GOVERNMENT OF KERALA

Abstract

Health & Family Welfare Department - Nipah Virus Infection - Revised Treatment Revised Guidelines - Approved - Orders issued.

HEALTH & FAMILY WELFARE (F) DEPARTMENT

G.O.(Rt)No.2363/2023/H&FWD Dated,Thiruvananthapuram, 16-09-2023

Read:- 1 Nipah Virus Infection Control Guidelines 2019 dated 06/2019

2 Management Plan for Nipah outbreak in Kozikode dated 05/09/2021

3 Nipah Treatment Protocol (Amendment) September, 2021 dated 05/09/2021

ORDER

The Nipah outbreak has been reported in Kozhikode District on 9th September, 2023 and received confirmation from NIV Pune. Nipah virus is a highly virulent zoonotic pathogen that can be transmitted between humans. For effective management of the disease, Government are pleased to approve and issue the ***"Nipah Virus Infection- Treatment Guidelines Revised - September 2023"*** incorporating Epidemiology, burden of disease, transmission, diagnosis and management of Nipah virus infection, as annexed to this order.

(By order of the Governor)
A P M MOHAMMED HANISH
PRINCIPAL SECRETARY

To:
The State Mission Director -National Health Mission, Thiruvananthapuram.
The Director of Health Services, Thiruvananthapuram.
The Director of Medical Education, Thiruvananthapuram.
All District Medical Officers (Health).
All Superintendents, Medical College Hospitals.
Principal Accountant General (A&E/Audit) Kerala.
Information & Public Relations (Web & New Media) Department.
Stock File/ Office Copy to F2/288/2023-HEALTH.

Forwarded /By order

Signed by
Vilasini K V
Date: 16-09-2023 16:09:14
Section Officer

Copy to:
Private Secretary to the Hon'ble Chief Minister
Private Secretary to the Hon'ble Minister (Health)
OSD Chief Secretary
PS to Principal Secretary (Health)

Annexure

Nipah Virus Infection- Treatment Guidelines– Revised September 2023

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Introduction:

Nipah virus is a highly virulent zoonotic pathogen that can be transmitted between humans. Nipah Virus (NiV) Infection recognized as a deadly infection in 1998 garnered attention in Kerala with the outbreaks in 2018, 2019 and 2021. Knowledge about the transmission dynamics, epidemiological aspects and the magnitude of the disease burden are essential to plan strategies for preparedness, early detection, timely management and appropriate interventions to tackle the situation on an urgent basis.

1.1 Epidemiology

- **Agent: Nipah Virus (**NiV) is a highly pathogenic RNA virus belonging to the *Paramyxoviridae* family and grouped under the genus *Henipavirus. Two NiV clades have been proposed so far; B genotype in Bangladesh, and M genotype in Malaysia.* The complete NiV genome of the Kerala strain had 85.14%–96.15% similarity with M and B NiV genotype.
- **Natural Reservoir:** Large fruit bats of *Pteropus* genus are the natural reservoir of NiV. Pigs are identified as intermediate hosts. In a study conducted during the outbreak in 2018, high positivity of NiV was detected in bat throat swabs, and showed persistence of virus for a couple of hours on contaminated fruits, which enhance the chances of human infection. NiV positivity was identified in bats from North Eastern Region states and Kerala. A recent ICMR/NIV serosurvey among bats demonstrated the presence of Nipah IgG among bats sampled from 9 states and one union territory.
- **Seasonality** was strongly implicated in NiV outbreaks in Bangladesh and India. All the outbreaks occurred during the months of December to May. But in 2021 the case was diagnosed in the month of September.
- **Incubation period:** varies from 4-21 days.

1.2 **Burden of disease:** In the 1998 to 1999 Malaysian outbreak, human infection occurred from infected bats through infected pigs as intermediate animal host by direct contact with respiratory secretions and urine from infected pigs. In Bengladesh and India the transmission happened from bat to human and later from human to human. So far three outbreaks have been reported from Kerala. From Kozhikode in 2018, Kochi in 2019 and Kozhikode in 2021. During the first outbreak reported from Kerala in May 2018, apart from the index patient, 18 confirmed and 4 probable cases were identified. Two confirmed patients survived in that outbreak. In Kochi, May 2019 one patient was confirmed of Nipah but no further spread was identified. In September 2021 one patient was diagnosed with Nipah in Kozhikode. India comes within the Nipah virus distribution map and there is a risk of spill over and transmission to humans. The delay in diagnosis will increase the chance of spread to humans through the risk of increased human to human spread. The knowledge about the ecology of bats and NiV and the seasonality of the disease is important in prevention of future outbreaks.

