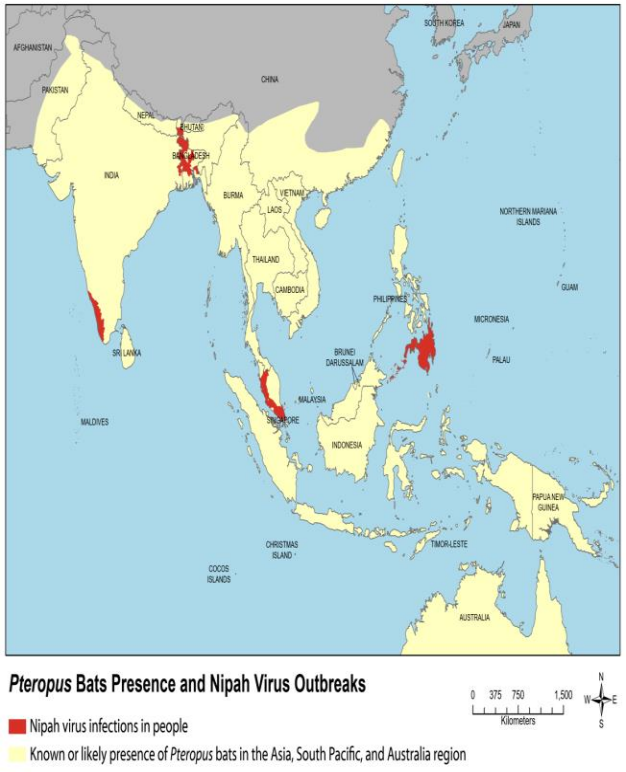
NIPAH MANAGEMENT GUIDELINES

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

NIPAH VIRUS(NiV)

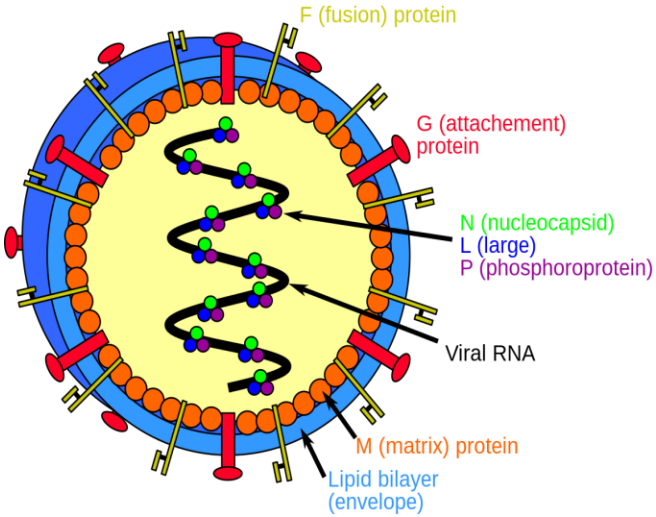
- In the 1998 to 1999- Malaysian outbreak by contact with respiratory secretions and urine from infected pigs.
- In Bangladesh and India - from bat to human and later from human to human.
- India comes within the Nipah virus distribution map (at risk of spill over and transmission to humans).



NiV in Kerala

- First outbreak - Kozhikode(May 2018)-18 confirmed and 4 probable cases identified(apart from index case). Two survived
- Second Outbreak- In Kochi(May2019) one patient was confirmed of NiV no spread.
- Third Outbreak –In Kozhikode(September 2021) one patient diagnosed .

EPIDEMIOLOGY



AGENT

- Highly virulent zoonotic pathogen
- Highly pathogenic RNA virus of *Paramyxoviridae* family , under the genus *Henipavirus*
- *Two NiV clades*
  - *B genotype in Bangladesh, M genotype in Malaysia.*
  - *Kerala genotype* 85.14% similarity with M and 96.15% similarity with B genotype.

