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REVIEW

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Nipah virus: a summary for clinicians

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Abstract

Objectives This article is one of a series on acute, severe diseases of humans caused by emerging viruses for which there are limited or no licensed medical countermeasures. Nipah virus (NiV) is recognized as a pathogen of concern by health experts and is included on the WHO list of emerging pathogens with pandemic concern. However, NiV is a relatively poorly understood pathogen, due to the small number of outbreaks and human clinical studies. The primary objective of this summary on NiV is to provide a global understanding of clinical perspectives, providing overviews of pathogenesis, clinical features, and diagnostics while emphasizing medical countermeasures. The focus is on potential therapies and vaccines that have demonstrated potential efficacy to combat NiV infection to provide clinicians candidates for use in an emergency situation or clinical research settings.

Methods A literature review was conducted for NiV vaccines and therapeutics tested in animal models of disease.

Results We identified two antiviral medications approved by the U.S. FDA with potential benefit for the off-label treatment of NiV infection, and a larger number of potential candidates are currently being evaluated in early development. Multiple vaccine platforms are in pre-clinical development for NiV prevention, but data from human clinical trials are not yet available.

Conclusion We provide specific background information on NiV and disease manifestations along with succinct summaries of medical countermeasures against NiV to provide clinicians a rapid reference to review the literature if faced with a patient in whom NiV infection is suspected. Moreover, the information provides several candidates for human clinical research studies in outbreak settings.

Introduction

Nipah virus (NiV), a paramyxovirus, is the causative agent of a highly lethal respiratory and neurologic disease with outbreaks centered in India, Bangladesh, and Southeast Asia. NiV has two recognized strains, defined by their initial outbreak location, NiV-Bangladesh (NiV-B) and NiV-Malaysia (NiV-M), respectively. In the past few decades, there have been intermittent outbreaks in these locations. Due to the small scale of outbreaks and rapid disease progression, clinical testing of vaccines and therapeutics has been limited for NiV. During the research for this review, we recognized multiple opportunities for future clinical research in laboratory, clinical, and outbreak settings. Recently, other reviews have been published which focus on epidemiology, transmission, and life-cycle of NiV [1]. Here, we focus on the information needs of clinicians in order to provide a rapid resource highlighting the clinical features of NiV infection,

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diagnostic testing, and medical countermeasures available for consideration in treating patients.

Methods

Using a standardized method, a literature review was conducted with a focus on recent updates in medical countermeasures from the last five years, although older studies were also included. Bibliography scans were also completed on review articles and meta-analysis publications. We focused on medical countermeasures against NiV with evidence from use in humans or non-human primates (NHPs).

This review is one in a series of planned articles on the management of severe diseases caused by emerging viruses, including Marburg, Crimean Congo hemorrhagic fever, Lassa fever, Nipah, and South American Hemorrhagic Fever viruses [2–4]. Viruses were selected by the members of the Clinical State of the Science Working Group of the Special Pathogens Research Network (SPRN) within the National Emerging Special Pathogen Training and Education Center (NETEC). The NETEC is funded by the Administration for Strategic Preparedness and Response (ASPR) and the Centers for Disease Control and Prevention (CDC) and aims to improve public health and healthcare systems in the United States to respond effectively to individuals infected with suspected or confirmed special pathogens. Criteria used to select the pathogens included the following: relative rarity of the diseases and severity of the illnesses they cause, their potential to cause large-scale outbreaks, the potential need for specialized infection control management based on their historic ability to cause nosocomial infection, and their paucity or lack of licensed medical countermeasures.

Following the publication of this article, updated information on the management of Nipah virus will be made available on the NETEC website: www.netec.org.

Epidemiology

The first recorded outbreak in humans occurred in 1998 in Malaysia as a severe encephalitis initially thought to be caused by Japanese encephalitis virus [5–7]. Epidemiologic investigation revealed that almost all cases had had close contact with pigs reported to have a respiratory illness, and virologic isolation revealed what is now referred to as NiV-M [5]. An associated smaller outbreak occurred in Singapore in abattoir workers where pigs from an infected area in Malaysia had been imported [6]. Contact with pigs or pig excreta were identified as risk factors, but human-to-human transmission was extremely rare [8]. Extensive culling of pig herds eventually brought the outbreak to an end [5]. Infection of pigs in the Malaysian outbreaks has been postulated to have occurred due to pig consumption of bat-contaminated mangoes from orchards in proximity to animal enclosures [9]. Subsequent outbreaks have almost exclusively occurred in India and Bangladesh, but were due to a different strain, now labelled NiV-B, and respiratory disease has been much more prominent [10, 11]. NiV-B has caused nearly annual outbreaks ranging from a few to over 60 cases. For NiV-B, transmission likely occurs through several pathways; contamination of date palm sap, which is consumed locally as a beverage, by the reservoir *Pteropus* bats appears to be common, and human-to-human transmission has been significant [12–16]. Although pigs have been found to be seropositive for NiV-B, contact with pigs has not been found to be a significant risk factor for this strain [8, 17]. A single outbreak has been described in the Philippines in 2014 and was associated with consumption of or contact with horses; this outbreak occurred after several deaths in horses associated with a neurologic syndrome had occurred in the area, and sequencing of the nucleoprotein was found to be identical to NiV-M [8, 18]. Bats of the family *Pteropodidae* were noted to be present in at least one of the villages affected. Unlike the Malaysia outbreaks, the pathway from reservoir bat species to horses in the Philippine outbreak has not been identified.