1.3 **Mode of Transmission:**

Human infection results from spillover transmission from bats or through human-to-human transmission. Direct bat-to-human transmission occur through fruits contaminated by bat's secretions -urine , saliva, reproductive fluids- or by consumption of raw date palm sap [*tari*] contaminated by bat saliva. In the Malaysian outbreak, human infection occurred through contact with respiratory secretions and urine from infected pigs, which got infected after consumption of partially bat eaten fruits dropped in pigsty. The infection got controlled once the cause of infection was identified and health education, barrier precautions were advised to people handling the pigs and pig culling operations were conducted. Unlike Malaysia and Singapore, the

outbreaks in Bangladesh and India pigs were not identified as intermediate hosts and transmission was from bat to human and human to human. In the 2014 Philippines outbreak, infected horses were identified as the intermediate hosts.

Clustering of symptomatic cases mainly adults among close contacts and households is an important clinical clue to this infection. In 2018 Kerala outbreak, all cases except the index case the transmission was from human to human.

Diagnosis

Early identification and diagnosis is of prime importance in NiV infection. The case management includes strategic plans to prevent spread through contacts and this requires proper triaging and isolation. Understanding definition of cases and contacts becomes very important here.

2.1 Definitions - Case & Contact

1. **Case Definitions**

a. **Suspect Nipah Case**

Person from an area/ locality affected by a Nipah virus disease outbreak who has:

- Acute Fever with new onset of altered mental status or seizure and/or
- Acute Fever with severe headache and/or
- Acute Fever with Cough or shortness of breath

b. **Probable Nipah case**

- Suspect case-patient/s who resided in the same village where suspect/confirmed case of NIPAH were living during the outbreak period and who died before complete diagnostic specimens could be collected.

OR

- Suspect case-patients who came in direct contact with confirmed case-patients in a hospital setting during the outbreak period and who died before complete diagnostic specimens could be collected.

c. **<u>Confirmed Nipah Case</u>**

Suspected case who has laboratory confirmation of Nipah virus infection either by:

- Nipah virus RNA identified by PCR from throat swab, urine, serum or cerebrospinal fluid (optional).
- Isolation of Nipah virus from throat swab, urine, serum or cerebrospinal fluid.

d. **Definition of a contact:**

A Close contact is defined as a patient or a person who came in contact with a Nipah case (confirmed or probable cases) in at least one of the following ways.

- Was admitted simultaneously in a hospital ward/ shared room with a suspect/confirmed case of Nipah virus disease
- Has had direct close contact with the suspect/confirmed case of Nipah virus disease during the illness including during transportation.
- Has had direct close contact with the (deceased) suspect/confirmed case of Nipah virus disease at a funeral or during burial preparation rituals
- Has touched the blood or body fluids (saliva, urine, vomitus etc.) of a suspect/confirmed case of Nipah virus disease during their illness
- Has touched the clothes or linens of a suspect/confirmed case of Nipah virus disease

These contacts need to be followed up for appearance of symptoms of NiV for the longest incubation period (21 days). They must be transported to appropriate care facility if they develop symptoms with proper infection control practices.

2.2 Clinical features

- Fever, Altered mental status, Severe fatigue, Headache, Respiratory distress, Cough, Vomiting, Muscle pain, Convulsion, Diarrhoea

- In infected people, Nipah virus causes severe illness characterized by inflammation of the brain (encephalitis) or respiratory diseases.
- The syndromic presentations are ARDS, Myocarditis and Encephalitis. Patients can present with fever alone. All patients coming with fever with any other symptom having an epidemiological link and history of contact must be treated as NiV infection and must be tested for the NiV infection.
- In general, the case–fatality rate is estimated at 40–75%; however, this rate can vary by outbreak and can be upto 100%.

2.3 Laboratory diagnosis

2.3.1 Investigations to be done for confirmation of diagnosis

- Real-Time RT-PCR Viral RNA
- Anti-NiV IgM and IgG antibodies by enzyme-linked immunosorbent assay

2.3.2 Sample collection and transport and testing guidelines

Laboratory confirmation of a suspect and also a symptomatic with definite history of contact case can be made during the acute and convalescent phases of the disease by using a combination of tests**.** The samples have to be sent to designated laboratories identified as per protocols prepared.

Sample Collection and Transport Guidelines:

Universal, standard droplet and bio-containment precautions should be followed during contact with excretions, secretions and body fluids of suspected patient for Nipah virus. Adequate bio-safety precautions should be adopted during collection/transport/ storage/ processing of suspected sample.

