Review Article

Marburg Virus: A comprehensive examination of a critical pathogen

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Abstract

Marburg virus infection is a rare, severe zoonotic illness caused by the Marburg virus (MARV), with the primary reservoir being Egyptian fruit bats. Marburgviruses have reemerged on multiple occasions, resulting in a very high fatality ratio of up to 88% during the most significant outbreaks. MVD exhibits prominent clinical signs and symptoms such as haemorrhagic fever, coagulopathies, multi-organ failure in the affected individuals. This review provides insight into the MVD structure, genomic organisation, replication, clinical manifestations, and special emphasis on the available treatment strategies. Although no specific therapeutic interventions exist for management, supportive care like fluid administration and treatment of specific symptoms can improve survival rates and clinical outcomes. T-705 Favipiravir blocks the influenza virus's RNA-dependent RNA polymerase (RdRp) and suggests potential effectiveness in patients exhibiting lower viral loads. Remdesivir has shown efficacy in a study of MARV-infected Cynomolgus macaques; treatment improved clinical ratings, decreased plasma viral RNA, and boosted kidney and liver functions. BCX4430 Galidesivir showed 24-hour and 48-hour survival in animal groups after receiving the drug with no apparent toxicity and improved liver enzyme values.

MARV can induce significantly more severe epidemics than previously thought. These widespread outbreaks had a remarkably high mortality rate throughout a large geographical region, presenting substantial challenges in the field of medicine. High fever, haemorrhagic manifestation, organ failure, and coma are the prominent clinical signs of MVD. Supportive care and volume resuscitation are fervently recommended. Monoclonal antibodies and antivirals like Remdesivir and Favipiravir are potential treatment options; however, Galidesivir and Favipiravir can also be used.

Introduction

Marburgvirus, a genus within the Filoviridae family, is the cause of the rare viral haemorrhagic fever known as Marburg virus disease (MVD). MVD is a severe and often fatal zoonotic illness comprising two distinct strains: the Marburg virus (MARV) and the Ravn virus (RAVV). MVD is an RNA-type virus that exhibits a connection to the Ebola virus (EBOV) but with notable distinctions.[1,2] The goals of this review are to briefly provide background on MVD, i.e. structural organization of the Marburg virus, replication, clinical manifestations, and highlight the most recent practices for the treatment of MVD.

An extensive literature search was performed in PubMed, EMBASE, and Google Scholar. The author searched for published evidence from the databases using "Marburg Virus Disease", "Marburg Haemorrhagic Fever," and "Marburg Disease" as keywords for the review.

The disease was first identified in 1967 during outbreaks in two German cities: Marburg, Frankfurt, and the Serbian capital, Belgrade. Since then, sporadic outbreaks have occurred in Africa, with the most recent outbreak reported in Uganda in 2007. (Figure1) The primary reservoir for MARV is believed to be Egyptian fruit bats, *Rousettus aegyptiacus.*

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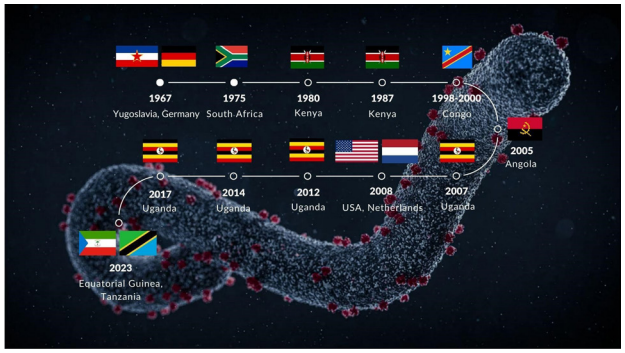

Figure 1: MVD outbreaks in different countries, 1967-2023.

Marburg virus structure

Marburg virions exhibit pleomorphic morphology, manifesting as rod or ring-shaped, hexagonal, or branching structures. Cryo-electron microscopy analysis of pure virions revealed that infected Vero cells, which have a filamentous morphology, form about one-third of the virions. In comparison, 37% displayed a hexagonal structure, and the remaining were spherical.[3] Although the size of MARV particles is significantly smaller than that of Ebola virions, the MARV genomic length is longer than that of EBOV.[4,5] The outer membrane of the viral particles is obtained from the host and is adorned with 5–10 mm-long, trimeric spiky structures, which are composed of highly glycosylated protein (GP) plays a key role in binding to receptive host cells. The ribonucleoprotein complex (nucleocapsid) which is located at the centre of the viral particles, comprises proteins from the nucleocapsid structure and the RNA genome from the MARV. The nucleocapsids are tubule-shaped and have diameters measuring 45–50 nm. The central axis is encircled by a helical capsid exhibiting cross-striations spaced at regular intervals of 5 nm.[4,5]

Genome organization

The viral genome consists of seven open reading frames (ORFs), specifically nucleoprotein (NP), virion protein 35 (VP35), VP40, VP30, VP24, GP, and big viral polymerase. These components are identified as single-stranded negative-sense RNA. (-ssRNA);[6,7]. The genes have exceptionally lengthy non-coding nucleotide sequences at their 3' and 5' ends, together with highly conserved transcription start and stop signals.[6,7]. The nucleocapsid made up of NP, VP35, VP30, and L, surrounds the viral genome.[8]