Clinical features

A number of reviews have been published describing clinical and pathological characteristics of NiV, but details are often lacking, especially for NiV-B, which has occurred in less resourced settings. Pathologic investigations are almost entirely of NiV-M patients.

Incubation period

The incubation period for NiV is generally quoted as being from 3 to 14 days [19, 20]. In the majority of cases, symptoms develop within 14 days following exposure with a mean incubation period of 8 days for NiV-M and 9.5 days for NiV-B [8, 10, 21–23]. Symptoms of NiV infection includes neurologic symptoms, discussed in Clinical spectrum of infection. There is a delay in presentation of neurologic symptoms that may be caused by virus incubation or persistence of infection ([22, 24, 25, 26]) One reported case occurred 11 years between reported exposure and symptomatic presentation [27]. This case may represent an initial asymptomatic infection followed by a recurrence of neurologic disease.

Pathogenesis

There are two distinct genotypes of NiV that have emerged in distinct geographic regions with the NiV-M strain in Malaysia, Singapore, and Philippines and the NiV-B strain in Bangladesh and India [28]. These two strains have an 8% variation in nucleotide sequence and which are proposed to account for differences in

clinical presentation and mortality (discussed in *Clinical Spectrum of Infection)* [11, 29, 30]. The cellular receptor for both strains of NiV is Ephrin B2 and Ephrin B3, molecules which are widely distributed throughout the body [31–33]. Ephrin B2 is expressed in endothelial and smooth muscle cells in arterial vessels, cortex and epithelial cells in the brain, lungs and bronchial epithelial cells, and cells of the placenta, spleen, and lymph nodes; Ephrin B3 is expressed on cells of the CNS including neurons and brain and spinal cord endothelial cells. NiV glycoprotein, G, binds to Ephrin B2 or Ephrin B3 and triggers a conformational change in the NiV fusion protein, F, bringing the cellular and viral membranes in close contact for fusion. Following membrane fusion, the ribonucleoprotein complex is released into the cytoplasm of the bound cell. Expression of the NiV F protein on the surface of infected cells can lead to the formation of syncytia, or multinucleated cells formed by cell-cell fusion.

Due to the widespread distribution of these entry receptors, NiV infection can occur in many sites and pathological changes can be seen in lymphoid tissue, endothelial cells, small arteries, and the brain. Primary cellular infection by NiV occurs in lymphoid tissues followed by systemic dissemination of the virus. Secondary cellular infection includes endothelial cells which leads to increased vascular permeability throughout the body. This increased permeability allows for viral infiltration of the brain and CNS, allowing for direct infection of CNS cells. The later stages of infection result in widespread vasculopathy marked by viral inclusions and syncytia formation affecting multiple organ systems, including the central nervous system (CNS) [21]. This vasculopathy can cause thrombosis and result in microinfarction and necrosis [21, 34–38]. Other cells noted to be infected by NiV include smooth muscle cells of blood vessels, neurons, and epithelial cells of the bronchiolar mucosa and renal tubules.

Following release of the ribonucleoprotein complex into the cytoplasm, the negative sense NiV genome is replicated by the viral polymerase, L, together with the phosphoprotein, P. Positive sense anti-genome is used by host ribosomes to generate additional viral proteins including L, P, the nucleoprotein, N, the matrix protein, M, and both glycoproteins, G and F. Additional proteins, C, V, and W, are also produced to modulate the immune response [39–41]. These proteins are encoded by the P open reading frame with V and W produced after polymerase stuttering at a co-transcriptional gene editing site resulting in a frame shift, and C produced using an alternative gene start codon [42, 43]. These immune modulating proteins block the ability of the host cell to detect foreign RNA by binding to the retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) RIG-I, melanoma differentiation-associated protein 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) as well as signal transducer and activator of transcription (STAT)-1 and −2 [44–50]. This in turn results in an inability to properly signal or respond through the interferon (IFN) pathway.

