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Review

Infections and Immunity of Nipah Virus Outbreaks

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Abstract

Nipah virus is an RNA virus and belongs to the genus Henipavirus. The virus can spread between people and also from other animals but requires a direct contact with the infected source. Nipah virus causes viral infection which is referred as Nipah virus infection (NiV) and the symptoms of NiV vary from none to fever, cough, headache, shortness of breath, confusion, death, etc. The infected patients may go into coma within a day or two with complications including inflammation of the brain and seizures. The NiV was first discovered in 1998 in Malaysia and the Nipah virus was isolated in 1999. To date there is no vaccine or specific treatment to treat NiV infections and the management of the disease is through supportive care. More than 700 cases of human infections are reported to be occurred, mostly in Malaysia and India, and more than 75% of the infected patients have died. Prevention of NiV is mostly through avoiding contact with bats and sick pigs.

Introduction

Viruses are prevalent pathogens that come from various sources to wreak havoc in humans, animals, and even plants [1]. They are obligate intracellular parasites, meaning that they rely on a host's cellular machinery to replicate and infect an organism [2]. Viruses have the capabilities to infect almost any kind of organism including bacteria and humans [3]. Once a virus enters the host, it latches onto a host cell and inserts its genome to replicate and create viral progeny to spread an infection [4]. Zoonotic viruses are classified as viral diseases that spread from animals to humans and/or vice versa [5]. These types of zoonotic viral infections are critical due to the large impacts they have on agricultural practices all over the world [6]. The Nipah virus is a relatively new zoonotic virus that humans have started falling victim to about 20 years ago [7 ,8]. This particular virus is similar to Ebola and Zika viruses in that these are all zoonotic viruses [9]. The Ebola virus is classified as a Filovirus, meaning that it is mainly contracted through "bushmeat" activities (handling wild animals) [10,11]. This deadly pathogen has been traced to potentially being hosted in African bats [12]. The severe aspect of this virus is that it normally presents like other common viral infections (such as influenza)but can quickly cause fatal symptoms such as hemorrhagic fever [13]. Zika virus is transmitted through mosquito bites, classifying it as an arbovirus in the Flavivirus family [14]. This virus normally produces a mild infection, but serious cases can amount to birth defects when contracted by pregnant women [15]. However, the Nipah virus is less dangerous than Ebola or influenza but more so than the Zika virus [9].

Nipah Virus and Hendra Virus Outbreaks

The Nipah virus's structure as an envelope, non-segmented, negative strand RNA virus, places it in the Paramyxoviridae family [8]. Its similarities to the Hendra virus groups it in a new Henipavirus genus [16]. Both the Nipah virus and Hendra virus are RNA viruses that share the same reservoir i.e. bats [17]. The Hendra virus first emerged in 1994 in Australia with a pattern of transmission from flying foxes (a type of bat) to horses to humans[18]. But, there are no evident cases of human-human transmission [19]. However, horses took the largest hit with having the highest rate of infection in 2011 [20]. The Nipah virus's natural hosts are fruit bats. These fruit bats come from the Pteropus genus in the Pteropodidae family and solely serve as the hosts for the Nipah virus with no apparent disease symptoms [19]. Nipah virus outbreaks have only been seen in Asia, claiming its first victims in Malaysia around 1998 [21]. The disease was first found in humans and pigs due to shared respiratory and neurological symptoms [17]. The pattern of transmission in the cases associated with the Malaysian outbreak of Nipah virus was determined to come from direct and unprotected contact with sick pigs or their

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contaminated tissues [22]. These pigs had received the virus through methods that ultimately traced to fruit bats. Later cases with similar symptoms arose in Bangladesh and India about three years later, in 2001 [23]. However, further research showed that this strain slightly varied from the strain initially found in Malaysia [24]. In addition, the path of transmission varied in this region of Asia. Cases arose from the consumption of fruits and fruit products contaminated with the urine and saliva of these fruit bats [25]. Human transmission was seen through close contact with infected people, especially in hospitals [25,24]. Although, the Malaysian outbreak has subsided, Nipah virus outbreaks arise annually in Bangladesh [17].