Sample collection:

The samples should be collected in all patients (suspect or symptomatic with contact with Nipah) as early as possible with all bio-safety precautions and documening the clinical details on the proforma (provided from the testing laboratory).

Sample collection should be done only AFTER ADMISSION into an isolation facility, and ensuring that the staff member doing the collection is following proper infection control practices.

During sample collection wear complete disposable Personal Protective Equipments (N 95 mask, double surgical gloves, gowns, goggles foot cover, etc). Wash hands with soap and water at least for 30 seconds and then clean hand using alcohol based hand sanitizer before and after collection of samples.

The recommended samples are

- Throat swab in viral transport medium
- Urine 10 ml in universal sterile container
- Blood in red vacutainer (5ml)
- CSF (1-2 ml) in sterile container

Transportation and Storage of samples:

- Samples should be safely packed in triple container packing and should be transported securely under cold chain (2-8°C) to the testing laboratory with prior intimation.
- Sample containing vials, tightly closed, should be kept in good quality zip-lock bags wrapped with sufficient absorbent cotton padding so that inside material should not come out of bag if it leaks. The plastic bag should be kept in another Zip-lock bag similarly, which should be sealed with adhesive tape. This carrier should be placed in a hard container sealed with impermeable tape or plaster and placed in thermocol box /vaccine carrier containing ice packs. The case sheets with complete information should be placed in plastic bag and should be pasted **outside the container**.

- Samples should be transported at 2-8°C to the have to be sent to NIV Pune, NIV field station, Alappuzha or as per the testing protocols.

2.3.3 Disposal of supplies/waste:

The proper disposal of biomedical waste is a challenge in such type of infections. Must be done adhering to strict infection control practices to ensure safety of all personnel involved. This has to be supervised and properly co-ordinated by the hospital infection control committee.

2.3.4 **Point of care testing (POC):**

Early diagnosis was a challenge for appropriate prompt management in outbreak 2018. High containment laboratory facility for quick diagnosis was identified as a need for the same. In Government Medical College, Ernakulam during 2019 outbreak a POC micro PCR assay for NiV detection and ELISA testing facility could be started with technical support from NIV, Pune. If such facilities are available, it must be utilized. The facility for screening dengue, Japanese encephalitis and West Nile virus infection in all NiV negative cases will help to narrow down the diagnostic possibilities in seriously ill patients. This will help to incorporate appropriate modifications in the management

2.3.5 Other Investigations for patient management

NiV infection is similar to any other viral infection and it is a clinical challenge to diagnose it early and to ensure all safety measures and infection control practices to prevent human to human transmission. Nipah virus is classified as a biosafety level 4 pathogen. The laboratory should be informed if a clinical suspicion is made and the facilities must be the same for all other investigations done for the patient considering its high pathogenicity in humans. All treatable cases like bacterial infections, malaria and herpes encephalitis must be included in the differentials depending on the clinical presentation. Tests must be ordered appropriately.

3. Management of Nipah virus infection

NiV infection is different from other viral infections or pathogens because of its potential of transmission from human to humans with high mortality with no definite treatment or vaccine so far identified. Hence the management essentially involves infection control practices , triaging, isolation and management of patients including intensive supportive care. The Emergency Department must be sensitized for early identification, proper isolation and management of patients suspected of NiV infection to minimize the risk of human to human transmission.

To manage the fever triage and isolation facility, a separate team should be trained and appropriately delegated for its implementation. The team should include health care providers as a single unit. The senior cadre nurses must be responsible for maintaining the overall co-ordination, in charge of movement and sick registers of the health care providers, ensuring the proper donning and doffing, auditing of the appropriateness of training of the health care providers, ensuring availability of all supplies including drugs, disposables , consumables, food and other supplies for patients in the isolation unit etc. The area must be strictly restricted to the purpose and clearly demarcated. Collection and transportation of samples must be documented and reports must be properly collected. The preparation and handling must be done as per protocols in designated area and with appropriate co-ordination.

The important points in management are discussed in detail below.

3.1 Triaging of patients

- **All patients having fever must report to Fever triage from where they will be sent to the isolation facility in case of epidemiological link.**
- Ensure strict adherence to proper Triaging
- **Proper infection control practices must be followed .**

- Ensure personal safety. Wear apron and gloves as appropriate.
- General measures – ABCDE approach (Airway, Breathing, Circulation, Disability, Exposure)
- Plan for appropriate care including intensive supportive care

The most important step in patient care is intensive supportive care.