The ribonucleoprotein is surrounded by a matrix consisting of VP40, VP24, and a lipid envelope with surface GP spikes.[9] The determination of cell and tissue tropism, as well as virus-cell membrane fusion, are regulated by the MARV GP protein. Furthermore, GP may contribute to immune evasion by neutralising the antiviral properties of tetherin, which is an interferon (IFN) that hinders viral transmission.[10,11] VP40, a virulence factor, primarily functions to inhibit host cell responses to IFN signalling.[12] VP40 counteracts the innate immune response and is a major matrix protein.[13] The main function of VP40 in MARV immunopathology is to suppress host cell responses to IFN signalling.[12] It also helps in the budding and binding of the matrix and nucleocapsid.[14] The VP35 protein serves as a multifunctional virulence factor, aiding immune escape by hindering the IFN response. Additionally, it plays a crucial role in the synthesis of viral RNA, functioning as an RdRp. VP24, a protein found in the minor matrix, blocks the cellular response to IFN. The L protein facilitates the process of genome replication and transcription.[11,15] The interaction between VP24 and NP plays a key role for the release of new virions.

Replication cycle

Currently, most studies dealing with the replication cycle of MARV have utilised recombinant techniques. MARV invasion is a three-step process: Attachment of the virus to the cell, endocytosis, and fusion. The replication cycle begins with the attachment of MARV to the cell surface molecules, which subsequently undergo caveolin-mediated endocytosis. GP helps with attachment and viral fusion. The endosomal cholesterol transporter Niemann-Pick C1 (NPC1), which is a MARV entry receptor, helps in the fusion.[16] Endosomal protease fragments GP1 and GP2 participate in the fusion process. After the release of the nucleocapsid in the cytoplasm, viral transcription starts.[17] Cellular C-type lectins, which include ASGP-R, dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN), DC-SIGNR, human macrophage galactose-type lectin (hMGL), and liver sinusoidal endothelial cell lectin (LSECtin), also play a vital role in the process.[8,18,19] Evidence suggests that macro- phagocytosis is the major entry pathway for EBOV[20] and the other way is the trafficking of virions in the endocytic vesicles.[21]

Transcription and replication

Upon the release of the nucleocapsid inside the cytoplasm, the viral RNA genome undergoes transcription and replication. At 12 hours after infection, electron microscopy investigation reveals the initial morphological indication of viral replication: the presence of granular substances in the cytoplasm which are primarily RNA and viral proteins. Afterwards, tubular nucleocapsids gradually appear in the granular structures.[5] MARV transcription is in line with the 'stop-start' model proposed for all different types of non-segmented negative-sense (NNS) RNA viruses.[22] The viral polymerase enters the genome and starts scanning until it reaches the first gene's GS signal, the point of the initialization of transcription. The polymerase complex, placed at the top of the newly formed mRNA, moves along the template until it identifies a GE signal, ending the transcription process. A poly-A tail is added to the newly formed mRNA facilitated by the polymerase, and it starts searching for the next GS signal to start transcription.[15] The newly formed nucleocapsids translocated to the budding site of the virus. VP40 mediates the release of the viral particles by budding at internal membranes and at the plasma membrane by using the coat protein complex II (COPII) vesicular transport and the endosomal sorting complex required for transport (ESCRT) machinery after encasing with the plasma membrane.[14]

Clinical sign, symptoms, complication

At present, there is a lack of clinical evidence that provides a comprehensive understanding of the specific illness progression and the underlying pathophysiological basis of Marburg haemorrhagic fever (MHF). Moreover, the clinical syndromes induced by filoviruses and their related disease severity might differ based on various circumstances, including the medical environment, host vulnerability, and the genetic makeup and virulence of the viral strain. Nevertheless, extensive clinical data were acquired during the initial

epidemic in 1967, and the subsequent outbreak in the Democratic Republic of Congo from 1998 to 2000 serves as the primary source of our current understanding of the development of MHF illness.[23–25]

In humans, the incubation period generally lasts between five and 10 days (ranging from 3 to 21 days).[17] Viral transmission does not happen during this period. The clinical course of the disease can be divided into three distinctive phases: the first generalised phase, which generally lasts 1-4 days, is associated with influenza–like symptoms commencing with a high fever (~40°C) accompanied by a severe headache, chills, myalgia, malaise anorexia, abdominal discomfort, severe nausea, vomiting, and diarrhoea[26,27] The next phase is the early organ phase, consisting of days 5 to 13, which signifies the beginning of the severe phase of MVD. This is followed by the late organ or convalescence phase, which occurs at 13+ days. Survivors seldom exhibit the most severe symptoms of the disease and may never proceed to the late organ phase.[28]