RESERVOIR

- Natural reservoir- Large fruit bats (*Pteropus* genus)
- Intermediate Hosts – Pigs
- Contaminated fruit harbor's virus for few hours
- Kerala and North Eastern states of India-Throat swab positive bats identified
- NiV exhibits seasonality (December- May), Breakthrough infection also reported (eg. September in 2023)

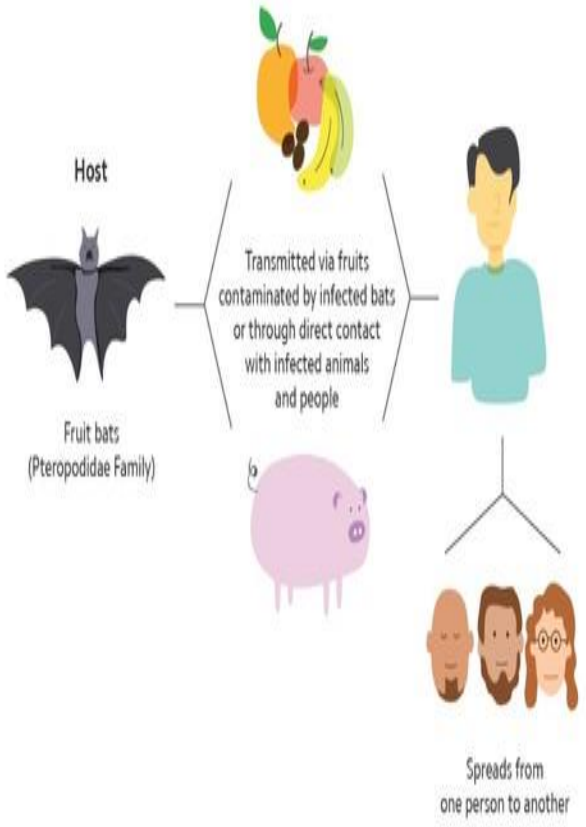
- **Incubation Period** :- 4 to 21 days

MODE OF TRANSMISSION

1. Spillover transmission

- From bats through fruits contaminated by bat's secretions - urine , saliva, reproductive fluids- or by consumption of raw date palm sap [*tari*]
- From pigs infected by consumption of contaminated fruits with NiV positive bat saliva through contact with their respiratory secretions and urine (Malaysia and Singapore)
- From infected horses (2014 Philippines)

2. Human-to-human transmission.



- **Important Clinical Clue**
  - Clustering of symptomatic cases mainly adults among close contacts and household.

Diagnosis

CASE DEFINITIONS

a. Suspect Nipah Case-

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

1. Acute Fever with new onset of altered mental status or seizure and/or
2. Acute Fever with severe headache and/or
3. 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

Ssuspect 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. **Confirmed Nipah Case**

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

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

DEFINITION OF A CONTACT

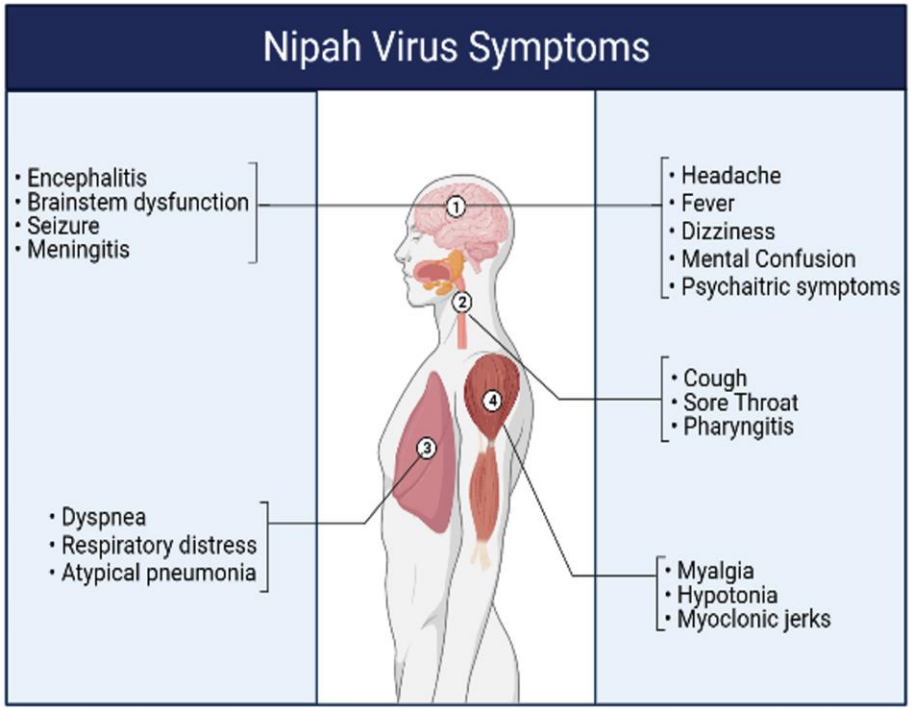
- A Close contact is defined as a patient or a person who came in contact with a Nipah case (confirmed or probable cases) in at least one of the following ways.