3.2 Setting up an isolation facility

Who should be kept in isolation facility/ward/ICU

- History of close contact with confirmed case presenting with fever or any symptoms suggestive of Nipah infection (*vide* clinical features)
- Health care provider who has come in contact with the patient with fever / severe headache/altered sensorium/breathlessness/cough
- Patients with high clinical suspicion – Encephalitis/ARDS/Myocarditis during an outbreak

Isolation facility

- Enter all the details of HCWs entering the isolation facility in the Register for ensuring appropriate follow up
- Only HCWs trained in infection control practices should be posted in the isolation facility.
- Monitor staff health, sick people should not be allowed at work.
- They must report immediately through the contact numbers provided if they develop any health related problems during the period and up to another 21 days after the last day of duty
- Infection control practices should be strictly adhered and audited
- Proper instructions should be followed while entering the room
- The entry of the health care provider should be through Donning area, and then to the triage or treatment area. The exit should be separate for the health care provider and there should be facility for doffing and appropriate facility for hand washing / bathing.
- Patient entry and shifting should be separately marked.

- The deceased should be handled separately as per protocols.
- Single room with attached toilet facility must be provided for each patient.
- Separate dedicated equipments (BP apparatus, Stethoscope, Thermometer, Pulse oximeter) for each room and only disposable consumables should be used.

3.3 Treatment

3.3.1 Supportive measures including Standard care of ARDS, Myocarditis and Encephalitis

Standard care must be provided as in any other infection presenting with Encephalitis, ARDS, and/ or Myocarditis.

Care should be individualized according to the clinical presentation and management decisions of the Institutional Medical Board.

The basic supportive measures are outlined below:

a. Isolation of patient in the isolation facility

b. Use of PPEs

c. Hand washing with soap & water before and after handling/visiting patients

d. Resuscitation (if needed): ABC : Airway,Breathing , Circulation

e. Care of unconscious patient: change of posture, care of eye, bladder, bowel and mouth

f. O2 inhalation if there is respiratory difficulty

g. Nutritional support: oral/NG tube feeding according to the condition of the patient

h. Maintain fluid and electrolyte balance (Adults: 5% DNS, Children: 5% DNS, half or quarter strength saline)

i. Fluid restriction: 30% restriction particularly in children. 2/3 of the daily maintenance can be given in children if the child is not in shock

j. Maintain intake output chart

k. Bronchodilators when needed may be given through spacers

3.3.2 **Drug Treatment options**

No approved drugs or vaccines are currently available. There is an unmet need for newer therapeutic options for NiV infection. In diseases like NiV infection, any new drug can be tried only during an outbreak situation and that too strictly adhering to the clinical trial protocol. Hence preparedness is a priority for any future outbreak as the need occur as an emergency. Nipah clinical research facility needs to be adhering to infection control practices, isolation facility, trained clinical and laboratory team and patient and family support for timely information and consent.

Currently the available treatment options are very limited.

3.3.2 .1 Ribavirin

Ribavirin is a nucleoside analogue with broad activity against several RNA and some DNA viruses. Used in Malaysian outbreak in an open label trial with 36% reduction in mortality, but further studies in animal models proved ineffective.

In the Kerala outbreak 2018, the drug was started in 10 patients.Both the survivors had received full course of treatment. The dose used was 2 g stat, 1 g 6 hourly 4 days followed by 500mg 6 hourly for 5 days (based on WHO guideline for other haemorrhagic fevers) on confirmation of NiV infection. (Available as 200 mg capsules – Day 1- 10 capsules stat, then 5 capsules of 200 mg 6 hourly for first four days followed by 200 mg capsules 3-2-3-2 for 5^{th} to 10^{th} day – total of 150 capsules). No major side effects reported with Ribavirin. In Kerala outbreak 2019, the one patient with confirmed NiV infection had received Ribavirin but started only on confirmation by 9^{th} day of illness.

Adverse effects of Ribavirin: Rare if used for short term. The Major adverse effects on long term treatment are hypersensitivity, hemolytic anemia, significant teratogenic and/or embryocidal effects in animal studies, bone marrow suppression. The complete haemogram and LFT need to be monitored. Patients who receive Ribavirin must be counselled about the teratogenicity as it may persist in non-plasma compartments for as long as 6 months. Hence effective contraception must be utilized upto 6-months after the drug use.

3.3.2.2 Monoclonal antibody M102.4

M102.4 recognizes the G envelope protein of NiV and appears to block the receptor binding site on the protein preventing adhesion to the Ephrin B2 protein and thereby inhibiting viral entry into the host cell.

