet-Calvet E, Garry RF, Grant DS, Khan SH, Leach M, Moses LM, Schieffelin JS, Shaffer JG, Webb CT, Wood JL. Using modelling to disentangle the relative contributions of zoonotic and anthroponotic transmission:

the case of lassa fever. PLoS Negl Trop Dis. 2015 Jan 8;9(1):e3398. doi: 10.1371/journal.pntd.0003398. PMID: 25569707; PMCID: PMC4288732.

16)Olayemi A, Oyeyiola A, Obadare A, Igbokwe J, Adesina AS, Onwe F, Ukwaja KN, Ajayi NA, Rieger T, Günther S, Fichet-Calvet E. Widespread arenavirus occurrence and seroprevalence in small mammals, Nigeria. Parasit Vectors. 2018 Jul 13;11(1):416. doi: 10.1186/s13071-018-2991-5. PMID: 30005641; PMCID: PMC6045851.

17)Madueme PU, Chirove F. Understanding the transmission pathways of Lassa fever: A mathematical modeling approach. Infect Dis Model. 2022 Nov 30;8(1):27-57. doi: 10.1016/j.idm.2022.11.010. PMID: 36582748; PMCID: PMC9762202.

18. Hossain, Md. I., Bhattacharya, P., & Islam, Md. A. (2023). Resurgence of Lassa fever in Nigeria: clinical features, epidemiology, pathogenesis, diagnostic methods, and treatment. *International Journal of Surgery: Global Health*, *6*(5).

https://doi.org/10.1097/gh9.0000000000000238

19. Ilesanmi, A. O., Oton, E., & Afolabi, A. (2021). Community engagement in the prevention and control of lassa fever in africa: A systematic review. In *Infection, Epidemiology and Microbiology* (Vol. 7, Issue 2). https://doi.org/10.52547/iem.7.2.187

20. Ogbaini-Emovon, E., Erah, F., Osagiede, E. F., Nnadi, C., Ogbetere, Y., Tobin, E. A., Asogun, D., Okonofua, M., Akpede, G., Akhideno, P., Erameh, C., Rafiu, M. O., Ovienria, W., Ephraim-Ogbaini, C., Ojide, C. K., Unigwe, U., Ireye, F., Günther, S., Duraffour, S., & Okogbenin, S. (2023). Lassa Fever Infection among Healthcare Workers during the 2018 Outbreak in Nigeria. *International Journal of Occupational Safety and Health*, *13*(3). https://doi.org/10.3126/ijosh.v13i3.44269

21. Raabe V, Koehler J. Laboratory Diagnosis of Lassa Fever. J Clin Microbiol. 2017 Jun;55(6):1629-1637. doi: 10.1128/JCM.00170-17. Epub 2017 Apr 12. PMID: 28404674; PMCID: PMC5442519

22. Mazzola LT, Kelly-Cirino C. Diagnostics for Lassa fever virus: a genetically diverse pathogen found in low-resource settings. BMJ Glob Health. 2019 Feb 7;4(Suppl 2):e001116. doi: 10.1136/bmjgh-2018-001116. PMID: 30899575; PMCID: PMC6407561.

23. Woolsey C, Cross RW, Prasad AN, Agans KN, Borisevich V, Deer DJ, Dobias NS, Fears AC, Harrison MB, Heinrich ML, Fenton KA, Garry RF, Branco LM, Geisbert TW. Monoclonal antibody therapy demonstrates increased virulence of a lineage VII strain of Lassa virus in nonhuman primates. Emerg Microbes Infect. 2024 Dec;13(1):2301061. doi:

10.1080/22221751.2023.2301061. Epub 2024 Jan 22. PMID: 38164768; PMCID: PMC10810630.

24. Arruda LB, Haider N, Olayemi A, Simons D, Ehichioya D, Yinka-Ogunleye A, Ansumana R, Thomason MJ, Asogun D, Ihekweazu C, Fichet-Calvet E, Kock RA. The niche of One Health approaches in Lassa fever surveillance and control. Ann Clin Microbiol Antimicrob. 2021 Apr 24;20(1):29. doi: 10.1186/s12941-021-00431-0. PMID: 33894784; PMCID: PMC8067790.

25. Hansen F, Jarvis MA, Feldmann H, Rosenke K. Lassa Virus Treatment Options. Microorganisms. 2021 Apr 7;9(4):772. doi: 10.3390/microorganisms9040772. PMID: 33917071; PMCID: PMC8067676.

26. Sulis G, Peebles A, Basta NE. Lassa fever vaccine candidates: A scoping review of vaccine clinical trials. Trop Med Int Health. 2023 Jun;28(6):420-431. doi: 10.1111/tmi.13876. Epub 2023 Apr 24. PMID: 37095630; PMCID: PMC10247453.

27. Reyna RA, Littlefield KE, Shehu N, Makishima T, Maruyama J, Paessler S. The Importance of Lassa Fever and Its Disease Management in West Africa. Viruses. 2024 Feb 7;16(2):266. doi: 10.3390/v16020266. PMID: 38400041; PMCID: PMC10892767.

28. Dwalu E, Jetoh RW, Shobayo BI, Pewu I, Taweh F, Wilson-Sesay HW, Akpan GE, Shannon F, Joseph BO, Umeokonkwo CD, Adewuyi P, Amo-Addae M, Nagbe TK, Gilayeneh J, MaCauley JA. Trend of Lassa fever cases and factors associated with mortality in Liberia, 2016 - 2021: a secondary data analysis. Pan Afr Med J. 2024 Jan 19;47:22. doi:10.11604/pamj.2024.47.22.42156. PMID: 38558556; PMCID: PMC10979808.