Clinical spectrum of infection

Clinical manifestations of NiV infection can range from asymptomatic or subclinical (estimated 8–15% of cases), to mild or severe cases [51–53]. After an average of 3–14 days, patients present with a non-specific flu-like illness that can resemble other common infectious diseases. These initial symptoms include fever, myalgia, vomiting, and malaise and can also include headache or altered mental status [10, 21–23]. As the infection spreads, the disease progresses rapidly to include encephalitis and CNS involvement such as areflexia, seizures, and coma [38, 54]. The time from fever onset to recovery or death is approximately 2 weeks.

Neurological symptoms and encephalitis are prominent features of severe NiV disease, regardless of strain [21–23]. A review of cases in Malaysia, for which neurologic disease was by far the most common presentation, indicated 92% presented within that time frame, but others presented later, up to 2 months after last contact (with pigs) [22]. In Bangladesh outbreaks, the incubation period has been reported as 3–14 days [24], and late onset neurologic disease after non-neurologic disease has not been clearly identified [55]. Onset of disease after 14 days is generally in the form of neurologic disease only and may be attributable to persistence of the virus in the brain [25]. Late onset neurologic disease, defined as neurologic diseases occurring greater than 10 weeks after initial infection, was identified in 4% of patients without acute neurologic disease in Malaysia, and relapsing disease in 9% of those with previous encephalitis [26]. No predictive factors for late onset or relapsing neurologic disease have been described. While it is unclear why some cases take weeks to months to develop, factors which increase the likelihood of secondary transmission include extended exposure to a case patient, case patient being male, case patient having difficulty breathing, and case patient succumbing to infection [24].

Brain abnormalities visualized via magnetic resonance imaging (MRI) exhibited confluent or multifocal discrete lesions in the cortex, white matter, and brainstem, and the presence of leptomeningeal enhancement [53, 56–60]. Further defining the delayed onset of neurological disease in the clinical spectrum, there have been documented cases where weeks to months after initial illness, neurological signs manifested include areflexia, coma, abnormal pupils, segmental myoclonus, meningism, seizures, nystagmus, cerebellar ataxia, bilateral ptosis, bilateral postural tremor, dysarthria, and focal cortical signs.

It is unclear whether this is due to inflammatory damage caused by the acute illness or persistent viral infection. Relapse of neurological disease has been observed in survivors. Relapse of neurological symptoms could occur between weeks and months post-convalescence. Currently, it is unknown what factors lead to delayed-onset or relapse of neurological disease. In a survey of survivors from the 1998 outbreak in Malaysia, there were 12 individuals with relapsed encephalitis and 10 patients with late-onset encephalitis in the 2 years since the outbreak, with a mean onset period of 8.4 months after infection [53]. Episodes lasted an average of 3.1 days before patients sought care and improvement was typically seen after 3 weeks. In two cases, the symptoms progressed for months.

While neurological disease is common to both NiV-M and NiV-B, respiratory symptoms are much more common in human cases of NiV-B infection [10, 61–63]. In an outbreak of NiV-B in Kerala, India, 83% of patients had respiratory involvement defined by shortness of breath or more significant acute respiratory distress syndrome (ARDS) [63]. In outbreak investigations, patients with respiratory involvement were more likely to transmit virus to secondary contacts.

In a non-human primate model of disease, the more involved respiratory component is also seen for NiV-B compared to NiV-M. While lungs from animals infected with either strain showed congestion, excess fluid in the pleural cavity, and multifocal areas of hemorrhage, animals infected with NiV-B had more engorged lung lobes with rounded edges [64]. As demonstrated in the a direct comparison of the two strains in a the African green monkey model of disease, NiV-B infection results in a much more pronounced respiratory disease than NiV-M [64]. In this model, interstitial pneumonia, edema, and hemorrhaging were more prominent in fatal cases NiV-B than NiV-M, as was the amount of NiV antigen found in lung tissue. In addition, the spleens of fatal NiV-B animals showed lymphoid depletion, near complete absence of white pulp, hemorrhaging, and the presence of syncytia. This is in stark contrast to NiV-M infected animals whose spleens were left mostly unchanged. As with the lungs, NiV-B infected animals had more NiV antigen than NiV-M infected animals in both the spleen and kidneys.