During the NiV outbreak in Kozhikode, Kerala in 2018 the m102.4 monoclonal antibody, an experimental therapeutic, was imported for treatment of NiV infected patients on compassionate ground. The SOP (Standard Operating Procedures) and protocols were prepared with the support from ICMR. But it was not used as the outbreak had ended by that time. In Kochi 2019 outbreak the m102.4 was not used as there were no new confirmed cases and the patient was towards the recovery phase when the NiV infection was confirmed. The m102.4 monoclonal antibody is an investigational drug and requires Emergency Research Response & Resources for using such an investigational drug. This becomes a high priority area because of the high mortality of this infection.

The indications and guidelines for use of m102.4 is prepared and to be used with appropriate knowledge and training of the research team as in any other clinical trials with Ethics committee approvals and consenting process. The protocols and SOPs must be referred in detail in this regard and to be modified appropriately according to the then available scientific knowledge.

3.3.2.3 Remdesivir

Remdesivir (GS-5734) is a nucleotide analog prodrug with broadspectrum antiviral activity that has shown to inhibit filovirus, coronavirus, and paramyxovirus replication. **R**emdesivir has been effective in nonhuman primates when given as post-exposure prophylaxis, and may be complementary to immunotherapeutic treatments. In vitro, remdesivir showed potent antiviral activity against both Malaysian and Bangladesh genotypes of Nipah virus and reduced replication of Nipah virus Malaysia in primary human lung microvascular endothelial cells by more than four orders of magnitude, warranting further testing of the efficacy of remdesivir against Nipah virus infection in vivo. Because of the poor stability of remdesivir in rodents, the therapeutic efficacy was tested in the African Green monkey [AGM] model of lethal Nipah virus Bangladesh challenge. Remdesivir may be effective in both the treatment of nipah virus infection as well as in post-exposure prophylaxis on a compassionate ground as data on the same is available only from in vitro studies. Dose of remdesivir for treatment and post exposure prophylaxis is not known. A loading dose of 200 mg iv followed by 100 mg iv once a day may be used for upto 12 days. Remdesivir should be used with caution in patients with creatinine clearance less than 30 ml/min and SGPT more than 5 times upper limit of normal. The same dose and duration may be used for post exposure prophylaxis. Recent studies have shown that Remdesivir was not associated with development of AKI or hepatotoxicity in patients with eCrCl < 30 mL. A recent study on AGM model by Emme de wit et al showed that remdesivir treatment initiation on 3 dpi [day post infection] provided partial protection from severe Nipah virus disease that was dose dependent, with 67% of animals in the high dose group surviving the challenge. However, remdesivir treatment did not prevent clinical disease, and surviving animals showed histologic lesions in the brain. Thus, early administration seems critical for effective remdesivir treatment during Nipah virus infection.In this study double the dose of remdesivir was used in high dose group. A case of meningoencephalitis from an Ebola virus relapse was treated daily for 14 days with 225 mg remdesivir (Jacobs et al., 2016); this is higher than the currently

recommended human dosing of 200 mg remdesivir loading dose followed by 100 mg daily. However, other than this single patient, there are no safety data to support the use of this treatment regimen. And hence in patients who are rapidly deteriorating due to Nipah due to nectosing pneumonia and encephalitis, a higher dose of remdesivir ie 200 mg loading and 100 mg twice a day may be administered. Alternatively, remdesivir treatment could be combined with other treatment options such as m102.4 monoclonal antibody treatment, which has shown efficacy in African green monkeys infected with Nipah virus, genotype Bangladesh, and was successfully tested in a phase 1 human clinical trial (Mire et al., 2016; Playford et al., 2020).

[Ref;

1. Remdesivir protects African green monkeys from NIpah virus challenge: Michael K. Lo et al: Sci Transl Med. 2019 May 29; 11(494): . doi:10.1126/scitranslmed.aau9242.