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

- Contacts to be followed up for appearance of symptoms of NiV for the longest incubation period (21 days).
- Must be transported to appropriate care facility if they develop symptoms with proper infection control practices

CLINICAL FEATURES

1. Fever
2. Severe fatigue
3. Muscle pain
4. Headache
5. Vomiting
6. Altered mental status
7. Convulsion
8. Cough
9. Respiratory distress,
10. Diarrhea



- Features of inflammation of the brain (encephalitis) , heart(myocarditis) or lungs (respiratory distress) **syndromic presentations are ARDS, Myocarditis and Encephalitis**.
- **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**.
- Case–fatality rate is estimated at 40–75% (vary by outbreak and can be up to 100%)

LABORATORY DIAGNOSIS

Investigations to be done for confirmation of diagnosis

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

- Samples have to be sent to designated laboratories identified as per protocols.
  - TVM to EKM to NIV Alappuzha
  - TSR to KSD to MCH KKD

- Universal, standard droplet and bio-containment precautions to be taken 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

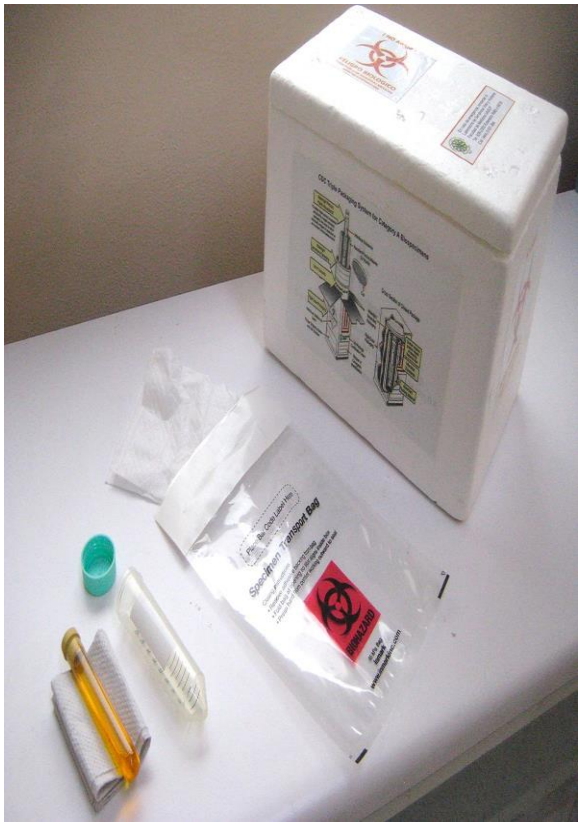
- In all suspect or symptomatic patients with contact with Nipah as early as possible with all bio-safety precautions
- ***Sample collection should be done only AFTER ADMISSION into an isolation facility, and ensuring that the staff member doing the collection is following proper infection control practices.***
- During sample collection wear complete disposable Personal Protective Equipment's (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

Document clinical details in the proforma (provided from the testing laboratory).

