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Review Paper

Nipah virus: a narrative review of viral characteristics and epidemiological determinants

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ABSTRACT

Objectives: The objectives of this article are to highlight the properties of the Nipah virus (NiV) and discuss its epidemiological determinants.

Study design: A review of conjectures, epidemiological and clinically related studies, and identification and discussion of preventive approaches is conducted.

Methods: A review of the current literature is performed going through online search engines: PubMed and Google Scholar. The search strategy was focused on two main components, first on the NiV ('Nipah' OR 'Nipah Virus') and subsequently on its epidemiology, including determinants and preventive measures ('Epidemiology/determinants' OR 'Epidemiology/prevention').

Results: NiV infection is an emerging zoonotic infectious disease causing sporadic outbursts in many developing countries within Asia, Africa, and South America. Pteroid bats are the natural reservoirs, but human-to-human transmission is possible. Clinical course ranges from non-specific influenza-like symptoms to rapidly progressive respiratory and neurologic complications. Vector control has been challenging because of its widely distributed ecological niche. Currently, no definitive treatment protocols are available in humans, but profound breakthrough in vaccine technology and successful equine vaccines has shown the way for the development of NiV vaccine and immunization in the near future.

Conclusions: The NiV poses a significant public health risk because of its intricate transmission cycle, unpredictable viral course, murky management protocol, and unavailability of vaccine. Complicated by emergence and subsequent reemergence, prevention and containment are the two most important public health promotion strategies. Early anticipation, intergovernmental preparedness and cooperation, and surveillance of zoonotic infections still remain the key to mitigate the risk.

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Introduction

Within the last decade, sporadic zoonotic infectious diseases have increased in both number and global importance. The discovery of the Nipah virus (NiV), complicated by its reemergence with high morbidity and mortality (40–70%), highlights the significance of vector-borne diseases in recent times.[1,2] NiV is a zoonotic virus of the Paramyxoviridae family with its natural reservoir being *Pteropus* bats. It is an emerging infectious disease of significant public health concern that has caused recent outbursts in many developing countries within Asia, Africa, and South America.

Methods

A review of the current literature is performed in accordance with NiV characteristics, distribution, and its clinical course. In particular, the focus has been centered on the discussion of the transmission cycle and the public health preventive measures. Information and evidence were gathered by going through the online search engines PubMed and Google Scholar. The search strategy focused on two principal components, first on the NiV ('Nipah' OR 'Nipah Virus') and subsequently on its epidemiology, including determinants and preventive measures ('Epidemiology/determinants' OR 'Epidemiology/prevention and control'). Peer-reviewed pertinent articles from 1998 to 2018 were analyzed based on the relevance to our objectives and search strategies.

History of NiV

The history of the NiV dates back two decades, with the first isolates obtained in Kampung Sungai Nipah and Negeri Sembilan, Malaysia, with preceding several large outbreaks in the neighboring villages of Ipoh city 1998–1999.[3] Presumed to be Japanese B encephalitis, during its initial stages, the outbreak lead to the discovery of a new viral strain.[4] The subsequent outbreak was reported in Singapore[5] in the same year, where a total of eleven cases were identified. Most of the victims were abattoir workers who dealt with live pigs imported from Malaysia.

The twenty-first century has witnessed the NiV with several large isolated outbreaks starting with Bangladesh and India in 2001.[6] Similar outbursts were also traced in two villages in the Philippines in 2014. The most recent upsurge began on May 2018 in Kerala, a South Indian state.[7] It is interesting to note that there were discernible strain variations between these different regional outbreaks, probably due to the different viral genotypes with the possibility of coevolution among their local natural reservoirs. Nevertheless, pathological strains of the NiV that were the cause of the fatal outbreaks in Bangladesh were seen to be genetically alike but not identical to the strains accountable to the latest outbreaks in Kerala.[8]