Nipah Virus Symptoms and Neurological Complications

The neurological symptoms and acute respiratory distress are the main concerns with the Nipah virus [26,27]. The virus has seen to be especially contagious in pigs. The incubation period in these animals lasts from four to fourteen days. Nipah virus symptoms in pigs can either range from no symptoms to acute fever to labored breathing and neurological symptoms [28]. Fortunately, the mortality rate is low except in piglets due to their weak immune systems. Case fatality in humans is reportedly higher with rates of ~40% in Malaysia/Singapore and ~70% in Bangladesh and India [29,30]. Even survivors of the severe neurological symptoms present with long-term neurological deficits or have a late-onset or relapse of encephalitis (inflammation of the brain) [30]. The main site of infection where the virus prevalently attacks is the endothelium. Signs and symptoms range from asymptomatic to acute respiratory illnesses to fatal encephalitis. Initial symptoms replicate those generally seen with influenza (fever, headaches, myalgia, vomiting, sore throat). These symptoms are usually followed by dizziness, drowsiness, altered consciousness, and other neurological signs associated with acute encephalitis. Extremely severe cases, which typically lead to death, progress from seizures to comas all within a 48-hour time span [17]. Humans share the same incubation period as that seen in pigs which is being four to fourteen days long [26].

Nipah Virus Outbreaks in Bangladesh and Malaysia

Comparing the outbreaks in Malaysia versus Bangladesh shows apparent differences [31]. More respiratory symptoms were seen in Bangladeshi patients than in Malaysian patients. Human to human transmission was very important to the accumulation of cases in Bangladesh most likely due to the higher respiratory symptoms seen in these cases [32]. The Malaysian outbreak was more related to the neurological symptoms such as brain inflammation as a cause of death (see Table 1). However, fatality was unfortunately high in the Bangladesh outbreak than the Malaysian outbreak [32]. The two possible genotypes are intrinsically different between the strain seen in Malaysian patients verses that seen in Bangladeshi patients [31,32,33]. However, studies done with Syrian hamsters and ferrets show that the difference in strains isn't the cause of clinical differences [31]. The clinical differences are more likely attributed to inoculation dose and route (transmission from pigs versus food-borne transmission), health care practices, and even cultural differences [17].

Table 1: Difference Between Malaysian and Bangladesh Strains of Nipah Virus

Malaysian strain (NiV-M)	Bangladeshi strain (NiV-B)
Transmission via intermediate amplifying host (pigs)	Direct transmission by bat-infected dap
Handling of pigs main source of outbreaks	Greater human-human transmission contributed to outbreaks
Cases presented more neurological symptoms	Respiratory signs more common

Viral Entry and Infection

As the Nipahvirus infects cells throughout the host, it has a very broad cell tropism, allowing it to easily spread through the body [34]. The cellular receptors responsible for this are ephrinB2 and ephrinB3, which might be widely available in host cells allowing multiple types of cells to be infected such as smooth muscle, neurons, macrophages, and alveolar cells [35]. Blood is the main form of transportation for the viral progeny, due to its replication in epithelial cells [36]. The Nipah virus was detected to be most present in neurons as nucleoprotein aggregates found in axons in order to spread throughout the central nervous system. Different animal models (Syrian hamsters, pigs, ferrets) were intranasally inoculated or ingested artificial palm sap (contaminated with the virus) to help researchers determine the various routes of entry that allow the virus to attack the CNS. Some examples of routes discovered using the previously mentioned methods are the disruption of the blood brain barrier, attaching to leukocytes and forceful entry into the brain parenchyma, and transport along olfactory neurons from nasal cavity [37]. It is important to note that intranasal inoculations could have skewed the experiments of where the virus was found in olfactory neurons due to the site of inoculation [20].