Evidence suggests that the disease intensifies on days 5–7, i.e., the initial days of the early organ phase, with a prominent characteristic haemorrhagic manifestation such as maculopapular rash and petechiae, bleeding from the GI tract, and the phlebotomy sites. Neurological changes are seen mainly in the later stages of the disease, which could lead to even coma.[29] Other symptoms include pain in the joints, uveitis, orchitis, reported during convalescence, inflammation of the liver, pericardium, prostration, dyspnoea, and poor mental health, which happens gradually.[28] Sustained high fever associated with neurological complications, including encephalitis, confusion, delirium, irritability, and aggression, are seen in these patients.[26,27,30] Multiple evidence from the outbreaks documented the severity of late stage of the early organ phase when multiple organs e.g. liver, pancreas and kidneys are affected. Prominent haemorrhagic manifestations such as petechiae, ecchymoses, haematoch ezia, melena, and hematemesis occurs at this stage. The late organ phase extends from day 13 until day 20 or beyond during the progression of the disease. During this stage, the MARV victim progresses to a gradually deteriorating condition, which is characterised by convulsions, major disruptions in metabolic pathways, widespread blood clotting abnormalities, failure of multiple organs, and shock. Significant dehydration leads to poor blood flow and anuria. Neurological complications include restlessness, obtundation, disorientation, and dementia.[24] Deaths usually happen during a period of 8 to 16 days after the symptoms first appear.[26,27]

Main clinical diagnostic criteria

Controlling MHF epidemics necessitates a combination of identifying cases, tracking contacts, isolating patients, and utilising laboratory tests. The diagnosis of MARV in the early phase cannot be made merely only on clinical examination, as it resembles not only other Filovirus haemorrhagic fevers but also exhibits signs and symptoms comparable to other prevalent infectious diseases like malaria, rickettsial infections, and typhoid.[31] This frequently leads to a significant delay in the implementation of infection control protocols and patient management. However, immediate isolation and laboratory investigations should be the primary steps to follow. First–line detection for MHF is based on the detection of the MARV RNA in clinical specimens by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR), or viral antigen detection by Enzyme-Linked Immunosorbent Assay (ELISA) in whole blood and serum with a high sensitivity and specificity.[32,33] Pan–MARV or pan–filovirus RT–PCR assays, which utilise consensus PCR primer sets, able to amplify all MARV strains or a wide array of filoviruses are used for rapid diagnosis,[34] which helps to curb the early outbreak, with a great advantage in epidemiological and epi-zoological perspective. For acute MHF diagnostics, IgG and IgM ELISA are frequently used by utilizing either hyperimmune serum or virus protein–specific (e.g., nucleoprotein) antibodies to capture MARV antigen[31,35] IgM response implies initial stages of infection from the the1st week of infection and peaks during the 2nd week, whereas the appurtenance of virus-specific IgG is the next event.[31,36] However, employing several distinct, responsive, and reliable diagnostic techniques is crucial instead of relying on a solitary test to confirm the diagnosis.

Treatment strategies

Supportive care

There is no specific prophylaxis as well as specific therapeutic interventions for managing MVD. The primary approach to management is the use of early and proactive supportive care measures, such as oral or intravenous fluid administration for rehydration and treatment of specific symptoms, which enhance overall survival rates and improve clinical outcomes significantly. Identifying Marburg virus illness triage is an essential initial measure in both disease outbreaks and solitary cases. Upon suspicion of the diagnosis, implementing patient isolation becomes an imperative initial measure to mitigate the risk of nosocomial transmission.[2] Patients with filovirus infection generally exhibit distinct variations in disease aetiology and clinical progression compared to those with other kinds of sepsis. However, it is noteworthy that patients can still be managed under established recommendations for severe sepsis or dengue care.[37] Fluid resuscitation should be done for patients with significant gastrointestinal volume loss, and replenishment should be done promptly. The first assessment of vital signs will guide the initial course of therapy. Fluid resuscitation is mandatory when a substantial loss of gastrointestinal volume is observed, and close monitoring is vital.[37,38] ≥ 5-10 L/day of intravenous or oral fluids is recommended for the maintenance of hemodynamic stability and replenishment of gastrointestinal fluid depletion.[39] Intricate monitoring and pre-emptive correction of acid-base disturbances and electrolyte imbalances (e.g., potassium) can mitigate the risk of potentially fatal arrhythmias and metabolic complications. Treatment with ceftriaxone, ciprofloxacin, or ampicillin is recommended to curb the migration of the bacteria from the gastrointestinal tract.[39,40]

Immunotherapy

Combined with the anti-MARV mAb MR191, it completely eradicated MARV infection in NHPs. King et al. employed structural analysis to illustrate how the monoclonal antibody MR191, which has protective and therapeutic properties, interacts with the receptor-binding region of the MVD GP. The resulting structure surpasses the host entry receptor NPC1 to counteract MVD. The structure also highlights hitherto disorganised, functionally significant areas of the MVD GP. The combination of the monoclonal antibodies (mAbs) blocks three essential phases of viral entry by inhibiting nonoverlapping epitopes in the GP trimer's apex and base.[41]