2. Late remdesivir treatment initiation partially protects African green monkeys from lethal Nipah virus infection Emmie de Wit et al, Antiviral Research Volume 216, August 2023

3. CDC-Treatment of Nipah]

Favipiravir

The viral RNA-dependent RNA polymerase (RdRp) inhibitor favipiravir was developed by as an antiviral for use against infuenza. It is currently licensed in Japan for the treatment of novel or re-emerging infuenza and has also undergone several phase 3 clinical trials in the United States and Europe for use against infuenza. Favipiravir acts as a purine analogue, which selectively inhibits viral RdRps. In addition to its potent anti-infuenza activity, favipiravir

has demonstrated efficacy against a wide variety of other RNA viruses including bunyaviruses, arenaviruses, floviruses, norovirus, faviviruses, alphaviruses, enteroviruses, and rhabdoviruses. Of note, recently completed phase 2 clinical trials for use in Ebola virus infection suggest that favipiravir treatment may result in reduced mortality when given to patients with moderate viral loads. Activity against paramyxoviruses has been demonstrated in vitro for respiratory syncytial virus, measles virus, human metapneumovirus (hMPV), human parainfuenza virus , Newcastle disease virus, and avian metapneumovirus and in vivo against hMPV in a hamster model.

In vitro studies and in vivo studies in Syrian hamster model study clearly demonstrate the efficacy of favipiravir against highly pathogenic henipaviruses, and provide a foundation for further studies regarding the optimization of doses, routes, and timing of treatment after infection. Additionally, while in vivo efficacy was demonstrated for NiV-M, efficacy must be confrmed against HeV and NiV-B.

Favipiravir may be used on a compassionate ground for the treatment and post exposure prophylaxis of nipah virus infection. Even though dose of favipiravir for treatment or post exposure prophylaxis in humans is not studied, a loading dose of 1800 mg twice a day for one day followed by 800 mg BD for next 13 days may be used. Favipiravir should be used with caution in patients with creatinine clearance less than 30 ml/min and SGPT more than 5 times upper limit of normal.

[Ref: Favipiravir protects against Nipah virus infection in the hamster model: Brian.E.Dawes et al ;Nature-scientific reports (2018) 8:7604 | DOI:10.1038/s41598-018-25780-3].

POST EXPOSURE PROPHYLAXIS

For post exposure prophylaxis on a compassionate ground Inj Remdesivir or Favipiravir may be used. Since remdesivir has been found to be effective

against NIV-B in both vitro and in vivo AGM, it may be preferred over favipiravir whose effectiveness was tested only in NIV-M.

Dose –

1.Inj Remdesivir 200 mg loading and 100 mg iv OD for 12 days

2.Favipiravir 1800 mg BD for 1 day followed by 800 mg BD for next 13 days.

Role of immunomodulators in treatment of Nipah virus infection

COVID-19, Ebola virus disease, Nipah virus infection, SARS, and MERS are suggested to be considered for a novel immunological reclassification as acute onset immune dysrhythmia syndrome (n-AIDS) due to altered monocytic, Th1/Th2, as well as cytokines and chemokines balances. n-AIDs is postulated to be the cause of the acute respiratory distress and multi-inflammatory syndromes which are described with fatal COVID-19, and immunomodulators are suggested to effectively manage the mentioned diseases as well as for other disorders caused by Th1/Th2 imbalance. Studies show that Nipah virus might manipulate the inflammatory and immunological response including the interferon homeostasis . Nipah virus infection was also shown to influence the pro-inflammatory and leucocyte attracting cytokines in a manner that determines the disease course and to induce a dysregulated immune recruitment that led to acute vasculitis among other several induced immune dysregulatory mechanisms.

- In diagnosed cases of Nipah encephalitis early administration of immunomodulators [steroid pulse therapy] may be considered in patients with features of raised ICT, GCS □8 or rapid neurological deterioration.

- As early use of immunomodulators in Nipah encephalitis is not supported by robust scientific evidence, the decision must be made based on opinion of institutional medical board on a case to case basis.
- Immunomodulators may also be considered if patient has features of cytokine storm Grade 3 or 4 or secondary HLH.

3.3.3. Standard care for Encephalitis, Myocarditis and ARDS

a. **Standard care for encephalitis**

Patients with increased intracranial pressure

- Management of fever, pain, control of cough and other strains. Manage Fever, pain with paracetamol, avoid NSAIDs
- Prevention of seizures
- Control of systemic hypertension
- Elevate head above the heart (usually 30 degrees)
- Furosemide 0.5 to 1.0 mg/kg IV and / or mannitol 1 g/KgIV over 30-60 minutes, Repeat dosing can be given as needed, generally every eight hours– provided circulatoryvolume is protected
- IV Sedation and mechanical ventillation

Seizures

- Lorazepam 4 mg IV or
- Phenytoin 100mg IV q6-8h or
- Fosphenytoin 150PE q8h IV or
- Levetiracetam 500mg q8-12h IV

Raised ICP (suspect in altered sensorium, anisocoria, lateral rectus palsy, decorticate or decerebrate posturing, abnormal breathing pattern, hypertension etc.)