Understanding the history of NiV emergence can bring insight into the past and future disease patterns. It is thought to be associated with anthropic adaptations that have influenced its pathogenic dynamism. The primordial NiV overflow into the pig population had happened when a fruit tree was planted proximally to a pig farm, which is thought to lure the fruit bats, allowing for cross-species transmission.[9] Malaysian pig farming had been for many decades, and it is conjectural as to why the disease spread to humans during the 1990s. One probable hypothesis relates it to the forest burning in Sumatra. This deforestation may have compelled the migration of bats from Sumatra into the Malaysian territory, where the virus was introduced to the pig population. When infected pigs were marketed to areas outside and beyond these domains, access for widespread human exposure and disease ensued. Urbanization also played a central role in disturbing the bat habitat and migration patterns.[10] Urban flowering has increased in recent years and has become a dependable and abundant food resource. With this new year-round supply of nectar, there is less need for the bats to migrate and forage elsewhere where nectar is irregularly and erratically dispersed. These anthropogenic changes have a detrimental impact on NiV historical emergence and its continuous disease spread.

Risk factors

As part of the RNA virus family (*Henipavirus*), the NiV is known to cause major disease in both humans and animals. The initial outbreak began through zoonotic transmission from an intermediate amplifying host in Malaysia, whereas in Bangladesh, it is attributed to the direct consumption of the fruit bat–contaminated palm sap.[11] Notably, more than half of the cases seen in Bangladesh by 2008 were solely interrelated with human-to-human contact through body fluids or nosocomial transmission.[12] In Bangladesh, healthcare workers and hospital patients were facing considerable risk from exposure to environmental pathogens through transmission from airborne fragments resulting from coughing and sneezing in poorly ventilated areas, as well as fomites and contact with bodily fluids or sharing beds. Overcrowding, uncontrolled pouring of visitors, and lack of hygiene practices such as handwashing are important factors that promote disease transmission.[13] Similarly, environmental factors such as deforestation and climate changes affecting fruit bats and pigs have been thought to have contributed to NiV emergence in the 1998 outbreak in Malaysia. Albeit the exact connection between the animal-human transmission and its impact on this zoonotic disease is known, egress has not been explicitly deciphered.[14]

Foodborne transmission through drinking raw date palm sap, a common cultural treat in Bangladesh, can aid in NiV transmission as bats frequent the trees and come in contact with the sap being collected.[15] The NiV can survive in the palm fruit juice or bat urine for days, and as date palm sap is usually consumed over a short span after collection, individuals are likely to ingest and become infected with the virus.[16]

Definitive burial and corpse rituals in high-risk countries are other possible risk factors for the transmission. During the performance of ritual purification, exposure to the NiV found in respiratory secretions of the corpse can occur during close hand and facial contact. Wearing gloves or masks is not

considered culturally appropriate in these rituals, leading to a high risk of contamination, particularly when the performer touches his/her own face, eyes, or nose during the process. Similarly, certain religion requires ritual bathing by pouring water on the body of the corpse. This contaminated water can be a source of infection once it comes in contact with the clothes and body. It is important to implement preventative measures to reduce this form of transmission from corpses with a goal to minimize respiratory, salivary, or bodily fluid exposure. Proper disposal of infected human waste and remains is the key to prevent transmission. Measures such as wearing gloves or masks during the washing process can be suggested, but more cost-effective practices such as frequent and thorough handwashing with soap after the cleansing ritual are recommended.[17]

Human-to-human transmission

Human-to-human transmission is a potential public health issue and a significant route for the infection. This can occur with direct contact with the infected individuals or their secretions. Direct contact can occur from physically touching or interacting with the patient during forced feeding or even during cradling for comfort. Human-to-human transmission also involves nosocomial transmission in which one is exposed to the patient's secretion that can occur from intubation or lack of protective wear.[18] Respiratory secretion and saliva have the greatest risk.[19] Sharing of eating utensils and drinking from the same glass with a sick person, as are the norms in many Eastern cultures, can facilitate transmission through saliva. Families with close sleeping arrangements due to lack of space and poverty or, at times, wish of the families and friends to be in close contact with the sick ones can expose the virus to other household and community members, leading to a chain of transmission. Isolation is crucial at these situations, particularly for their respiratory and urinary secretions.