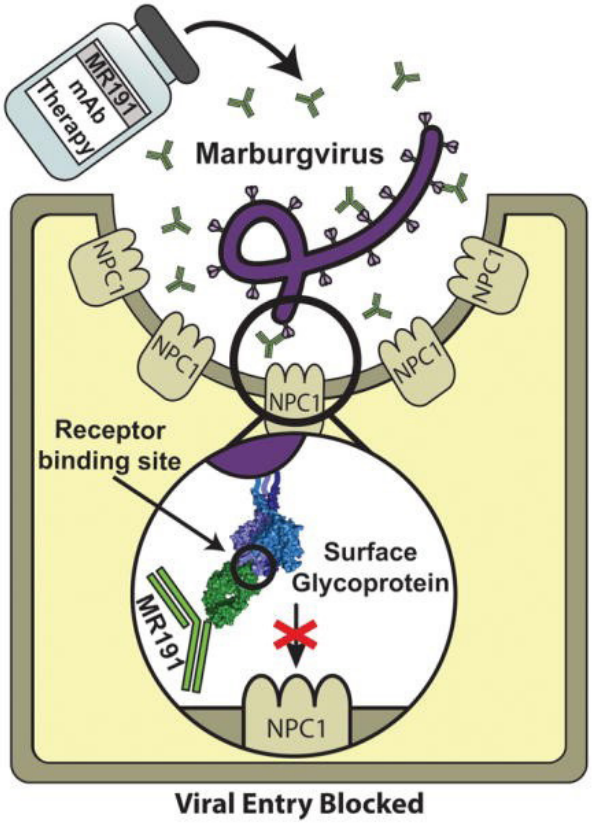

Figure 2: Mechanism of action of MR191 mAb[41]

The therapeutic antibody cocktail for pan-ebolavirus (PE) has high efficacy in suppressing all three pathogenic ebolaviruses that have caused human fatalities. The cocktail inhibits three essential steps of viral entry by blocking nonoverlapping epitopes situated at both the apex and base of the GP trimer. The combination allows for an anticipatory response to potential mutations that are not specific to attaching to particular antibodies, thus augmenting the likelihood of viral escape. Three antibody cocktails can prevent the viral transmission caused by both the ebolavirus and the Marburg virus. Due to the incorporation of both human and macaque components, the actions that elicit a response are completely carried out by the fully human Fc domains of these antibodies. In a rhesus macaque model infected with EVD, IFN-1a treatment has been demonstrated to increase survival.[42]

IFN-2b therapy in a Cynomolgus model infected with EVD decreased viremia and extended the time to death. Five naive rhesus macaques were given an intramuscular injection of the MARV with a target dosage of 1,000 pfu. Within 15 to 30 minutes, MARV-specific immunoglobulin G (IgG) therapy was started in the three experimental macaques. The other two macaques received either a phosphate-buffered saline (PBS) solution or non-specific fractionated IgG as a therapy as part of the control group. Four and eight days following the challenge, further treatment dosages were administered. The control macaques died with the characteristic symptoms of filovirus haemorrhagic fever, but the MARV-specific IgG provided 100% protection with no illness or detectable viremia. A re-challenge with Marburg exhibited complete protection 77 days later. In another study, the first dosage was administered intravenously 48 hours after the challenge, and the next doses were administered on days 4 and 8. Despite one animal suffering a little illness, all three animals survived.[43]

Antiviral therapy

Galidesivir

Cynomolgus macaques, which are infected with wild-type MARV (Musoke variant) obtained from humans, are given intramuscular 15 mg kg−1 BCX4430 twice daily, beginning 1–48 hours post-infection, for two weeks. The virus-inoculated controls were dead by day 12, with the signs and symptoms of filovirus infections reflected in raised hepatic markers, e.g., aspartate aminotransferase and bilirubin, with subsequent higher levels of prothrombin time (PT) and activated partial thromboplastin time (aPTT). Macaques administered with BCX4430 beginning 24 or 48 hours post-infection survived. 83% of animals survived with BCX4430 beginning 1 hour after MVD infection.[44] BCX4430 treatment significantly diminished the viral load without inducing type I IFN responses, as seen in c3-Npc A in mice.[45]

Favipiravir

T-705 Favipiravir is a guanidine nucleoside analogue that works against many RNA viruses. It blocks the RdRP of the influenza virus. The initial studies showcased the effectiveness of mouse models against EBOV and sparked considerable interest in their potential use during the MVD outbreak in West Africa. The outcomes of a large-scale Guinea study (JIKI) yielded ambiguous findings, albeit suggesting potential effectiveness in patients exhibiting a lower viral load (Ct value 20).[46] The trial used historical controls, but a Guinea study showed a better survival rate in the treatment group without statistical significance except for its influence on survival time.[47] Intravenous administration of Favipiravir to six Cynomolgus macaques twice a day for 2 weeks, beginning on Day 1 of the challenge, with 1000 PFUs of MVD, showed that five animals survived. Oral dosage had not demonstrated any medical efficacy.[48]

Therapeutic efficacy was observed when MARV-infected nonhuman primates were treated with remdesivir (GS-5734). 83% of the Cynomolgus macaques treated with remdesivir with a loading dosage of 10 mg/kg, and 50% of the 5 mg/kg survived. Compared to vehicle-control mice, animals treated with remdesivir showed improved clinical ratings, a decreased viral RNA load, and enhanced renal, hepatic, and coagulopathy function indicators. Remdesivir is a prodrug of an adenosine analogue, a widely used broad-spectrum antiviral drug. Profound efficacy of antiviral activity against respiratory syncytial virus, SARS-CoV, MERS-CoV, and other coronaviruses, as well as paramyxoviruses. The drug is currently in use for EVD in NHPs. Treatment with Remdesivir (OD, 5 mg or 10 mg for 12 days) showed improved health in MVD-exposed Cynomolgus macaques 4-5 days after treatment. Survival rates with double doses are promising: 50% and 83%.[49] Jacobs et al. reported that an MVD-infected nurse treated with remdesivir had convalesced. However, the patient suffered from meningoencephalitis.[50] The viral load was higher in cerebrospinal fluid (CSF) than in blood, and a high dose of steroid therapy reduced the virus load to undetectable levels. A preterm baby delivered by an Ebola-infected pregnant lady also received remdesivir. The baby received ZMapp (a cocktail of monoclonal antibodies) along with leukocytes and survived the treatment.[51] Treating MVD-affected macaques with a combination of MR186-YTE and remdesivir starting at 6 days post-infection (dpi) protected them significantly (80%), which extended the therapeutic window.[52]