Sequelae

Long-term neurologic sequalae resulting from infections of either strain of NiV have been documented up to 2 years after resolution of acute illness, including fatigue, headache, and focal neurological deficits [52, 53]. Examination of a cohort from the 1998–1999 Malaysian NiV-M outbreak indicated that 7.5% of patients who experienced encephalitis during the acute phase and survived went on to experience at least one recurrent neurological episode of encephalitis [51, 53]. In addition, of those who had either an asymptomatic infection or were not diagnosed with encephalitis during the acute phase of fever and symptoms, 3.4% went on to develop symptoms consistent with encephalitis within 8 months of potential infection [53]. One study showed that NiV persisted in the brains of two non-human primates who survived the acute infection. These animals were euthanized at the study endpoint of 32 days so it is unclear if neurological symptoms would have been observed at a later point or how long it would take to clear the virus [65]. Autopsies of fatal cases from the Malaysian outbreak demonstrate the presence of NiV antigen in the CNS during the acute phase. One survivor of the acute phase, who relapsed a few months later and died, also had NiV antigen in the CNS [21]. Further, long-term neurological sequelae, including disabling fatigue, ataxia, myoclonus, and cranial nerve palsies can occur [55] Pediatric survivors were observed to have varied neuropsychiatric and behavioral changes, including violent outbursts, bedwetting, and nightmares [27, 52, 53, 66, 67].

Mortality risk factors

Depending on the outbreak, the case fatality rates (CFR) can vary from 9 to 100% [6, 68, 69], with higher mortality reported in settings where higher level of intensive care, including external ventilation, or supportive treatment was not available [61]. There have been observed differences in CFR between NiV-B and NiV-M strains with NiV-B exhibiting higher mortality [7, 70]. It was observed that NiV-B exhibited a CFR of 75% where NiV-M had a CFR of 40–50% [7, 18, 70]. A meta-analysis of published case series describing outbreaks suggested an overall CFR of 61% [12]. Risk factors for mortality include increasing age (> 45 years), seizures, segmental myoclonus, areflexia, elevated transaminases, and lower platelet counts compared to standard levels at admission [23, 71]. Interestingly, there was no correlation between abnormal cerebral spinal fluid (CSF) findings, including elevated white cell counts or protein levels, and severity of disease [23]. In a 2018 outbreak in Kerala, India, 19 of 23 patients had developed ARDS and encephalitis and 18 of those died [63]. Scarcity of supportive care such as external ventilation in areas where NiV-B occurs may contribute to increased mortality given the propensity for more severe respiratory disease.

Pathology

A study of clinical and autopsy findings was performed for 32 patients who died of NiV-M during the Malaysia outbreak [21]. Patients were 13 to 75 years of age, and there was a 29:3 male to female ratio. Macroscopic changes were infrequently observed except for occasional

small areas of necrosis in CNS tissue. On the microscopic level, small-vessel vasculitis occurred in the CNS, lung, heart, and kidneys. and was characterized by endothelial destruction and mural necrosis, often fibrinoid. Thrombosis was additionally seen in both inflamed and non-inflamed vessels. Syncytial or multinucleated giant endothelial cells were seen in multiple organs, including brain, lungs, and kidneys [21]. In the CNS, the previously described vascular involvement of both gray and white matter was seen throughout, including the spinal cord in some cases. Neural parenchymal inflammation was found in 67% of cases. Lungs were found to have vasculitis. Further, lungs exhibited evidence of alveolar hemorrhage, pulmonary edema, and aspiration pneumonia. Spleen and lymph nodes showed acute necrotizing inflammation and occasional hemophagocytosis in the absence of vasculitis. In the kidneys, 34% of cases showed focal glomerular fibrinoid necrosis and vasculitis was noted in a similar proportion of hearts. Other tissues did not show significant pathology.

Diagnostic testing

To diagnose NiV infection, a clinician should perform multiple steps to differentiate from other infectious diseases that present with fever. Along with physical features like fever and ARDS (described above), other information should be gathered to confirm diagnosis.

Standard patient evaluation can help identify NiV infection. The history of the patient should identify risks such as residing in or traveling to areas where NiV outbreaks are ongoing, or the virus is endemic. Further, understanding other risk activities should be noted, including ingesting date palm sap and associating with pigs or other livestock. Common clinical testing, including common hematologic analysis, can begin to point to NiV infection by recognizing anomalies described above, including thrombocytopenia, leukopenia, and increased liver enzymes.

Clinical testing for NiV infection diagnosis can be performed by multiple analytic processes, including viral culture, reverse transcription polymerase chain reaction (RT-PCR), serology, and immunohistochemistry. Samples collected for diagnosis include blood, nasal and throat swabs, urine, and CSF, if available, from suspected cases or organ tissue collected during autopsy following a fatal outcome [72]. Due to the high mortality associated with NiV infection, clinicians should be aware that all infectious clinical sample or laboratory isolate handling and processing should be performed under high biocontainment precautions, preferably biosafety level (BSL)-4. However, following inactivation of the virus, diagnostic testing can be performed at BSL-2.