Pathogenesis

The pathogenesis is not fully understood. The only possible way to analyze it is to observe visible differences in severity, duration, and recurrence when comparing the outbreaks. These discrepancies may be due to the variations in the transmission route and dose, as witnessed by de Wit and Munster[20] in the Syrian mice experiment. The severity of the infection is associated with frequent mutations, a characteristic of an RNA virus. The high infection rate of mammals, as opposed to other animals, is due to the specificity of the ephrin-B2 and ephrin-B3 receptors.[21] These host cell receptors for the NiV, ephrin-B2 and ephrin-B3, were determined to be responsible for infection of both animals and humans. NiV entry occurs through a process of membrane fusion that is pH independent and mediated by fusion and attachment of glycoproteins. Ephrin-B2 and ephrin-B3, family of ligands of receptor tyrosine kinases, were seen to contribute to cell fusion and permissiveness of the host cell to the NiV. These receptors, NiV-binding sites, are commonly found in mammalian epithelial cells, with the highest expression in the lungs and are modulators of cell migration in the nervous system. The commonality of these receptors contributes to the wide distribution of infected mammals.

Infection is initiated once the viral particles are inhaled. After inhalation, endothelial cells were determined to be the target cells, although viral spread to the central nervous system (CNS) has also been observed. But this mechanism is not completely understood.[22] The NiV infects respiratory epithelia through inducing inflammatory cytokines that cause resultant recruitment of the immune cells with progression to acute respiratory distress syndrome–like condition. These key mediators are interleukin 6, interleukin 8, interleukin 1 alpha, monocyte chemoattractant protein 1, granulocyte colony-stimulating factor, and granulocyte-monocyte colony-stimulating factor. These mediators are not as readily expressed in the lower respiratory tract such as the trachea or bronchi, making it consistent with reports of NiV cases showing little or no inflammation in these regions. Within the respiratory epithelium, the virus replicates and spreads to the endothelium. The NiV can then enter the circulation and be distributed throughout the host body, targeting key vital organs such as the CNS, spleen, and kidneys causing viremia and even multisystem organ failure. The NiV also binds to CD3+ leukocytes. In a study conducted in pigs, the NiV was shown to infect monocytes, CD6, CD8 + T lymphocytes, and natural killer cells. CD6 attaches to activated leukocyte adhesion molecules that are present on microvascular endothelial cells that make up the blood-air barrier and blood-brain barrier (BBB). It is not clear whether NiV binding to CD6 leads to CNS entry. Furthermore, NiV entry and subsequent encephalitis can occur through the olfactory nerve or choroid plexus and cerebral vessels after disrupting the BBB. Inflammatory cytokines, tumor necrosis factor alpha and interleukin 1 beta, have been implicated in BBB permeability. These cytokines can be discharged from infected microglia. It is hypothesized that BBB disturbance may be a result of viral replication within microvasculature in the brain or through the release of cytokines from neurons and microglia.

Histological presentation of endothelial damage, syncytial giant cell formation, viral inclusions, vasculitis of the brain, white and gray matter plaques, and other associated viscera are usually evident. Typically small vessels and capillaries were shown to have evidence of vasculitis, most severely in the brain, and were characterized by segmental endothelial destruction, mural necrosis, and karyorrhexis.[23] Furthermore, the spinal cord in some cases was shown to have pathological lesions similar to those found in the brain. The most common microscopic features were necrotic plaques, perivascular cuffing thrombosis, and vasculitis. Similarly, fibrinoid necrosis and vasculitis in the lung and intranuclear inclusions in alveolar spaces are also observed.

Factors that influence virulence include host cell entry, viral assembly, subsequent budding, and immune escape. Restriction of viral entry and therefore pathogenicity can occur through proteolytic cleavage of the viral fusion protein precursor to a mature protein by ubiquitous proteases.[24] Owing to the restrained tissue distribution of this enzyme, NiV infection most commonly occurs within the respiratory system. Furthermore, attachment of glycoproteins to

receptors of target cells also determines pathogenicity. The NiV receptor–binding domain consists of a six-bladed fold that gives its specificity; however, it has low conservation in its sequence for the folding of the receptor attachment domain, allowing the NiV to adapt to various host cell receptors.