Treatment for the children

Healthcare professionals or paediatricians should provide supportive care and volume resuscitation for afflicted children. In the West Africa Ebola outbreak from 2014 to 2016, robust parenteral fluid resuscitation and widespread use of oral rehydration solutions were encouraged, which can be followed in the present outbreak.

Particularly for "wet" individuals with complications such as active vomiting or diarrhoea, intravenous fluid delivery is more desirable. Children who cannot tolerate an intravenous route might be prioritised for intra-osseous and subcutaneous routes. Using pre-packaged or readily available therapeutic food and treating undernourished children in accordance with malnutrition guidelines should be a top priority. Clinical expertise and scant evidence-based guidelines serve as the foundation for treatment recommendations.[53]

Conclusion

Recent outbreaks have demonstrated that MARV can cause far more severe outbreaks than previously believed. These major outbreaks exhibited extremely high fatality rates within a broader geographic area and posed significant clinical hurdles. The extensive research carried out in this work provides insight into the intricate genetic makeup, replication of MV, clinical manifestations, diagnosis, and treatment strategies. Our understanding of the MARV pathophysiology and treatment strategies relies substantially on early case reports and analogies to EBOV. The primary approach to managing MVD is to use early and proactive supportive care measures, such as oral or intravenous fluid administration, rehydration, and treatment of specific symptoms. Fluid resuscitation is mandatory when a substantial loss of gastrointestinal volume is observed, and close monitoring is vital. Antibody treatments show great potential for preventing, treating, and providing therapeutic treatment for MVD. Anti-viral therapies with mAbs, FVM04, and CA45 protect NHPs. Galidesivir, Favipiravir and Remdesivir results are promising for MVD treatment. The therapeutic options would significantly improve future MHF outbreaks and infections. The insights from previous epidemics highlight the significance of readiness, cooperation, and ingenuity in tackling this recurrent threat. By implementing coordinated endeavours, we can anticipate preventing future MV outbreaks and reducing their impact on human lives.

Abbreviations:

Cerebrospinal fluid (CSF),

Cholesterol transporter Niemann-Pick C1 (NPC1)

Coat protein complex II (COPII),

dendritic cell-specific ICAM-grabbing non-integrin (DC-SIGN),

Ebola virus – Sudan virus (SUDV),

Ebola virus (EBOV),

Ebola Virus Disease (EVD),

Endosomal sorting complex required for transport (ESCRT),

Enzyme-Linked Immunosorbent Assay (ELISA)

Glycoprotein (GP),

Human macrophage galactose-type lectin (hMGL),

Immunoglobulin G (IgG),

Interferon (IFN),

Liver sinusoidal endothelial cell lectin (LSECtin),

Marburg hemorrhagic fever (MHF),

Marburg virus (MARV),

Marburg virus disease (MVD),

Monoclonal antibodies (mAbs),

Nonhuman primates (NHPs),

Nonsegmented negative-sense (NNS),

Nucleoprotein (NP),

Open reading frames (ORFs),

Phosphate buffered saline (PBS),

Ravn virus (RAVV),

RNA-dependent RNA polymerase (RdRp),

Virion protein 35 (VP35)

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References

1. Kuhn JH, Adachi T, Adhikari NKJ, Arribas JR, Bah IE, Bausch DG, et al. New filovirus disease classification and nomenclature. Nat Rev Microbiol. 2019 May;17(5):261-3.
https://doi.org/10.1038/s41579-019-0187-4
PMid:30926957 PMCid:PMC6637750

2. Marburg (Marburg Virus Disease) | Marburg (Marburg Virus Disease) | CDC [Internet]. 2023 [cited 2024 July 31]. Available from: https://www.cdc.gov/vhf/marburg/index.html

3. Bharat TAM, Riches JD, Kolesnikova L, Welsch S, Krähling V, Davey N, et al. Cryo-Electron Tomography of Marburg Virus Particles and Their Morphogenesis within Infected Cells. Rey FA, editor. PLoS Biol. 2011 Nov 15;9(11):e1001196.
https://doi.org/10.1371/journal.pbio.1001196
PMid:22110401 PMCid:PMC3217011

4. Geisbert TW, Jahrling PB. Differentiation of filoviruses by electron microscopy. Virus Res. 1995 Dec;39(2-3):129-50.
https://doi.org/10.1016/0168-1702(95)00080-1
PMid:8837880

5. Ryabchikova E, Price BBS. Ebola and Marburg Viruses: A View of Infection Using Electron Microscopy. 1st edition. Battelle Press; 2002. 211 p.