RT-PCR

RT-PCR has become the gold-standard for detecting NiV due to the sensitivity and ease of performing the assay. It can be performed to detect viral RNA in multiple patient sample types, including blood, throat swabs, urine, and CSF [73, 74]. Multiple NiV RT-PCR kits are commercially available and RT-PCR is most effective when employed during viremia. It is highly sensitive, detecting from 10^3 to 10^4 genome copies/mL, which is well-within the levels during NIV infection of an individual presenting with symptoms [75, 76]. It should be noted that false negatives can occur due to mismatches between kit reagents and circulating virus sequences. Therefore, if clinical presentation suggests NiV infection and PCR results are negative, secondary testing should be conducted.

Serologic testing

Antibodies are produced against NiV in almost every case. Blood product samples can be analyzed for the presence of anti-NiV antibody through interaction with purified NiV antigens in commonly used enzyme-linked immunosorbent assays (ELISA). ELISA testing can detect IgM antibodies in the first week after symptom onset and peak at 9 days. IgM antibodies can persist for 3 months after illness onset. IgG antibodies can be detected after the second week of illness. Antibodies can persists for over 8 months [77]. However, it is important to note that strain variability with minor variants may lead to poor recognition of standardized antigens by antibodies present in patients and clinicians should not rely solely on a negative serology result [70].

Virus culture

Infectious virus can be isolated from patient samples, including respiratory aspirate, 7–10 days after infection (e.g., 1–4 days after symptom onset). Importantly, handling infectious virus samples has inherent challenges and safety concerns. Only experienced laboratories should be employed to perform virus cultures. Sample specimens are incubated in NiV-permissive cell lines, including Vero-E6 cells, and monitored over 3–7 days for cytopathic effect or plaque formation [5, 76, 78, 79]. Confirmation of the infecting viruses is performed from positive cultures using techniques such as immunofluorescence or western blot to detect NiV-specific viral antigens. These virus isolates can be classified through genetic sequencing. Virus culture can be difficult and may not yield results.

In cases of suspected NiV infection, clinicians should contact their local public health authority to assist with NiV diagnostic testing and shipping of specimens for diagnostic purposes to an appropriate laboratory.

Potential treatment or prophylactic countermeasures

Pre-Exposure prophylaxis

Currently, there is no licensed vaccine for NiV although multiple vaccine candidates are in preclinical development (Table 1). In the NHP model, administration of a live, recombinant vesicular stomatitis virus (VSV) vaccine expressing the NiV glycoprotein (NiV-G) protein (VSV-NiV-G) led to 100% survival when administered 7 days prior to challenge and 67% survival when administered 3 days prior to challenge [80].

A subunit vaccine approved in Australia for equine use against a closely related paramyxovirus, Hendra virus, demonstrates cross-protection against NiV challenge in cats, ferrets, and NHPs [86–88].

Post-Exposure prophylaxis

Currently, there are no licensed post-exposure prophylactics for use in human NiV infections. Several of the agents discussed as potential therapeutics have been offered for post-exposure under compassionate use but have not been assessed in controlled trials.

Treatment of infection

Currently, there are no FDA-approved available treatments specific for NiV infection. Several antiviral drugs have been investigated with varying results (see Table 2). The most common treatment for NiV infection is symptomatic management through supportive care.

Supportive care The primary treatment course for NiV infection is supportive care. This approach manages symptoms of the individual. The patient is provided hydration, painkillers, and anti-inflammatory drugs to minimize symptoms as they occur. External ventilation may be required for patients exhibiting extreme difficulty breathing.

Antivirals The only antiviral compound that has been evaluated to date as a treatment in human NiV infection is ribavirin. Ribavirin is approved in the US for the treatment of chronic Hepatitis C infection and for respiratory syncytial virus, and it has been used for the treatment of Lassa virus for many years. Patients receiving ribavirin should be monitored closely due to a relatively high rate of side effects, in particular for evidence of developing anemia and for hyperbilirubinemia, although clinically significant liver disease is rare. Side effects including gastrointestinal complaints, fatigue, and flu-like symptoms. Ribavirin is a teratogen and should not be administered to pregnant women or their partners [105, 106].

In an open label trial of NiV-M patients in Malaysia, mortality was reported to be reduced by 36% in 140 patients who received oral or IV ribavirin compared to 54 controls (historical and patients who declined therapy) [102]. However, a report from one of the 2 institutions which included 78 patients who received ribavirin was published during the time period of the above referenced study, and it mentions that no survival difference was seen. This suggests that survival may have been influenced by factors other than receipt of ribavirin, such as institution, improved clinical management later in the outbreak, or availability of IV vs. oral ribavirin. Of note, ribavirin was not effective in hamster models [68].

Ribavirin has been used as post-exposure prophylaxis for 8 healthcare workers who had been exposed to a NiV infected patient (providing care without appropriate personal protective equipment) during an outbreak in 2018 in Kerala, India [107]. Within 72 h of exposure, all of the healthcare workers were started on 14-day course of ribavirin, in accordance with a Lassa fever post-exposure protocol (1000 mg orally 3 times daily for 14 days) and none developed NiV infection [107]. However, as this was not a controlled trial, the effectiveness of ribavirin for post-exposure prophylaxis of NiV infection is unknown.