Diagnosis of Nipah Virus Infection

Diagnosis of the Nipah virus presents to be difficult at the onset of the disease because the initial signs and symptoms are nonspecific to viral infections [26]. This poses a problem in that it hinders accurate diagnosis and outbreak detection in a timely manner. The main diagnostic tools used to identify the virus have been real time polymerase chain reaction (RT-PCR) of bodily fluids and antibody

detection via enzyme-linked immunosorbent assay (ELISA) [38]. Unfortunately, no drugs are vaccines have been developed yet for the Nipah virus but intensive support care is recommended for those with severe respiratory and neurological complications [20].

Controlling the Nipah Virus Outbreak

Transmission is always very important issue for zoonotic viruses because humans aren't the only main concern [39]. In Malaysia, pigs were very susceptible and efficient spreaders in order for the virus to impact so many humans [40]. Prevention of outbreaks involving animal farms should include routine and thorough cleansing and disinfection of animal quarters. If an animal is suspected to have the virus, it should be quarantined. If one must handle an infected animal, he/she should wear protective gear such as gloves and a mask to prevent being infected. Should an animal die of viral infection, burial or incineration of carcasses would help reduce the risk of transmitting the virus to humans and other possible animals [39,40].

In India and Bangladesh, the date palm sap was infected via the urine, saliva, and feces of the fruit bats [17]. Reducing the risk of infection in people would be raising awareness of the risk factors and measures to reduce exposure. Decreasing the consumption and access to date palm sap and other fresh food products that fruit bats may potentially infect would help prevent exposure to the virus. However, it is important to keep in mind that access to the date palm sap and its collection is a form of livelihood for many members in communities where consumption of the product is high [41]. In addition, fruits that are collected should be thoroughly washed and peeled. Interventions should be made to keep bats away from date palm sap collection sites to prevent contamination of the sap. The sap should also be boiled to kill any pathogens that could cause infection [41].

It's important to note that in the 2018 in northern Kerala, which is the Nipah virus's most recent outbreak, about 75% of the cases were spread through nosocomial transmission, meaning that a majority of the outbreak was caused by infected contacts through hospital wards [42,43]. This fact points to a major clue in order to help contain and prevent the spread of infection. Avoiding close unprotected physical contact with infected patients and regular handwashing would certainly diminish the growth of cases through human-to-human contact. Controlling the infection in hospitals and clinics should occur through standard infection control practices and trained staff handling samples in equipped labs. In addition, only essential personnel should come into contact with infected patients to stop the spread to family and friends [43].

Treatment Options for Nipah Virus Infections

General virus infections (such as ones that are not so fatal), are left to resolve on their own, such as influenza or the common cold [44]. A person's body normally is strong enough to use its own immune system to fight off the infection (unless the person is immuno compromised). Medications are given to people to help alleviate their symptoms but not to fight off the infection. However, a certain class of medications called antiviral medication have been developed for certain viruses (Bala et al, 2016) (see Table 2). This type of medication either helps prevent the host cell from being infected or prevents the virus from replicating and producing progeny in the host's body [45]. Antiviral medications can be proven to be very beneficial when taken at the start of symptoms during an outbreak [44].

Table 2: Currently Available Antiviral Drugs to Treat Viral Diseases

Drug Names	Indicated for	Comments
Abacavir (ABC)	Treatment and prevention of HIV/AIDS, used in conjunction with other HIV medications (not recommended by itself)	Administered orally by tablet or solution; nucleoside analog reverse-transcriptase inhibitor (NRTI)
Acyclovir (ACV)	Herpes Simplex virus, chickenpox, shingles, prophylaxis for severe cytomegalovirus infections post-transplants and Epstein-Barr virus infection complications	Administered orally, topical cream, or IV
Adefovir	Chronic infections with Hepatitis B virus	Administered orally
Amantadine	Antiviral for influenza and antiparkinsonian drug	Resistance and effectiveness as both an antiviral and antiparkinsonian drug so no longer recommended as treatment; useful building block in organic synthesisby inserting adamantyl group