6. Feldmann H, Mühlberger E, Randolf A, Will C, Kiley MP, Sanchez A, et al. Marburg virus, a filovirus: méssenger RNAs, gene order, and regulatory elements of the replication cycle. Virus Res. 1992 Jun;24(1):1-19.
https://doi.org/10.1016/0168-1702(92)90027-7
PMid:1626422

7. Sanchez A, Kiley MP, Klenk HD, Feldmann H. Sequence analysis of the Marburg virus nucleoprotein gene: comparison to Ebola virus and other non-segmented negative-strand RNA viruses. J Gen Virol. 1992 Feb 1;73(2):347-57.
https://doi.org/10.1099/0022-1317-73-2-347
PMid:1538192

8. Becker S, Spiess M, Klenk HD. The asialoglycoprotein receptor is a potential liver-specific receptor for Marburg virus. J Gen Virol. 1995 Feb 1;76(2):393-9.
https://doi.org/10.1099/0022-1317-76-2-393
PMid:7844558

9. Olejnik J, Mühlberger E, Hume AJ. Recent advances in marburgvirus research. F1000Research. 2019 May 21;8:704.
https://doi.org/10.12688/f1000research.17573.1
PMid:31131088 PMCid:PMC6530603

10. Gordon TB, Hayward JA, Marsh GA, Baker ML, Tachedjian G. Host and Viral Proteins Modulating Ebola and Marburg Virus Egress. Viruses. 2019 Jan 3;11(1):25.
https://doi.org/10.3390/v11010025
PMid:30609802 PMCid:PMC6357148

11. Messaoudi I, Amarasinghe GK, Basler CF. Filovirus pathogenesis and immune evasion: insights from Ebola virus and Marburg virus. Nat Rev Microbiol. 2015 Nov;13(11):663-76.
https://doi.org/10.1038/nrmicro3524
PMid:26439085 PMCid:PMC5201123

12. Valmas C, Basler CF. Marburg Virus VP40 Antagonizes Interferon Signaling in a Species-Specific Manner. J Virol. 2011 May;85(9):4309-17.
https://doi.org/10.1128/JVI.02575-10
PMid:21325424 PMCid:PMC3126248

13. Valmas C, Grosch MN, Schümann M, Olejnik J, Martinez O, Best SM, et al. Marburg Virus Evades Interferon Responses by a Mechanism Distinct from Ebola Virus. Kawaoka Y, editor. PLoS Pathog. 2010 Jan 15;6(1):e1000721.
https://doi.org/10.1371/journal.ppat.1000721
PMid:20084112 PMCid:PMC2799553

14. Kolesnikova L, Berghöfer B, Bamberg S, Becker S. Multivesicular Bodies as a Platform for Formation of the Marburg Virus Envelope. J Virol. 2004 Nov 15;78(22):12277-87.
https://doi.org/10.1128/JVI.78.22.12277-12287.2004
PMid:15507615 PMCid:PMC525088

15. Mühlberger E, Trommer S, Funke C, Volchkov V, Klenk HD, Becker S. Termini of All mRNA Species of Marburg Virus: Sequence and Secondary Structure. Virology. 1996 Sep;223(2):376-80.
https://doi.org/10.1006/viro.1996.0490
PMid:8806574

16. Carette JE, Raaben M, Wong AC, Herbert AS, Obernosterer G, Mulherkar N, et al. Ebola virus entry requires the cholesterol transporter Niemann-Pick C1. Nature. 2011 Sep 15;477(7364):340-3.
https://doi.org/10.1038/nature10348
PMid:21866103 PMCid:PMC3175325

17. Brauburger K, Hume AJ, Mühlberger E, Olejnik J. Forty-Five Years of Marburg Virus Research. Viruses. 2012 Oct 1;4(10):1878-927.
https://doi.org/10.3390/v4101878
PMid:23202446 PMCid:PMC3497034

18. Matsuno K, Kishida N, Usami K, Igarashi M, Yoshida R, Nakayama E, et al. Different Potential of C-Type Lectin-Mediated Entry between Marburg Virus Strains. J Virol. 2010 May 15;84(10):5140-7.
https://doi.org/10.1128/JVI.02021-09
PMid:20219911 PMCid:PMC2863822

19. Gramberg T, Hofmann H, Möller P, Lalor PF, Marzi A, Geier M, et al. LSECtin interacts with filovirus glycoproteins and the spike protein of SARS coronavirus. Virology. 2005 Sep;340(2):224-36.
https://doi.org/10.1016/j.virol.2005.06.026
PMid:16051304 PMCid:PMC7111772

20. Hunt CL, Kolokoltsov AA, Davey RA, Maury W. The Tyro3 Receptor Kinase Axl Enhances Macropinocytosis of Zaire Ebolavirus. J Virol. 2011 Jan;85(1):334-47.
https://doi.org/10.1128/JVI.01278-09
PMid:21047970 PMCid:PMC3014168

21. Misasi J, Chandran K, Yang JY, Considine B, Filone CM, Côté M, et al. Filoviruses Require Endosomal Cysteine Proteases for Entry but Exhibit Distinct Protease Preferences. J Virol. 2012 Mar 15;86(6):3284-92.
https://doi.org/10.1128/JVI.06346-11
PMid:22238307 PMCid:PMC3302294

22. Whelan SP, Barr JN, Wertz GW. Transcription and replication of nonsegmented negative-strand RNA viruses. Curr Top Microbiol Immunol. 2004;283:61-119.
https://doi.org/10.1007/978-3-662-06099-5_3
PMid:15298168

