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EMERGING TRENDS OUTBREAKS OF NIPAH VIRUS AND FUTURE PERSPECTIVES

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Abstract

Nipah virus (NiV) is an RNA virus has the ability to cause pandemics due to its zoonotic nature and the ability to be transmitted between humans. NiV mostly affects the central nervous system (CNS) and respiratory system causing acute encephalitis and acute respiratory distress syndrome at a high case-fatality rate. In the early stages of the infection, NiV was found in the epidermal cells especially bronchioles and alveoli of the animal models. Epithelial cell infection provokes the release of cytokines and triggers the development of acute respiratory distress syndrome (ARDS). Favipiravir, which is an RNA polymerase inhibitor viral dependent, showed efficacy in hamster model against fatal NiV-MY infection when given face-to-face to hamsters over fourteen days. Modern studies have focused on new vaccine designs that use immunoinformatics and computational methods. Currently, very little has been done in this regard, monoclonal antibodies have been the farthest in preclinical trials, but antibody drug is sometimes expensive, and highly disease-specific. In addition to the growth in antibody therapeutic studies, more advances should focus on the creation of small-interfering RNAs, small-molecule drugs, repurposing of already approved drugs in the demonstration of Nipah virus efficacy, and, most significant, developing broad-spectrum antivirals.

Introduction

Nipah virus (NiV) is an RNA virus with a family of Paramyxoviridae. It falls under the genus Henipavirus that also contains Hendra virus (HeV) and more recently discovered Cedar virus. Natural reservoir of Henipaviruses is bats [1]. Though Cedar virus has not been shown to cause an infection in any given animal, NiV and HeV have been linked to fatal respiratory and or neurological infection [2]. NiV is one of the pathogens that are classified by the World Health Organization as of high priority of research and development because of its tendency of outbreak [3]. The first outbreak of the virus occurred in Malaysia in the year 1998 and it has since then resulted in various outbreaks in South and South East Asia. NiV is not only highly pathogenic in a great variety of mammalian hosts but also has the ability to cause pandemics due to its zoonotic nature and the ability to be transmitted between humans [4]. Pteropus bats, which are

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the hosts of the reservoirs, are distributed worldwide. Therefore, new geographic areas that are hosting such bats can be the areas of future spillover. This new risk is exemplified by a recent outbreak in a new geographic area, which is Kerala, India [5]. Small number of cases and difficulty in diagnosis have been a hindrance to research progress. Being a Biosafety Level 4 (BSL-4) pathogen, NiV places a strong limitation on laboratory accessibility in most of the countries. Aggressive research into its epidemiology, transmission pattern and possible preventive and control strategies is necessary.

NiV mostly affects the central nervous system (CNS) and respiratory system causing acute encephalitis and acute respiratory distress syndrome at a high case-fatality rate. An organized plan to improve patient treatment is still lacking, and the existing management can be limited to supportive therapy. It is important to enhance clinical management of victims of Nipah virus disease (NiVD) to achieve better results even in the current outbreak as well as to respond to a potential outbreak in the future [6,7].

The monoclonal antibodies and small-molecule antivirals are examples of potential candidates of NiVD that can be used in treatment currently undergoing the research and development pipeline. On animal models, there is evidence supporting human trials with m102.4, Hu1F5 and remdesivir, as monotherapy or a combination. Phase 1 safety data on m102.4 are based on an Australian trial but since the stronger Hu1F5 has shown greater efficacy in non-human primate models, m102.4 development is blocked as Hu1F5 passes to phase 1 clinical trials in the US. The future analysis of these new and reformed therapeutics will extensive clinical experiments to determine safety and efficacy [8, 9].