Two other antiviral medications licensed for other indications, remdesivir and favipiravir, have been shown to be effective against NiV both in vitro and in vivo in both hamster and NHP models [97, 101, 108].

Remdesivir, an adenosine analog licensed to treat COVID-19, disrupts both NiV RNA replication and translation [101, 108], and provided full protection from NiV disease in an NHP model [101]. In the model, African green monkeys were challenged with a lethal dose of NiV-B and started on remdesivir 24 h later, continuing for 12 days. The remdesivir animals survived whereas all the controls succumbed. Extensive experience with remdesivir and its encouraging safety profile has been gained during the COVID-19 pandemic. However appropriate dosing for humans infected with NiV is unknown. The dose used in the NHP model was 10 mg/kg/day, which is 4–8 times higher than the pediatric or adult dosing used for COVID-19.

Favipiravir, another adenosine analog licensed to treat influenza in Japan, has shown efficacy in vitro and hamster models against NiV, but no NHP or human trials with NiV have been conducted.

Peptide-based viral fusion inhibitors have been developed which block the NiV F protein mediated conformational change which allows target cell entry. Conjugation to a lipid moiety resulted in products with good protection in small animal models. One lipopeptide product VIKI-dPEG4-Toco demonstrated improved survival when applied intratracheally in highly lethal NiV NHP challenge models with 2 of 6 treated animals surviving an NiV dose later recognized to be 2–3 logs higher than necessary for a lethal challenge. Besides treatment, aerosolization of viral fusion inhibitors to block infections via the respiratory tract is proposed as a potential

Table 1 Vaccine candidates for Nipah virus infection

Vaccine platform	Manufacturer or source/contact	Description	Human Trials	NHP studies	Other animal studies
Adenovirus		ChAdOx1 NiV-B G			A single dose vaccination in Syrian hamsters confers 100% protection against both NiV-B and NiV-M. Animals challenged with NiV-M displayed mild to moderate brochointerstitial pneumonia and viral RNA was detected in type I pneumocytes [81]
Adeno-associated virus (AAV) vector		AAV8 NiV.G Encoding NiV G protein			Immunized golden hamsters had 100% survival, no signs of clinical disease, and no detectable antigen [82]
Canarypox virus (ALVAC) vector		Combination of vCP2199 with NiV G protein (ALVAC-G) and vCP2208 with NiV F protein (ALVAC-F)			Landrace female pigs were vaccinated with either ALVAC-G, ALVAC-F, or a combination of both. Pigs vaccinated with ALVAC-G or ALVAC-F/G had no viral RNA detected in nasal or pharyngeal samples, 1 pig vaccinated with ALVAC-F had detectable viral RNA in these samples. Viral RNA was detected in organ tissues of animals in the ALVAC-G and ALVAC-F groups. Mild meningitis or encephalitis was present in all groups. No clinical signs of disease were observed in any of the vaccinated animals [83]
Measles virus vector		rMV-EdG or 4MV-HL-G encoding NiV G protein		AGMs vaccinated with 2 doses of rMV-Ed-G were completely protected from signs of illness (non-lethal challenge dose used) [84]	Hamsters receiving 2 doses of either recombinant vaccines expressing NiV G from measles HL strain (rMV-HL-G) or Edmonston strain (rMV-Ed-G) had 100% survival and no clinical signs of disease [84]
mRNA		1. HeV-sG mRNA LNP 2. NiV-pre-F/G	1. N/A 2. Phase 1 (NCT05398796)		1. Syrian hamsters receiving a 30 ug dose of vaccine prior to NiV challenge resulted in 70% survival. Of the survivors all but 1 showed clinical signs of illness during the study [85]
Subunit	Zoetis, Inc	HeV-sG	Phase 1 (NCT04199169)	AGMs receiving 2 doses at 6 and 3 weeks prior to challenge had 100% survival and no detectable antigen in target organs [86]	Ferrets immunized 20 days or 14 months prior to NiV challenge had 100% survival and no detectable antigen in target organs [87] Cats immunized with 3 doses 2 months prior to challenge had 100% survival and no detectable antigen in target organs [88] Pigs immunized with 2 doses 3 weeks apart did not protect against NiV infection as viral RNA and infectious virus was detected in respiratory and lymph node samples [89]
Subunit		NiV-sG			Cats immunized with 3 doses 2 months prior to challenge had 100% survival and no detectable antigen in target organs [88]
Vaccinia virus vector		Encoding NiV G (VV-NiV.G) and NiV F (VV-NiV.F) proteins			Hamster vaccinated with 2 doses of either VV-NiV.G, VV-NiV.F, or a combination of both induced 100% survival to challenge 3 months after completion of the vaccine series [90]