Amprenavir	HIV infection	Administered orally; protease inhibitor
Ampligen(trade name for Rintatolimod)	Chronic fatigue syndrome symptoms (low-strength evidence); boost cellular defenses against viruses and tumors (could be synergistic with other antivirals for avian influenza)	Administered IV
Arbidol (trade name for Umifenovir)	Influenza in specifically Russia and China	Administered orally
Atazanavir	Treatment and prevention of HIV/AIDS, used with other antiretrovirals, used for prevention after needlestick injury or other potential exposure of the virus	Administered orally; protease inhibitor
Atripla (trade name for Efavirenz/Emtricitabine/ Tenfovir)	HIV/AIDS	Administered orally (fixed-dose combination of drugs can be taken with other antiretroviral medications)
Cidofovir	Cytomegalovirus retinitis in patients with AIDS	Administered IV
Combivir (trade name for Lamivudine/Zidovudine)	HIV/AIDS	Administered orally (fixed-dose combination of drugs can be taken with other antiretroviral medications)
Dolutegravir (DTG)	Antiretroviral medication used along with other medications to treat HIV/AIDS, used as post-exposure prophylaxis to prevent HIV infection	Administered orally; integrase strand transfer inhibitor
Darunavir (DRV)	Treatment and prevention of HIV/AIDS, recommended use along with other antiretrovirals, used for prevention after needlestick injury or other potential exposure of the virus	Administered orally; protease inhibitor
Delavirdine (DLV)	Part of highly active antiretroviral therapy (HAART) for treating HIV type 1	Administered orally by tablet or solution; nucleoside reverse-transcriptase inhibitor (NRTI)
Didanosine (DDI)	HIV/AIDS, part of highly active antiretroviral therapy (HAART)	Administered orally; reverse transcriptase inhibitor
Docosanol (behenyl alcohol)	Reduces duration of cold sores caused by herpes simplex virus	Administered topically, saturated fatty alcohol used as emulsifier/thickener in cosmetics and nutritional supplements; contained in OTC medication Abreva
Edoxudine	Herpes simplex virus	Analog of thymidine nucleoside
Efavirenz (EFV)	Treatment and prevention of HIV/AIDS, recommended use along with other antiretrovirals, used for prevention after needlestick injury or other potential exposure of the virus	Administered orally; non-nucleoside reverse-transcriptase inhibitor (NNRTI)
Emtricitabine (FTC)	Treatment and prevention of HIV infection	nucleoside reverse-transcriptase inhibitor (NRTI)

Enfuvirtide	HIV-1 infection	Administered subcutaneously; HIV fusion inhibitor
Entecavir (ETV)	Hepatitis B virus infection	Administered orally; nucleoside reverse transcriptase inhibitor (NRTI)
Famciclovir	Various herpesvirus infections (commonly for herpes zoster)	Administered orally
Fomivirsen	Cytomegalovirus retinitis in immunocompromised patients (those with AIDS)	Administered by intraocular injection; antisense antiviral drug
Fosamprenavir	HIV infections	Administered orally; pro-drug of protease inhibitor Amprenavir
Foscarnet	Viral infections involved Herpesviridae family	Administered IV ;DNA polymerase inhibitor
Imunovir (trade name for Inosonepranobex)	Mucocutaneous infections from Herpes simplex virus (type 1 and 2)	Combination of inosine and dimperanol acedoben
Idoxuridine	Herpesvirus infections	Administered topically; nucleoside analogue of deoxyuridine
Imiquimod	Genital warts, superficial basal cell carcinoma, actinic keratosis	Administered topically
Indinavir (IDV)	Component of HAART for HIV/AIDS	Administered orally; protease inhibitor
Lamivudine (3TC)	Treatment and prevention of HIV/AIDS (typically taken with other antiretrovirals), chronic Hepatitis B (when other options unavailable), post-exposure therapy for those potentially exposed to HIV	Administered orally; analogue of cytidine
Lopinavir	HIV infections (fixed-dose combination with Ritonavir)	Administered orally; protease inhibitor
Maraviroc	HIV; reduces graft-versus-host disease in patients treated with allogenic bone marrow transplant for leukemia	Administered orally; entry inhibitor; CCR5 receptorantagonist
Metisazone	Inhibits mRNA and protein synthesis (especially in pox viruses), used previously to treat smallpox; used as prophylaxis	
Nelfinavir	HIV-1	Administered orally; protease inhibitor
Nevirapine (NVP)	Treatment and prevention of HIV/AIDS (specifically HIV-1), typically used with other antiretrovirals, may be used to prevent mother to child spread of HIV infection	Administered orally; non-nucleoside reverse transcriptase inhibitor (NNRTI)
Nitazoxanide	Broad-spectrum antiviral drug and broad-spectrum antiparasitic drug for helminthic, protozoal, and viral infections, can be used to treat influenza	Administered orally; thiazolide
Norvir (trade name of Ritonavir)	Used along with other medications to treat HIV/AIDS, part of HAART	Administered orally; protease inhibitor