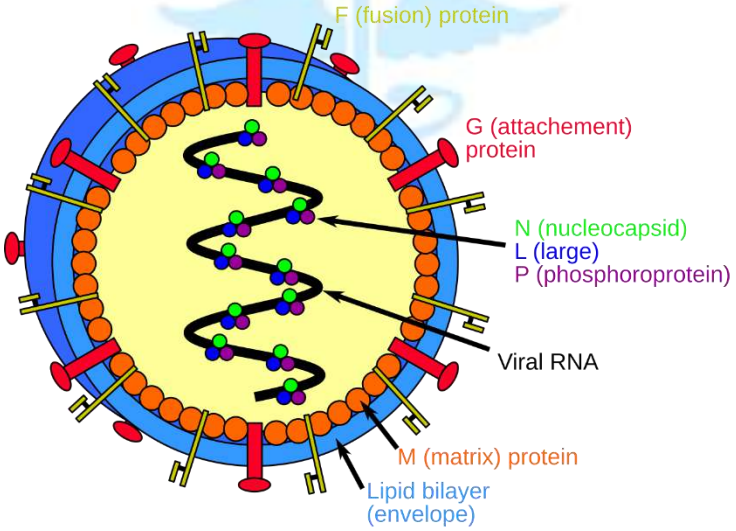

Figure 1. Shows the structural features of Nipah virus and biochemical aspects

Pathogenesis features

In the early stages of the infection, NiV was found in the epidermal cells especially bronchioles and alveoli of the animal models. Epithelial cell infection provokes the release of cytokines and triggers the development of acute respiratory distress syndrome (ARDS). In later phases of infection, further secretion of inflammatory mediators (interleukins and granulocyte colony stimulating factors) occurs [9,10]. Through the respiratory tract epithelium, NiV enters into the pulmonary epithelial cells. Later in the course of the disease, the virus spreads to the blood and affects various organ systems such as respiratory tract, gastrointestinal tract, urinary system, and CNS. Two main pathways of viral spread are hematogenous pathway and olfactory nerve. NiV breaks the blood-brain barrier (BBB) in the hematogenous route, which causes IL-1B and tumor necrosis factor signalling, which eventually causes translocation to the olfactory bulb via the cribriform plate [10, 11].

The viral attachment and entry into cells are controlled by the F and G glycoproteins that are integrated into the NiV envelope. The G protein receptor is ephrin -B2 (EFNB2) and ephrin -B3 (EFNB3) on epithelial cells and

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neurons respectively. The apex of the G protein globular head is interacted in seven consecutive residues that interact with the EFNB2 receptor [12, 13]. Engaging receptors reveals the stalk domain of the G protein, which causes the F protein in its pre-fusion form to change its conformation to a pre-hairpin intermediate, and then to a post-fusion form that is oriented towards membrane fusion. The existence of a KKR motif in the cytoplasmic tail of the F protein induces the pH-independent viral membrane fusion with the host cells, thus facilitating virion penetration. The F protein exists in the form of a precursor (F0), which then goes through the proteolytic maturation. The processing is probably catalysed by cathepsin L in Vero cells and cathepsin B in MDCK cells and results in the formation of disulfide-linked F1 and F2 subunits, which form a mature fusogenic F heterodimer. F 1 subunit is mainly involved in the fusion of the viral membrane with the host cellular membrane [14, 15].

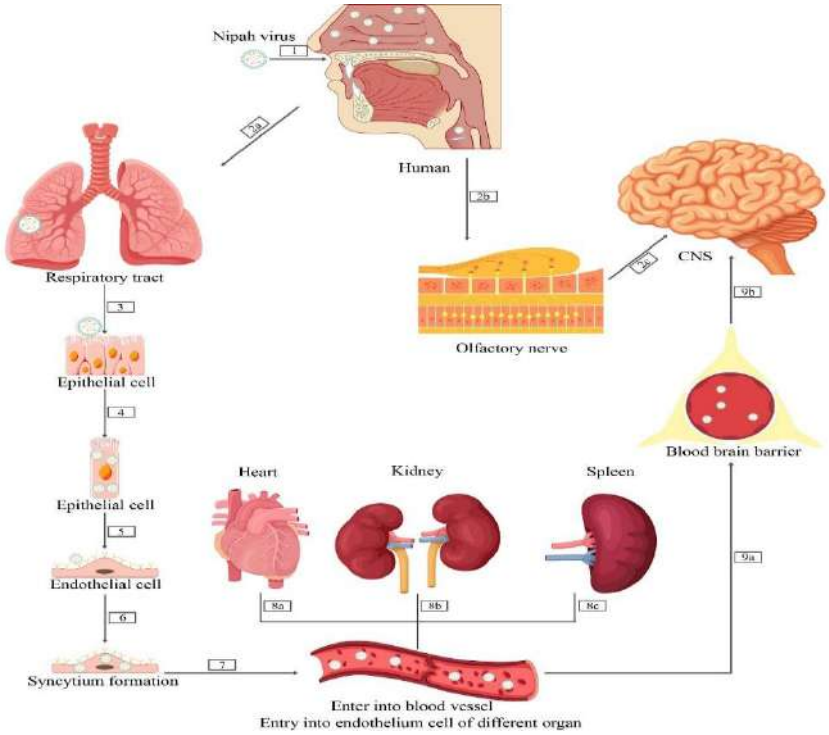

Figure 2. Shows the pathogenies features of Nipah virus and risk factors

Treatment and effective measures

An antiviral drug, T-705, known as favipiravir (FUJI), has been developed in Japan as an inhibitor of the Nipah virus (NiV) RNA polymerase, which is an RNA-dependent polymerase. Not only does it inhibit the replication of the viral genome and the release of the progeny virions in infected cells, but it also prevents the spread of the virus to the uninfected cells. A Syrian hamster model, when exposed to NiV twice per day orally or once per day subcutaneously, provided protection against a lethal NiV challenge when exposure was made fourteen days after treatment was reflected by the hamsters [16]. Since NiV was identified, outbreaks in Malaysia and Singapore were treated empirically using ribavirin. Ribavirin is a broad-spectrum antiviral agent with DNA and RNA virus susceptibility and has the ability to cross into the blood-brain barrier; It was found that mortality was reduced by 36 percent in an open-label trial involving 140 patients and 54 controls, but later studies using animal models, have failed to support its effectiveness [17,18].