Table 1 (continued)

Vaccine platform	Manufacturer or source/contact	Description	Human Trials	NHP studies	Other animal studies
Vesicular stomatitis virus (VSV) vector		Three candidates: 1. rVSV-NiV-B/F, rVSV-NiV-B/G, rVSV-NiV-B/F + rVSV-NiVB/G 2. rVSV-ZEBOV-GP-NiVF, RVSV-ZEBOV-GP-NiVG, rVSV-ZEBOV-GP-NiVN 3. VSV-ΔG-NiVF, VSV-ΔG-NiVG 4. rVSVΔG-EBOV GP-NiV G	1. N/A 2. N/A 3. N/A 4. Phase 1 (NCT05178901) Phase 1b (NCT06221813)	1. AGMs immunized with a single dose of either rVSV-NiV-B/F, rVSV-NiV-B/G, or a combination of both had 100% survival and no clinical signs of illness. Animals in all groups had transient detection of viral RNA in nasal swabs and 2 animals had viral RNA in oral swabs. No vaccinated animals were viremic [91] rVSV-NiV-B/G was further shown to confer 100% protection in AGMs when administered 7 days prior to infection and 67% protection when administered 3 days prior to challenge [80] 2. AGMs vaccinated with rVSV-ZEBOV-GP-NiVG had 100% survival and no clinical signs of disease compared to a 67% survival in control animals all of which showed signs of disease. Limited viral RNA was detected in tracheal samples from 2 vaccinated animals [92] 3.–	1. Ferrets immunized with a single dose of either rVSV-NiV-B/F, rVSV-NiV-B/G, or a combination of both had 100% survival and no clinical signs of illness except for fever in 1 animal. 1 vaccinated animal had detectable viral RNA in the spleen, and all vaccinated animals had detectable viral RNA in the blood at day 6 post-challenge which became undetectable by terminal day 21 [93] 2. Hamsters vaccinated with either rVSV-ZEBOV-GP-NiVF or rVSV-ZEBOV-GP-NiVG had 100% survival with no clinical signs of disease, those vaccinated with rVSV-ZEBOV-GP-NiVN had 33% survival [94] 3. Hamsters vaccinated with either VSV-ΔG-NiVF, VSV-ΔG-NiVG all survived challenge and showed no clinical signs of disease [95]
Viral-like particles (VLP)		VLP-NiV M/F/G Expressing NiV G, F, and M proteins. Adjuvanted with Alum, MPLA, and CpG ODN			Golden Syrian hamsters receiving a single dose of a VLP vaccine had 100% survival and no clinical signs of disease, model was not uniformly lethal, and adjuvant alone also induced some protection from death [96]

pre-exposure strategy which can be scaled and delivered to rural areas to reduce transmission [109]. These fusion inhibitors have not been trialed in humans for safety or effect.

Monoclonal Antibodies A monoclonal antibody against NiV, known as m102.4, is available for compassionate use in Australia following exposure to NiV or Hendra virus. In a ferret model, antibody m102.4 conferred complete protection against clinical disease when given 10 h after infection [36], and protection from fatal disease has been shown in NHPs infected with both NiV as well as Hendra virus when given up to 3 days post infection. However, the same NHP model suggests that there may be a shorter time frame in which m102.4 therapy is successful in NiV-B infections as compared to NiV-M, consistent with previously mentioned evidence of greater pathology with the former; [64] NHPs infected with NiV-M survived even if dosed 5 days after infection whereas those with NiV-B did not. A phase I clinical trial of m102.4 showed no severe adverse events and similar adverse event rates between treatment and control groups [98]. There have

Table 2 Therapeutic candidates for Nipah virus

Treatment	Brand name and Manufacturer or source/ contact	Description	Human Trials	NHP studies	Other animal studies
Favipiravir	Avigan	Purine nucleoside analog			[97]
m102.4	Aurobindo Pharma	Monoclonal antibody against glycoprotein	[98]	[64, 99, 100]	[36]
Remdesivir	Veklury, Gilead	Adenosine nucleotide analog		[101]	
Ribavirin	Copegus: Genentech Rebetol: Merck Sharp & Dome Ribasphere: Kadmon Pharmaceuticals Generic: Sandoz Generic: Teva	Guanosine nucleoside analog	[102]		[103, 104]

been no reported adverse reactions to m102.4 among 14 humans who received the medication as post exposure prophylaxis under compassionate use [110, 111]. Some experiments have shown NiV mutants which can escape neutralization by the m102.4 antibody have been developed in vitro, which if naturally occurring could limit the benefit from m102.4 treatment [112, 113]. However, no such escape mutants were seen in the animal models discussed above.