Oseltamivir	Treatment and prevention purposes of influenza A and B	Administered orally; especially indicated for for patients who have complications or at high risk of complications w/n 48 hrs of first symptoms of infection; clinician discretion for prescribing for patients at lower risk presenting with first symptoms w/n 48 hrs of infection
Pegylated interferon alfa-2a	Hepatitis B and C	Administered subcutaneously
Penciclovir	Various herpesvirus infections	Administered topically; guanosine analogue
Peramivir	Influenza	Administered IV; neuraminidase inhibitor
Pleconaril	Prevents asthma exacerbations, common cold symptoms for patients exposed to picornavirus	Administered orally and intranasally
Podophyllotoxin (PPT)	Genital warts and molluscum contagiosum	Administered topically
Raltegravir (RAL)	Used along with other medications to treat HIV/AIDS, post-exposure prophylaxis to prevent HIV infection	Administered orally; HIV integrase strand transfer inhibitor
Ribavirin	RSV infection, Hepatitis C, viral hemorrhagic fever (Lassa fever, Crimean–Congo hemorrhagic fever, and Hantavirus infection but not Ebola or Marburg)	Administered orally or inhaled; guanosine analogue
Rimantadine	Influenza A (when take w/n 1-2 days of developing symptoms to decrease duration and severity of influenza)	Administered orally; prevents viral replication
Ritonavir	Used along with other medications to treat HIV/AIDS, part of HAART	Administered orally; protease inhibitor
Saquinavir	Used along with other medications to treat HIV/AIDS	Administered orally; protease inhibitor
Sofosbuvir	Hepatitis C, only recommended with some combination of other retrovirals	Administered orally; inhibits Hepatitis C NS5B protein
Stavudine (d4T)	Treatment and prevention of HIV/AIDS, generally recommended for use with other antiretrovirals, prevention of HIV infection after needlestick injury	Administered orally; nucleoside analogue of thymidine
Telaprevir (VX-950)	Hepatitis C	Administered orally; protease inhibitor
Tenofovir disoproxil	Chronic Hepatitic B, treatment and prevention of HIV/AIDS (generally recommended with with antiretrovirals), prevention of HIV infection after needlestick injury	Administered orally; nucleotide analog reverse-transcriptase inhibitor (NtRTI)
Tipranavir (TPV)	Used with Ritonavir in combination therapy for HIV infection	Administered orally; nonpeptidic protease inhibitor
Trifluridine (TFT)	Herpesvirus infections	Administered by eye drops or orally; nucleoside analogue of deoxyuridine

Trizivir (trade name for Abacavir/Lamivudine/ Zidovudine)	HIV infection, useful for pregnant women to decrease risk of mother-to-child transmission	Administered orally; fixed-dose combination of 3 reverse transcriptase inhibitors
Tromantadine	Herpes simplex virus	Administered orally; inhibits viral replication
Truvada (trade name for Emtricitabine/Tenofovir)	Treatment and prevention of HIV/AIDS	Administered orally; fixed-dose combination of two antiretroviral medications
Valaciclovir	Outbreaks of herpes simplex or herpes zoster, prevent cytomegalovirus following kidney transplant	Administered orally
Valganciclovir	Cytomegalovirus infection in patients with HIV/AIDS or following organ transplant	Administered orally; prodrug for ganciclovir which is a synthetic analog of 2'-deoxy-guanosine
Vicriviroc	HIV infection	Administered orally; pyrimidine CCR5 entry inhibitor of HIV-1; currently under clinical trials
Vidarabine	Herpes simplex and varicella zoster viruses	Originally intended as anti-cancer drug; nucleoside analog of adenosine
Zalcitabine (ddC)	HIV/AIDS (used as part of combination regimen)	Administered orally; nucleoside analog reverse transcriptase inhibitor (NRTI)
Zanamivir	Treatment and prevention influenza A and B viruses	Administered IV or inhalation; neuraminidase inhibitor
Zidovudine (ZDV)	Treatment and prevention of HIV/AIDS, may be used to prevent mother-to-child spread during birth of after needlestick injury	Administered orally, IV, and rectal suppository; thymidine analogue