The use of acyclovir (zovirax) was used alongside ceftriaxone to treat nine abattoir workers during the 1999 NiV outbreak in Singapore; 8 people survived the illness [18, 19]. NiV patients have not received any therapeutics besides a couple of antiviral compounds which have been tested. In a lethal

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challenge African green monkey model infected with NiV-BD, remdesivir experienced a 100 percent survival rate after daily intravenous doses of remdesivir started 24 hours post-infection and lasted twelve days. Favipiravir, which is an RNA polymerase inhibitor viral dependent, showed efficacy in hamster model against fatal NiV-MY infection when given face-to-face to hamsters over fourteen days. Additionally, Poly (I)-poly (C12U), a potent interferon inducer, had low efficacy in the case of NiV infection in vitro and in a hamster model. Soluble ephrin B2, which is an active receptor of NiV G glycoprotein, blocked the viral fusion in vitro [20,21]. The G protein of NiV m102.4 monoclonal antibody was found to be effective in an animal model and is currently undergoing phase-I human trials. Adverse events related to 86 treatments were reported; no significant difference between placebo and treated cohorts in incidence rates was observed, which implies that single and repeated administration of m102.4 is safe and well tolerated. The other new therapeutic agent is the cross-reactive humanized monoclonal antibody h5B3.1, which is a target to the NiV F protein. The antibody had a potential to protect ferals against NiV and Hendra virus (HeV) infections. Structural study through the NiV F glycoprotein in complex with mAb h5B3.1 has shown that the anti-membrane fusion effect was effectively inhibited by locking F glycoprotein in a pre-fusion conformation by the antibody in question. Antiviral activity of algae-derived griffithsin in vitro cell-culture studies has revealed antiviral activity against NiV at the nanomolar range of concentration levels [21,22].

Modern studies have focused on new vaccine designs that use immunoinformatics and computational methods. To develop strong immune response, a multi epitope vaccine against the NiV nucleoprotein was developed. The vaccine, which was derived using linkers and adjuvants, had a high antigenicity (0.56), was non-allergenic, and non-toxic. Docking studies indicated that it binds well to the ephrin B2 receptor (around -920kcal/mol), and immune simulations suggested high levels of IgG and IgM that was found to cover a large proportion of the global population (88.3 percent). Likewise, reverse vaccinology was used to examine the holome of the NiV proteome with the view to determining antigenic B -cell and T -cell epitopes. The vaccine candidate exhibited strong interactions with toll-like receptors TL-R2 and TL-R4 and computational immune-response modelling indicated that the vaccine caused a great deal of immune activation [23,24]. However, the two papers highlighted the need to carry out additional experiments before the clinical trials can begin. Such results indicate positive prospects in the NiV vaccine trials, but regulatory leniency and long-term investment are necessary to develop such candidates to the licensure stage [25, 26].