Clinical characteristics

The clinical presentation varies in severity with involvement of respiratory and neurological complications. After an initial incubation period of 6–11 days, although it varies and can last longer, patients typically complain of fever, drowsiness, myalgia, headaches, altered consciousness, and respiratory symptoms such as cough and dyspnea.[25,26] NiV infection was suspected when the triad of fever, headache, and an altered mental state was seen during the outbreaks. High fever, hypertension, and tachycardia are associated with a destitute outcome.[27,28] Subsequently, patients can develop hypotension that can be fatal, depicting the seriousness of the NiV clinical outcome. As the disease progresses, the notable changes include an altered mental status and signs of acute encephalitis. A peculiar clinical viral encephalitis depicts segmental myoclonus, areflexia, hypertension, and tachycardia. Some cases report respiratory distress and coma, after a 24-h period of seizures following encephalitis.[29]

Management

Investigation

Rapid investigations and screening strategies play a crucial role in diagnostic utility. Laboratory analyses can identify infection during the acute and convalescent phases of the disease. At earlier stages, nasal, throat, and cerebrospinal fluid samples allow for viral isolation via reverse transcription polymerase chain reaction (RT-PCR). Urine analysis, complete blood workup, serum neutralization tests, and IgG-IgM antibody detection by Enzyme-linked Immune Sorbent Assay (ELISA) are used to further consolidate the diagnosis. In fatal cases, the autopsy of tissues followed by an immunobiological analysis is the most effective confirmation technique. However, in addition to the current diagnostic procedures, animal inoculation studies can be used to enhance the diagnosis with greater sensitivity.[30]

Biosafety level four (BSL-4) facilities are required for serum neutralization and are considered to be the confirmatory diagnostic test. The NiV has been grouped into risk group four and only allowed to be handled within BSL-4 facilities as it is transmitted through aerosols and has a high mortality rate in humans, and no successful and effective therapies or vaccines are available at present.[31] However, the NiV has been shown to be relatively labile, thereby easily killed and inactivated with the use of detergents.[32] Once the virus has become inactivated or neutralized, it is sufficient enough to be handled through BSL-2 containment if a BSL-4 facility is not available. Halpin et al.[33] in 2007 developed an in-vitro reverse genetics system that does not necessitate the use of the infectious virus, allowing its use and further study of the NiV in BSL-2 facilities once the virus has become inactivated via reverse transcription.

Precise PCR and histology-based testing with the use of specific viral antibodies have begun to substitute standard serum neutralization testing methods in many countries.[34] Although most neutralization tests must be conducted in a BSL-4 facility, another diagnostic test involving a rapid neutralization assay using *Vesicular stomatitis virus*–pseudotyped particles expressing the F and G glycoproteins as target antigens can be conducted in BSL-2 containment.[35] This new diagnostic tests were shown to have comparable results with the existing tests. As such, it possesses the potential to become a rapid and cost-effective diagnostic test in epidemics, mainly in regions lacking high-level biosafety facilities.

Use of more advanced molecular techniques offers high sensitivity, specificity and speed. But there are very few of these techniques that have been adopted routinely in laboratories in those countries where the NiV is a cause for serious disease outbreaks. Despite the continuous advancements in the diagnostic technologies, emergence and reemergence of NiV infection can be attributed to factors limiting accurate and efficient diagnosis.[36] Pathogen identification by conventional methods can be laborious, difficult, and time-consuming. Lack of funding and laboratory facilities and training needed to effectively perform and accommodate these procedures are some of the challenges to standardize these advanced techniques. It is important that the instruments for molecular diagnosis should be built in a way that requires minimal operation, allowing these instruments to be deployed rapidly to remote areas in developing countries.

Treatment

Owing to the complex nature, treatment is limited to supportive care and direct resolution of symptoms. In severe cases, intensive care is required to treat the respiratory and neurologic complications. Ribavirin, an antiviral agent, is effective against the virus and was used during the 1998 Malaysian NiV outbreak, but there are inadequate animal and human studies on the efficacy of this drug, which leads to a high level of uncertainty.[37]

Current experimental studies using passive immunization with a human monoclonal antibody (mAb) targeting the Nipah G glycoprotein and active immunization with human vaccination are under different phases of the study and are expected to be available soon.[38] There is also an ongoing preclinical trial in the US and Australia[39] for the use of a mAb against pre-exposure and postexposure. The mAb m102.4h has been proven to be a potent neutralizer of the NiV in humans after evidence of its postexposure eradication of the infectious virus in animal models.