Infection prevention and control recommendations

A physician should perform a history to understand the potential source of infection. Information regarding the patient's exposure to bats and livestock, especially pigs, should be obtained, especially in endemic areas. Also, it should be determined if the patient has consumed raw date palm sap or fallen fruit, which can contain infectious NiV. Further, human contacts should be identified to determine if the patient acquired NiV from another individual. Conversely, if it is determined the patient was infected through contact with animal or consumption of food or beverages, contact information should be gathered to track individuals who may have been exposed to NiV through interactions with the patient, including family members. The information regarding suspected sources of infection should be provided to public health authorities to conduct surveillance and educate the community about the potential for exposure in certain areas.

When possible, the CDC recommends placement of a suspected or confirmed NiV patient in an airborne isolation room (e.g., a single patient negative pressure room) or transfer as soon as is feasible to a facility where an airborne isolation room is available. The suspected or confirmed patient should wear a facemask when in common areas and during transportation to limit potential onward transmission. Standard, contact, and airborne precautions are recommended (gown, gloves, fit-tested N95 respirator or higher level of protection, face shield or goggles). Strict adherence to the correct use of PPE, including attention to hand hygiene and prevention of self-contamination, especially during doffing, is required.

WHO-supported Bangladeshi guidelines recommend isolation in a separate ward, barrier precautions including mask, gown, gloves, and shoe covers, with enforced hand hygiene. N-95 respirator is recommended for procedures with an aerosol risk such as intubation and suction. Eye protection is not mentioned; however, goggles or face shields should be used if available. It should be noted that these guidelines are recommended in the setting of very minimal baseline infection control practices in many facilities of the country and would be difficult to achieve in some settings. In a more resourced setting, it would be reasonable to recommend eye protection be added for the care of a patient with any pulmonary symptoms.

Patients should be placed in a single room with dedicated bathroom or commode. All body fluids and secretions of a laboratory confirmed NiV patient should be considered infectious until proven otherwise. To reduce possible occupational and accidental exposures, the use of needles and sharps should be minimized. Procedures that can produce aerosols or droplets require extreme caution, with providers in individually fitted respiratory protection.

In several outbreaks, there have been characterized human to human transmission, including caregiver infection from infected patients [11, 18, 63, 114–116]. The transmission likely resulted from small aerosol or droplet exposure during close interactions with the infected individual. This transmission risk increases the need for strict adherence to PPE precautions and engineering controls.

Previous studies found NiV RNA was present on surfaces, including bedsheets and bedrails [11, 117]. Caretakers should be aware of this hazard during patient management. A US Environmental Protection Agency (EPA)-registered hospital disinfectant with efficacy against enveloped viruses should be used to disinfect environmental surfaces. Other studies have shown efficacy of other disinfecting agents against NiV [118, 119].

Waste generated in the care of the patient should be considered infectious. In the US, waste generated in the care of suspect cases or patients with confirmed NiV infection is subject to procedures set forth by local, state, and federal regulations. Bedding and clothing should be removed and bagged. Any sharps should be placed in puncture-proof boxes. When possible, the waste bags and boxes should be steam sterilized in an autoclave. In resource-limited environments, burning or incineration should be employed.

Caution must be taken when handling the remains of the deceased as previous research has found corpse-to-human transmission occurs when remains are handled without appropriate protections [120]. Decedents should be considered infectious, and safe and dignified burials should be incorporated with local customs [121]. Individuals handling the deceased should use the same PPE precautions as those providing care to infected individuals in the hospital. Ideally, human remains should be cremated as soon as possible to decrease the potential exposure to infectious body fluids [122].

Taken together, NiV-infections and suspected infections should be treated with the highest level of precaution. Personal protection should be employed for all clinical staff to ensure safe treatment of patients.

Summary

Nipah virus infection remains a persistent threat in South Asia. Although difficult to identify based on clinical symptoms alone, a variety of testing options are available to aid with the diagnosis of NiV. Multiple vaccines are in development for NiV, although all are still in pre-clinical development or early clinical trials and none are currently approved for use. A monoclonal antibody against NiV is currently available for compassionate post-exposure prophylaxis in Australia.

As with other emerging viral pathogen infections, there are no FDA-approved available therapies and supportive care remains the primary mode of treatment for NiV infections. Initiation of antiviral therapy within the first few days after infection may confer some survival benefit, but the exact impact on disease outcome remains unclear. Historically, ribavirin has been the first line of antiviral therapy for NiV infections, but potential harmful side effects exist that should be taken into consideration. Off-label use of other antiviral medications, including favipiravir and remdesivir, shows potential benefit in animal models of disease. To mitigate risk of continued transmission, infected individuals should be isolated, and caregivers should adhere to infection prevention and control measures.

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Authors' contributions
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Declarations

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