23. Martini GA. Marburg Virus Disease. Clinical Syndrome. In: Martini GA, Siegert R, editors. Marburg Virus Disease [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 1971 [cited 2024 Feb 2]. p. 1-9. Available from: http://link.springer.com/10.1007/978-3-662-01593-3_1
https://doi.org/10.1007/978-3-662-01593-3_1

24. Bausch DG, Nichol ST, Muyembe-Tamfum JJ, Borchert M, Rollin PE, Sleurs H, et al. Marburg Hemorrhagic Fever Associated with Multiple Genetic Lineages of Virus. N Engl J Med. 2006 Aug 31;355(9):909-19.
https://doi.org/10.1056/NEJMoa051465
PMid:16943403

25. Slenczka WG. The Marburg virus outbreak of 1967 and subsequent episodes. Curr Top Microbiol Immunol.
https://doi.org/10.1007/978-3-642-59949-1_4
PMid:9893378

26. Martini GA, Knauff HG, Schmidt HA, Mayer G, Baltzer G. Über eine bisher unbekannte, von Affen eingeschleppte Infektionskrankheit: Marburg-Virus-Krankheit. DMW - Dtsch Med Wochenschr. 1968 Mar;93(12):559-71.
https://doi.org/10.1055/s-0028-1105098
PMid:4966280

27. Gear JS, Cassel GA, Gear AJ, Trappler B, Clausen L, Meyers AM, et al. Outbreake of Marburg virus disease in Johannesburg. BMJ. 1975 Nov 29;4(5995):489-93.
https://doi.org/10.1136/bmj.4.5995.489
PMid:811315 PMCid:PMC1675587

28. Mehedi M, Groseth A, Feldmann H, Ebihara H. Clinical aspects of Marburg hemorrhagic fever. Future Virol. 2011 Sep;6(9):1091-106.
https://doi.org/10.2217/fvl.11.79
PMid:22046196 PMCid:PMC3201746

29. Shifflett K, Marzi A. Marburg virus pathogenesis - differences and similarities in humans and animal models. Virol J. 2019 Dec;16(1):165.
https://doi.org/10.1186/s12985-019-1272-z
PMid:31888676 PMCid:PMC6937685

30. Borchert M, Muyembe-Tamfum JJ, Colebunders R, Libande M, Sabue M, Van Der Stuyft P. Short communication: A cluster

of Marburg virus disease involving an infant*. Trop Med Int Health. 2002 Oct;7(10):902-6.
https://doi.org/10.1046/j.1365-3156.2002.00945.x
PMid:12358627

31. Grolla A, Lucht A, Dick D, Strong JE, Feldmann H. Laboratory diagnosis of Ebola and Marburg hemorrhagic fever. Bull Soc Pathol Exot 1990. 2005 Sep;98(3):205-9.

32. Rowe AK, Bertolli J, Khan AS, Mukunu R, Muyembe-Tamfum JJ, Bressler D, et al. Clinical, Virologic, and Immunologic Follow-Up of Convalescent Ebola Hemorrhagic Fever Patients and Their Household Contacts, Kikwit, Democratic Republic of the Congo. J Infect Dis. 1999 Feb;179(s1):S28-35.
https://doi.org/10.1086/514318
PMid:9988162

33. Ksiazek TG, Rollin PE, Williams AJ, Bressler DS, Martin ML, Swanepoel R, et al. Clinical Virology of Ebola Hemorrhagic Fever (EHF): Virus, Virus Antigen, and IgG and IgM Antibody Findings among EHF Patients in Kikwit, Democratic Republic of the Congo, 1995. J Infect Dis. 1999 Feb;179(s1):S177-87.
https://doi.org/10.1086/514321
PMid:9988182

34. Ogawa H, Miyamoto H, Ebihara H, Ito K, Morikawa S, Feldmann H, et al. Detection of all known filovirus species by reverse transcription-polymerase chain reaction using a primer set specific for the viral nucleoprotein gene. J Virol Methods. 2011 Jan;171(1):310-3.
https://doi.org/10.1016/j.jviromet.2010.11.010
PMid:21093485 PMCid:PMC3393132

35. Saijo M, Georges-Courbot MC, Fukushi S, Mizutani T, Philippe M, Georges AJ, et al. Marburgvirus Nucleoprotein-Capture Enzyme-Linked Immunosorbent Assay Using Monoclonal Antibodies to Recombinant Nucleoprotein: Detection of Authentic Marburgvirus. Jpn J Infect Dis. 2006 Oct 28;59(5):323-5.
https://doi.org/10.7883/yoken.JJID.2006.323
PMid:17060700

36. Kortepeter MG, Bausch DG, Bray M. Basic Clinical and Laboratory Features of Filoviral Hemorrhagic Fever. J Infect Dis. 2011 Nov;204(suppl_3):S810-6.
https://doi.org/10.1093/infdis/jir299
PMid:21987756

37. Clark DV, Jahrling PB, Lawler JV. Clinical Management of Filovirus-Infected Patients. Viruses. 2012 Sep 20;4(9):1668-86.
https://doi.org/10.3390/v4091668
PMid:23170178 PMCid:PMC3499825

