Clinical Management Protocol for Nipah Virus Disease

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1. Introduction:

Nipah virus (NiV) infection is an emerging zoonotic disease which was first recognized in a large outbreak of 276 reported cases in Malaysia and Singapore from September 1998 to May 1999.

In India, two outbreaks in human were reported from Siliguri (2001) and Nadia (2007), West Bengal.Fruit bats of *Pteropus* genus are the natural reservoir of NiV. There is circumstantial evidence of human-to-human transmission in India in 2001. During the outbreak in Siliguri, Forty-five (75%) of the 60 patients had a history of hospital exposure, i.e., they were members of the hospital staff or had attended to or visited patients in the hospital, suggesting nosocomial infection.

2. Epidemiology

2.1. Agent: NiV is a highly pathogenic paramyxovirus.

2.2. Natural Reservoir: Fruit bats of *Pteropus* genus are the natural reservoir of NiV. Pig is an amplifying host. It may become infected after consumption of partially bat eaten fruits that dropped in pigsty (as was evident in the Malaysia outbreak in 1998).

2.3. Host factors:
In Siliguri outbreak, all the 66 cases investigated by National Institute of Virology, Pune were above 15 years. In the current outbreak in Kerala, it is the economically productive age group which is involved and there is no sex differential.

2.4. Environmental Factors
Seasonality was strongly implicated in NiV outbreaks in Bangladesh and India. All of the outbreaks occurred during the months from December to May.

2.5. Mode of Transmission: Transmission of Nipah virus to humans may occur after direct contact with infected bats, infected pigs, or from other Nipah virus

infected people. Routes of transmission of Nipah virus have also been identified from its natural reservoir to human through drinking of raw date palm sap contaminated with NiV. However, human to human transmission has been attributed as one of the major modes of transmission in the epidemic in Siliguri and in the current outbreak in Kozhikode (Kerala)(May, 2018), India.

2.6. Incubation period: It varies from 4-21 days.

2.7. Period of Communicability: There is no clinical studies to suggest the period for which a patient will shed virus in different body fluids. In the absence of evidence, it is presumed that a person may be infective from the day of onset of symptoms till 21 days.

3. Pathogenesis.

The exact pathogenetic mechanism of Nipah infection is still not very clearly documented. Nipah infection primarily involves the blood vessels in the form of vasculopathy and vasculitis resulting in perivascular cellular infiltration, inflammation and necrosis. Due to high viremia it is very likely that several cytokines and chemokines are released causing vascular damage. Severity of the clinical symptoms and organ involvement are most likely dependent on the extent of vascular damage.

Post-mortem evaluation in one of the cases has revealed gross cerebral and pulmonary oedema. Cross-section of the brain and lungs showed evidence of gross pulmonary haemorrhage and cerebral congestion.

Pathological findings include :

- Vasculopathy and necrotizing vasculitis
- Cerebral oedema, with vascular congestion and focal haemorrhages.
- Pulmonary oedema with or without associated diffuse alveolar damage and haemorrhage.
- Neurons adjacent to vasculitic vessels may showeosinophilic infiltration and nuclear viral inclusions.
- In relapse cases, histopathology revealed cerebral oedema,

inflammation, endothelial syncytia, thrombosis and parenchymal necrosis.

4. Clinical features

4.1. Symptoms

Incubation period ofNipah infection is from 4 to 21 days. Initially non specific symptoms may be fever, headache, dizziness and vomiting. The hallmark of Nipah viral infection is the acute onset of following symptoms.

1. Moderate to high grade fever
2. Headache
3. Vomiting
4. Cough
5. Breathlessness
6. Change in behaviour/sensorium
7. Seizures/abnormal movement
8. Myalgia
9. Fatigue

In the Siliguri outbreak, the patients initially had fever (100%), headache and myalgia (57%), vomiting (19%), altered sensorium (confusion to coma, 97%), respiratory symptoms (tachypnea to acute respiratory distress, 51%), and involuntary movements or convulsions (43%).

In the current outbreak of Nipahvirus disease in Kerala it has been noted that most of the patients presented with moderate to high grade fever, headache often severe, vomiting and general weakness along with myalgia. Cough and breathlessness were also one of the presenting complaints seen in the majority of the patients. Breathlessness often progressed rapidly resulting in overt respiratory failure requiring use of supplementary oxygen and at times ventilator support. Respiratory failure requiring ventilator support was risk factors for high mortality.
Commonly observed neurological symptoms were headache, altered sensorium and seizures from the 3rd day of onset of fever. Most of the time headache was

associated with vomiting and altered behaviour.Thirty to forty percent of the patients presented with generalized or focal seizures which were controlled in most of the cases with the use of anticonvulsant medications.

Behavioural changes were often one of the initial presenting features before development of altered sensorium and unconsciousness. In a significant number of patients, the disease rapidly progresses to coma within five to seven days. Few cases may also show signs of cerebellar dysfunction.

Few patients also developed myocarditis, heart failure and pulmonary oedema often associated with or without cardiogenic shock. Coagulopathy may be seen in some of the cases with thrombocytopenia and raised d-Dimer.

4.2. Physical findings

Fever usually high grade and persists 5-7 days. In the Kozhikode, Kerala cohort, tachycardia and tachypnoea were noted in all of the patients and several of them progressed to overt respiratory distress with oxygen desaturation. At presentation most of the patients had normal blood pressure, no rashes, no haemorrhagic spot or bleeding from any sites.

Systemic examinationusually does not show any significant abnormalities. However, with the progress of the disease process there is often evidence of gradual fall in the haemodynamic parameters with failure of respiratory and cardiac compensatory mechanism evolving in to state of respiratory and cardiac failure. This is evident in the form of falling partial pressure of oxygen saturation levels and fall in blood pressure. Signs of overt cardiac failure may be present in some of the cases in early stages.

Conscious level could vary from fully alert to deeply unconsciousness. Feature of encephalitis or few cases of meningo-encephalitis may be present on 2nd or 3rd day onwards. Signs of meningeal irritation may not be present among these patients. Patients may be in altered sensorium, stuporous and violent behaviour.
On examination of the abdomen mild hepatomegaly with tenderness may be noted. On ultrasound or CT scan mild ascites and/or pleural effusion has been