Vaccines are also another form of prevention to the spread of cases [46]. Some viral vaccines have a weakened or killed version of the virus particle which helps stimulates one's immune system to help them create an immune response to the particles [47]. However, the virus contained in the vaccine isn't strong enough to cause the actual infection, just mimics the response the body would have for the actual live virus by producing the antibodies needed to fight off the infection [48]. The person's immune system will now retain the "memory" to fight off the infection should they actually come into contact with the virus [47]. The more people that are vaccinated, it prevents the spread of the infection because more people are able to kill the infection. This produces the concept of herd immunity because even if some aren't vaccinated, those few individuals have a smaller chance of contracting the virus[48].

If any effective vaccinesare developed for the Nipah virus, it can be used to drastically decrease the number of infected people in areas that are more prone to the virus [49]. Although there is no strict treatment regimen for the Nipah virus developed yet, valiant efforts have been made throughout the years from its initial exposure to help decline the severity of the infection [49]. For example, passive immunization using human monoclonal antibody targeting Nipah G glycoprotein evaluated in post-exposure therapy in ferret model found to be beneficial [50]. In addition, an antiviral drug called ribavirin is a common initial treatment approach for viral infections that shows antiviral activity to a wide range of DNA and RNA viruses [51]. Although studies determining ribavirin's activity against the Nipah virus, specifically, using animal models such as hamsters shows promising results, other studies using humans presents inconclusive results in humans so cannot be relied on for effective usage [20]. Another antiviral medication that has been seen to work effectively in protecting the host against the Nipah virus is Favipiravir (T-705) [52]. This medication inhibits viral RNA-dependent RNA polymerase and was developed by the Toyama Chemical Company in Japan initially as an antiviral for influenza [52]. However, the medication has also shown activity against many other RNA viruses such as flaviviruses and filoviruses. Experiments were conducted using Favipiravir to test its effectiveness towards Nipah and Hendra viruses. Part of the study looked at in vitro Nipah and Hendra virus replication and another part looked at a Syrian hamster model that infected with a lethal dose of the Nipah virus. Results of the study found that Favipiravir was able to inhibit viral replication in vitro and oral administration of the medication completely protected the hamster model [52].

Conclusion

The Nipah virus can be noted as an emerging deadly virus in southeast Asia. The virus infection in humans causes a spectrum of clinical symptoms that can quickly turn fatal, with a case fatality rate is estimated at 40% to 75%. The human infection caused by the Nipah

virus presents as a range of asymptomatic infection to acute respiratory infection and fatal encephalitis. The severity of Nipah virus outbreaks heavily depends on local capabilities for epidemiological surveillance and clinical management. This gives a huge reason for concern to learn more about the virus and treatments as soon as possible. According to the 2018 annual review of the WHO R&D Blueprint list of priority diseases indicates that there is an urgent need for accelerated research and development for the Nipah virus [53].

Nipah virus can be transmitted to humans from animals (such as bats or pigs), or contaminated foods and can also be transmitted directly between humans. Since transmission of the virus occurs frequently in rural areas, the containment of the infection is possible through more awareness. In addition, there is no current definitive treatment or vaccine available for either people or animals. The primary treatment for humans is supportive care. However, with more research into the virus, affected communities would not have to rely on just preventive care in the near future.

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