38. Bebell LM, Riley LE. Ebola Virus Disease and Marburg Disease in Pregnancy: A Review and Management Considerations for Filovirus Infection. Obstet Gynecol. 2015 Jun;125(6):1293-8.
https://doi.org/10.1097/AOG.0000000000000853
PMid:26000499 PMCid:PMC4443859

39. Fowler RA, Fletcher T, Fischer WA, Lamontagne F, Jacob S, Brett-Major D, et al. Caring for Critically Ill Patients with Ebola Virus Disease. Perspectives from West Africa. Am J Respir Crit Care Med. 2014 Oct 1;190(7):733-7.
https://doi.org/10.1164/rccm.201408-1514CP
PMid:25166884

40. Uyeki TM, Mehta AK, Davey RT, Liddell AM, Wolf T, Vetter P, et al. Clinical Management of Ebola Virus Disease in the United States and Europe. N Engl J Med. 2016 Feb 18;374(7):636-46.
https://doi.org/10.1056/NEJMoa1504874
PMid:26886522 PMCid:PMC4972324

41. King LB, Fusco ML, Flyak AI, Ilinykh PA, Huang K, Gunn B, et al. The Marburgvirus-Neutralizing Human Monoclonal Antibody MR191 Targets a Conserved Site to Block Virus Receptor Binding. Cell Host Microbe. 2018 Jan;23(1):101-109.e4.
https://doi.org/10.1016/j.chom.2017.12.003
PMid:29324225 PMCid:PMC5772738

42. Smith LM, Hensley LE, Geisbert TW, Johnson J, Stossel A, Honko A, et al. Interferon-β Therapy Prolongs Survival in Rhesus Macaque Models of Ebola and Marburg Hemorrhagic Fever. J Infect Dis. 2013 Jul 15;208(2):310-8.
https://doi.org/10.1093/infdis/jis921
PMid:23255566 PMCid:PMC3685222

43. Dye JM, Herbert AS, Kuehne AI, Barth JF, Muhammad MA, Zak SE, et al. Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease. Proc Natl Acad Sci. 2012 Mar 27;109(13):5034-9.
https://doi.org/10.1073/pnas.1200409109
PMid:22411795 PMCid:PMC3323977

44. Smith DH, Isaacson M, Johnson KM, Bagshawe A, Johnson BK, Swanapoel R, et al. MARBURG-VIRUS DISEASE IN KENYA. The Lancet. 1982 Apr;319(8276):816-20.
https://doi.org/10.1016/S0140-6736(82)91871-2
PMid:6122054

45. Bray M, Raymond JL, Geisbert T, Baker RO. 3-Deazaneplanocin A induces massively increased interferon-α production in Ebola virus-infected mice. Antiviral Res. 2002 Jul;55(1):151-9.
https://doi.org/10.1016/S0166-3542(02)00018-9
PMid:12076759

46. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. Lipsitch M, editor. PLOS Med. 2016 Mar 1;13(3):e1001967.
https://doi.org/10.1371/journal.pmed.1002066
PMid:27284977 PMCid:PMC4902188

47. Laboratory Findings, Compassionate Use of Favipiravir, and Outcome in Patients With Ebola Virus Disease, Guinea, 2015-A Retrospective Observational Study | The Journal of Infectious Diseases | Oxford Academic [Internet]. [cited 2024 July 31]. Available from: https://academic.oup.com/jid/article/220/2/195/5350975

48. Bixler SL, Bocan TM, Wells J, Wetzel KS, Van Tongeren SA, Dong L, et al. Efficacy of favipiravir (T-705) in nonhuman primates infected with Ebola virus or Marburg virus. Antiviral Res. 2018 Mar;151:97-104.
https://doi.org/10.1016/j.antiviral.2017.12.021
PMid:29289666

49. Porter DP, Weidner JM, Gomba L, Bannister R, Blair C, Jordan R, et al. Remdesivir (GS-5734) Is Efficacious in Cynomolgus Macaques Infected With Marburg Virus. J Infect Dis. 2020 Nov 9;222(11):1894-901.
https://doi.org/10.1093/infdis/jiaa290
PMid:32479636

50. Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. The Lancet. 2016 Jul 30;388(10043):498-503.
https://doi.org/10.1016/S0140-6736(16)30386-5
PMid:27209148

51. Dörnemann J, Burzio C, Ronsse A, Sprecher A, De Clerck H, Van Herp M, et al. First Newborn Baby to Receive Experimental Therapies Survives Ebola Virus Disease. J Infect Dis. 2017 Jan 9;jiw493.
https://doi.org/10.1093/infdis/jiw493
PMid:28073857 PMCid:PMC5583641

52. Cross RW, Bornholdt ZA, Prasad AN, Borisevich V, Agans KN, Deer DJ, et al. Combination therapy protects macaques against advanced Marburg virus disease. Nat Commun. 2021 Mar 25;12(1):1891.
https://doi.org/10.1038/s41467-021-22132-0
PMid:33767178 PMCid:PMC7994808

53. Trehan I, Kelly T, Marsh RH, George PM, Callahan CW. Moving Towards a More Aggressive and Comprehensive Model of Care for Children with Ebola. J Pediatr. 2016 Mar;170:28-33.e7.
https://doi.org/10.1016/j.jpeds.2015.11.054
PMid:26778094