Vaccination and its Related challenges

There are many limitations to effective vaccine production due to the unpredictive outbreaks and limited cases. The lack of a biocontrolled environment and imperativeness of performing virulent NiV assays is a major hurdle. Researchers are

looking into pseudo-type viruses and multiplexed microsphere or ELISA assays that can overcome these limitations and allow assays to be performed under safety levels achievable at the majority of laboratories.

More research into reagent standardization and assay conditions between the antibody and immune protection is needed for an effective outcome. Over the last decade, there has been a conservable focus on the pathogenic strain, particularly on the search for host reservoirs, genome characteristics, and viral receptor identity. Other potential platforms that are of focus include subunit or live-vectored vaccines. Efforts have been made in developing a vaccination and other immunologic strategies for human cases; however, no such vaccine exits to date.

The NiV envelope glycoproteins have particularly been studied to determine their role in the infectious process. In 2012, Australia[40] released Equivac HeV, using a soluble recombinant and oligomeric form of G glycoprotein, the first veterinary subunit vaccine against the BSL-4 agent for prophylactic treatment in postexposed equines in an effort to prevent possible transmission. This vaccine was prepared from 293 F human embryonic kidney or Chinese hamster ovary cells. The latest evidence infers that a successful vaccine in preventing NiV infections is in fact possible.

Preventive measures

Owing to the unavailability of a vaccine at present, prevention is aimed at controlling the vector and possible transmission to humans. Infected bats shed the virus through saliva and urine on fruits while feeding, which can be a source of possible transmission in humans.[41] Sap collectors hang an earthen pot to collect the sap that drips out from the tapped tree, and these sap pots usually are found covered in bat feces, making them a source of contamination as well. Harvesters attempt to remove the fecal droppings through filtering with a net-like material before selling the sap, but neither this is always done nor it is a form of proper decontamination.[42] Nonetheless, different preventive measures have been used in different parts of the world, which can range from the application of a bamboo skirt and lime to more sophisticated modern scientific techniques.

Bamboo skirts[43] cover the tree, making it hard for bats to gain entry. This method is not commonly used because of its labor-intensive and time-demanding assembly. Similarly, smearing lime (calcium carbonate) on the tree and sap-collecting vessels acts as a bat repellent because of its pungent taste. These practices are indigenous to Northwest Bangladesh and can potentially provide local communities with a cost-effective solution to reduce chances of bat-to-human transmission. However, the precise efficacy of these methods is yet to be proven.

An alternative preventative outlook is to minimize future pathogenesis of the disease. Standard infection control practices and proper barrier medical techniques are valued in preventing nosocomial infection within hospitals. Hospital staff and more commonly female relatives provide care to patients particularly by feeding, bathing, cleaning the nose and mouth and other body parts, discarding of bodily fluids, and administration of medicines.[44] In many Eastern cultures, feeding is done by the hand, and family members feed the patient with direct contact. Furthermore, during the time before suspected death, family members desire to be closer to their loved ones. In addition, when family members suspect that the infection has reached its final stages and death is imminent, they may opt to bring their patient from the hospital to be taken care at home, where the chance for disease spread is comparatively very high.

Preventative measures to attain disease isolation, identifying active infectious cases, safe disposal of human corpses, and training of all healthcare workers should be executed in all at-risk regions.[45] Moreover, proper precautions such as protective clothing and gloves should be worn when handling patients with NiV infection. It is strongly advised that handwashing with soap and water should be followed strictly after dealing with an infected person or equipment that has come in contact with an infected person.[46] Evidence showed that the lack of protective equipment used in patient care in the home setting, as well as use of gloves, facial mask, and eye protection worn by healthcare workers in the clinical setting, has contributed to NiV disease spread.[47] Enhancing preparation provisions for future outbreaks should comprise amplified supervision of cases and their patterns, coordinated diagnostic measures, efficient training of the equipment operation, stocking adequate protective equipment supplies, and information on proper quarantine etiquette.[48]

Overall, current regulations for the obtainment and transport of diagnostic specimens should be altered to better integrate public health standards within NiV studies. Hospital staff, community, and religious leaders should educate local people and discourage such risky cultural practices in light of the consequences.[49] As a response to the annual outbreak, actions should be rapid and targeted with the primary focus being placed on biosecurity and biosafety.