- Keep head in mid position and head end elevation 15-30 ^{0} to facilitate venous drainage
- 3% saline 5ml/kg (especially if BP low) or mannitol 2.5 to 5 ml per kg
- IF GCS <8 Intubate with Rapid Sequence Intubation raised ICP protocol
- Maintain euthermia, euglycemia, normal Blood pressure.
- Avoid hypoxia and Hypercarbia.
- Adequate sedo-analgesia

b. Standard care for myocarditis

Supportive therapy for symptoms of acute heart failure with use of diuretics, nitroprusside, ACE inhibitors.

- Inotropes- Dobutamine- 2–5 micrograms/kg/ min, titrated up to 20 micrograms/kg/min- Inotrope and potential vasodilator; lowers blood pressure; give as individual agent as long as systolic blood pressure (SBP) 90. Can use as combination therapy with Noradrenaline in patients with low systolic blood pressure.
- Dopamine-3–5-micrograms/kg/ min, titrated up to 20micrograms/kg/ min as needed-Inotrope and vasoconstrictor; increases left ventricular end-diastolic pressure and causes tachyarrhythmias Can be used with dobutamine.
- Norepinephrine-2 - 50 micrograms/min (0.02 – 2 micrograms/kg/minute) titrate to response-Vasoconstrictor and inotrope; preferred as a single agent over dobutamine if SBP <70. Can use combined with dobutamine.

c. Standard of care for ARDS

- For mild ARDS, non invasive ventilation stands as the first-line approach.
- Patients who have a diminished level of consciousness, vomiting, upper GI bleed, or other conditions that increase aspiration risk are not candidates for NIPPV.
- Other relative contraindications include hemodynamic instability, agitation, and inability to obtain good mask fit

- Severe ARDS is often associated with refractory hypoxemia, and early identification and treatment of hypoxemia is mandatory.
- For mechanical ventilation specific settings are recommended: limitation of tidal volume (6 ml/kg predicted body weight), adequate high PEEP , a recruitment manoeuvre in special situations, and a 'balanced' respiratory rate (20-30/min)for appropriate baseline minute ventillation. Consider the use of incremental FiO_2/PEEP combinations to achieve oxygenation goal (PaO_2 55-80 mm Hg or SpO_2 88-95 %)

3.3.4 Other therapeutic options

As there are no approved drug so far and as NiV is an infection with definite potential for human to human transmission and high mortality we must be ready to accept newer therapeutic options in any future outbreaks. The preparedness for research well in advance of the outbreak is the priority in this infection.

3.3.4: Psychosocial interventions: For the patient, for those contacts kept in isolation facility for testing, family members and community contacts must be planned and administered.

3.4 Criteria for discharge and follow up

Criteria for discharge of a patient from isolation facility presented with suspected Nipah and tested negative

1. Tested negative and totally symptom free can be discharged with observation at home for total of 21 days.
2. Tested negative and continue to have fever and other symptoms need a repeat testing after two days to exclude NiV infection .If there is, a strong history of contact with NiV infected patient/sample, the suspect should be subjected to repeat testing every two days till patient becomes symptom free.
3. No need of repeat testing if tested negative on two occasions found negative and an alternate diagnosis is made.

Criteria for discharge of confirmed case

- Clinically stable
- Nipah RT-PCR from all three samples (Throat swab, Urine and blood) reported negative on two occasions at least 5 days apart.
- To be decided by the treating clinician and confirmed by the Medical board