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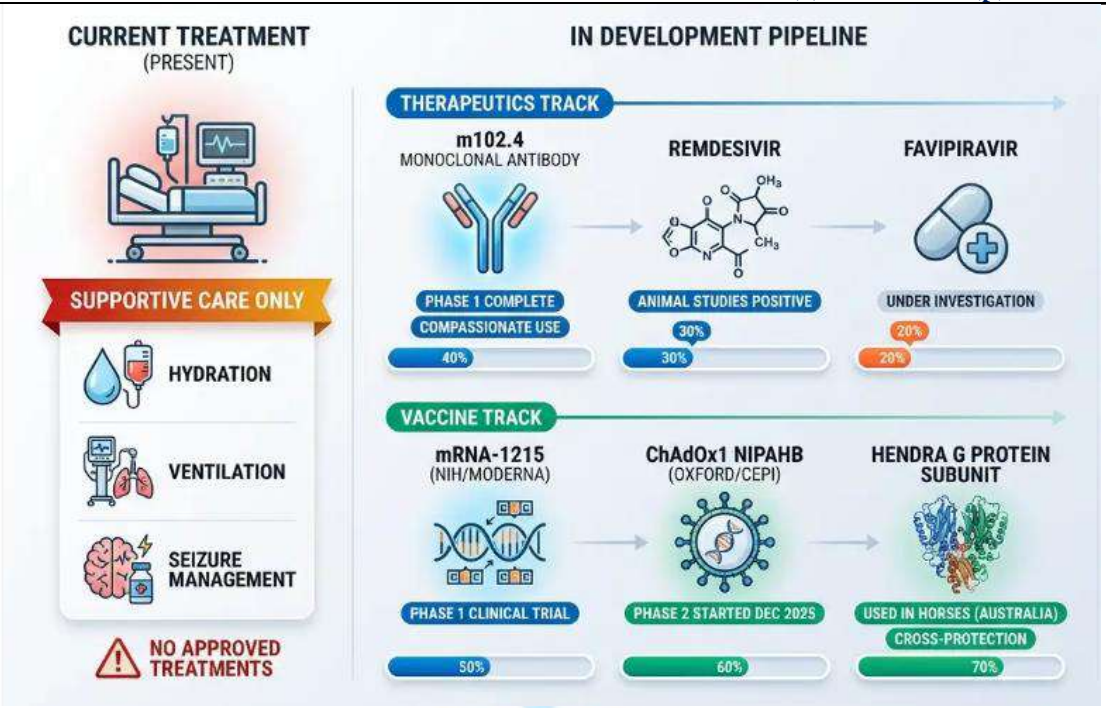

Figure 3. Shows the treatment of Nipah virus and prevention

There are no approved NiV vaccines or therapeutics, and as of 30 March 2025, there are vaccine candidates including ChAdOx1 Nipah B in clinical trials. The first in human trial of this vaccine is being undertaken in the University of Oxford and is enrolling 51 participants with the help of CEPI. NiV, which carries up to 75 per cent fatality rate, has caused outbreak in Southeast Asia, including Singapore, Malaysia, Bangladesh and India with the latest outbreak in Kerala in September 2023 [26, 27]. The infrequence of NiV outbreaks makes the traditional phase-III efficacy studies impractical; a study estimated that a cluster-randomized ring-vaccination trial in Bangladesh would take 516 years to finish in the present incidence levels. Other trial designs, such as controlled animal studies, surrogate immune markers, and other regulatory approval pathways have been put forward. The regulators like the US FDA, EMA, and the national regulators in Bangladesh and India ought to consider emergency pathways similar to those that were used during the Ebola outbreak in 2014-2016 that prove the effectiveness of investigational stockpiles and ring-vaccination experiments [28, 29]. Immuno surrogate endpoint-based vaccines against other diseases (e.g., influenza, smallpox, COVID-19) have been approved, and this same model can be used in NiV vaccine development. Given the possibility of increased transmissibility of NiV, WHO, CEPI, and NIAID sustain the vaccine research and development [30, 31].

Future and new emerging strategies.

Subunit and vectored systems are used in the present generation of vaccine candidates. The most developed are those that utilize a vesicular stomatitis virus virus in which they have proven to protect against hamsters, ferrets and African green monkeys. Human clinical trials of such vaccines are unlikely to be funded by the academic sector and the pharmaceutical industry has traditionally been shy to invest in the research and development of vaccines against low incidence diseases with a devastating pandemic potential even when a disease has a high pandemic potential. As CEPI moves vaccine candidates into clinical trials, the development of new therapeutics and targets is one field where academic science can play a critical role in the coming 10 years. Currently, very little has been done in this regard, monoclonal antibodies have been the farthest in preclinical trials, but antibody drug is sometimes expensive, and highly disease-specific. In addition to the growth in antibody therapeutic studies, more advances should focus on the creation of small-interfering

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RNAs, small-molecule drugs, repurposing of already approved drugs in the demonstration of Nipah virus efficacy, and, most significant, developing broad-spectrum antivirals. The ability to target host proteins or RNAs is associated with the benefit of complication of resistance emergence and high chances of attaining broad-spectrum antiviral efficacy, since these pathways are often used by various viral agents.

Conclusion

The outbreak of Nipah virus poses a great challenge to the population health; it is characterized by illusory conditions with serious clinical manifestations and an invincible threat in the form of outbreaks and single cases. Early identification, routine monitoring, and increased awareness of healthcare workers and ordinary citizens are critical towards the early identification and proper control. The research efforts should be continued in order to clarify the pathogenic processes of the virus, create effective diagnostic modalities, and explore possible treatment options. A coordinated global response is impossible without the international collaboration and open flow of information, and the strengthening of the population health system and proactive measures, such as vaccination campaigns, are all the essential aspects of a comprehensive approach towards the mitigation of risks. Whether it comes to colossal complexities of the new infectious diseases, continuous dedication to preparedness, scientific research, and collaboration will be the most significant step towards protecting the world health and avoiding the new crises in the future.

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