Possible Alternatives and recommendations

The future direction should be to incorporate the use of a *Henipavirus* minigenome system and advancements made in the field of reverse genetics.[50] Recent progress uses live cell imaging techniques to study the morphogenesis and 'virus-like proteins' in relation to viral budding. This critically high-level research generated a better understanding of the basic viral properties and its surviving ability. This advanced information helps in epidemiological investigations during an atypical virus outbreak. By understanding how the reservoir hosts maintain asymptomatic infections, the evolution of cutting-edge strategies for detection and surveillance can be studied to present novel therapeutic alternatives.

Discussion

The NiV outbreak is a global health concern because of its high fatality and frequent reemergence. Its infection leads to severe disease affecting many systems of the body, particularly the brain, causing encephalitis.[51] Rapid disease progression is worsening, illustrating the need for controlling the outbreaks.

There has not been a successful treatment strategy for combating NiV infection thus far. The sporadic nature of these outbreaks along with the wide geographical niche of the fruit bat makes it highly challenging to control.[52] Prospective vaccines have been proposed using antigens from NiV outer membrane glycoproteins or fusion proteins to create defensive reactions in preclinical models. Nonetheless, these potential vaccine antigens are not well defined because of 'antibody neutralization' that prevents binding and fusion of the NiV within the host cells.

The NiV has caused a handful of outbreaks and has left radical devastations along its path. Although it infects a broad array of animal species, contamination by infected bats is the most common reason for disease spread. Domestic animals such as pigs, horses, goats, and sheep can also acquire the disease, helping in the transmission chain. Effective control of this epidemic viral crisis can be achieved by obtaining strict government regulations and surveillance. Routine farm inspections and quarantine of animal sites should be implemented for meticulous disinfection. Strictly regulated disposal of infected animals should be carried out along with safe burial and incineration of the remains. Furthermore, many challenges remain to reduce bat-to-human transmission through date palm sap consumption as the importance of this beverage in certain countries, such as Bangladesh, is deeply rooted in people's culture and way of life. Health education is lacking, and efforts made to communicate the ramifications associated with consumption of the date palm sap have been inadequate.[53] Undoubtedly, reducing ingestion of this drink would lower risk of NiV infection, and raising awareness about the NiV and its transmission patterns will strengthen the preventative efforts.

Definitive policies are also necessary to reduce human-to-human transmission. Nosocomial transmission can be reduced by restricting direct contact with an infected patient. Most people who are infected through this transmission were healthcare employees and caregivers.[54] It is complicated by the fact that many cultural norms dictate that the sick be looked after by family members, in the home or hospital settings. Low-income hospitals may not have the resources needed to adequately follow international infection control guidelines. But taking care of personal hygiene and handwashing can play an important role in controlling the infection during epidemics. It is necessary that hospitals restrict this leniency of allowing family members to take the main role of providing patient care during outbreaks and come up with new guidelines.[13] Communities, as well as hospital members, need to have a better understanding of the contagious process, and although culture dictates a high degree of hands-on care, the importance of refraining from such practices is essential to keep the NiV from spreading and killing further individuals and to ensure that these biosafety protocols are being followed. Communities, where the NiV is endemic, show high importance to religious leaders; therefore, educating these religious leaders and then advising them to teach others can help in better control of disease spread. Better training and more workshops on infection control protocols should be provided.

Understanding the reservoir host interactions and disease transmission cycle creates an opportunity for the evolution of cutting-edge strategies for early detection, better diagnostic techniques, a successful vaccination, and novel therapeutic agents. Overall, the most effective strategy is to anticipate the possible outbreak and be prepared at ground level. This starts with intergovernmental cooperation and sharing of information between different authorities.[55] Moreover, all the stakeholders including government, communities, and public and private sectors should acknowledge the problem, formulate preventive strategies, and work together to educate and spread awareness for long-term prevention and control.

Conclusion

The increasing number of NiV cases, especially in developing countries with limited resources, is a rising concern for global health. The unpredictability and limited cases pose challenges for diagnosis and management. Evidence of infection spread, possibly through consumption of swine, contaminated fruits, or even human-to-human contact, contributes to the growing importance of social practices. It is necessary to acknowledge these social norms for their definitive role in management of the outbreaks in addition to the vector control strategies. As such, anticipation, early preparedness, and partnership from both public and private government sectors are needed to effectively tackle this endemic crisis.

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