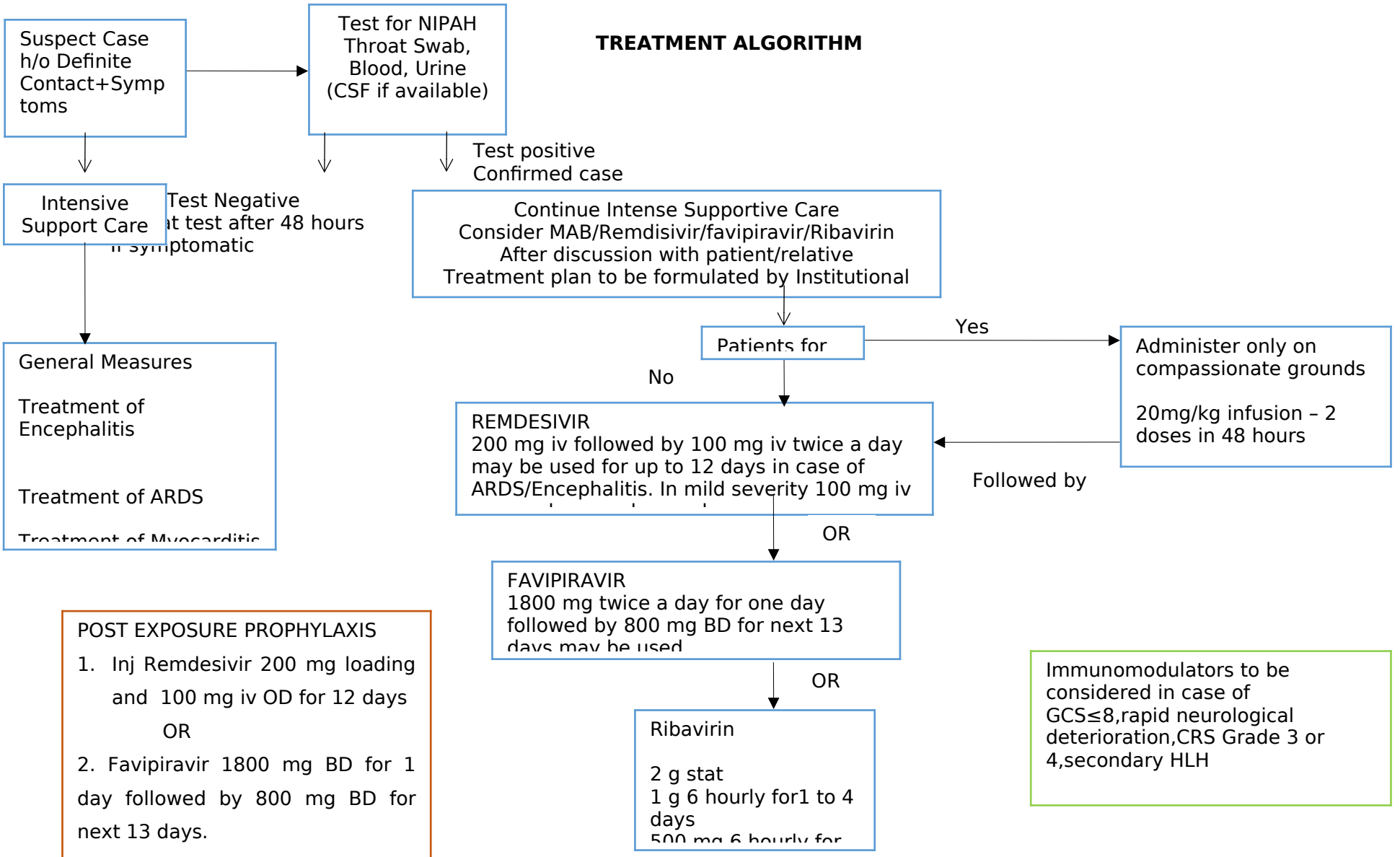
Follow up

The discharged patient should remain in isolation at their residence for 4 weeks after the discharge.

Patient is advised follow up on 28days, 56 days and 90 days of discharge

All patients with confirmed NiV infection should be kept under long term follow up as there are reports of relapse and late onset encephalitis in an earlier series.

Treatment algorithm


TREATMENT ALGORITHM
Suspect Case h/o Definite Contact+Symptoms
Test for NIPAH Throat Swab, Blood, Urine (CSF if available)
Test positive Confirmed case
Intensive Support Care
Test Negative
Continue Intense Supportive Care
Consider MAB/Remdisivir/favipiravir/Ribavirin
After discussion with patient/relative
Treatment plan to be formulated by Institutional
General Measures
Treatment of Encephalitis
Treatment of ARDS
Yes
No
Administer only on compassionate grounds
20mg/kg infusion – 2 doses in 48 hours
REMDESIVIR
200 mg iv followed by 100 mg iv twice a day may be used for up to 12 days in case of ARDS/Encephalitis. In mild severity 100 mg iv
Followed by
OR
FAVIPIRAVIR
1800 mg twice a day for one day followed by 800 mg BD for next 13 days may be used
OR
Ribavirin
2 g stat
1 g 6 hourly for1 to 4 days
POST EXPOSURE PROPHYLAXIS
1. Inj Remdesivir 200 mg loading and 100 mg iv OD for 12 days
OR
2. Favipiravir 1800 mg BD for 1 day followed by 800 mg BD for next 13 days.
Immunomodulators to be considered in case of GCS≤8,rapid neurological deterioration,CRS Grade 3 or 4,secondary HLH