TRANSPORTATION AND STORAGE

1. Packed in triple container packing
2. Under cold chain (2-8°C) to the testing laboratory with prior intimation.
3. 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.
4. The plastic bag should be kept in another Zip-lock bag similarly, which should be sealed with adhesive tape.
5. 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.
6. The case sheets with complete information should be placed in plastic bag and should be pasted **outside the container**.
7. Sent to NIV Pune, NIV field station, Alappuzha or as per the testing protocols.



- Adhere to strict infection control practices
- Supervision and coordination by the hospital infection control committee.
- Nipah virus is classified as a biosafety level 4
- The laboratory should be informed if a clinical suspicion is made
- All other investigations done for the patient in same laboratory facility.
- Tests for other treatable conditions like bacterial infections, malaria, herpes encephalitis as per the clinical presentation , Screen for dengue, Japanese Encephalitis, West Nile fever.
- **Point of care testing (POC)-** Started in GMC, EKM during 2019 outbreak a POC micro PCR assay for NiV detection and ELISA testing facility could be started with technical support from NIV, Pune.

TREATMENT

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

Supportive Care

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. Care of unconscious patient: change of posture, care of eye, bladder, bowel and mouth
e. O2 inhalation if there is respiratory difficulty
f. Nutritional support: oral/NG tube feeding according to the condition of the patient
g. Maintain fluid and electrolyte balance (Adults: 5% DNS, Children: 5% DNS, half or quarter strength saline)
h. 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
i. Maintain intake output chart
j. Bronchodilators when needed may be given through spacers
k. Resuscitation (if needed): ABC : Airway, Breathing , Circulation

TREATMENT

1. Ribavirin

- A nucleoside analogue
- Available as 200 mg capsules

- Dosage - Day 1- 10 capsules(2gm) stat, then 5 capsules(1gm) 6 hourly for first four days followed by 3-2-3-2 capsules for 5th to 10th day
- Total of 150 capsules

- Side effects
  - Mainly on long term treatment
  - Hypersensitivity
  - Hemolytic anemia,
  - significant teratogenic and/or embryocidal effects in animal studies
  - Bone marrow suppression.
  - Monitor CBC and LFT

MONOCLONAL ANTIBODY M102.4

Mechanism of action → 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.

- The SOP (Standard Operating Procedures) and protocols were prepared with the support from ICMR.
- It is an investigational drug and requires Emergency Research Response & Resources for using such an investigational drug.
- To be used with appropriate knowledge and training of the research team as in any other clinical trials with Ethics committee approvals, consenting process following protocol and SOP

REMDESIVIR

- (GS-5734) , a nucleotide analog prodrug
- Broad spectrum antiviral activity
- Inhibit filovirus, coronavirus, and paramyxovirus replication.
- Effective in nonhuman primates for postexposure prophylaxis.
- In vitro- reduced replication of Nipah virus in primary human lung microvascular endothelial cells .

  - Dosage - loading dose of 200 mg iv followed by 100 mg iv once a day may be used for up to 12days.
  - Adverse Drug Effects - AKI or hepatotoxicity.
  - Early administration seems critical for effective treatment.
  - Remdesivir treatment could be combined with other treatment options such as m102.4 monoclonal antibody treatment, which has shown efficacy in various studies
  - Successfully tested in a phase 1 human clinical trial

FAVIPIRAVIR

- The viral RNA-dependent RNA polymerase (RdRp) inhibitor favipiravir
- An antiviral for use against infuenza.
- Favipiravir acts as a purine analogue and selectively inhibits viral RdRps.
- Efficacy against a wide variety of other RNA viruses
- Favipiravir may be used on a compassionate ground for the treatment and post exposure prophylaxis of NIPAH virus infection.
- 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.
- Can effect hepatic and renal function- Screen RFT, Creatinine clearance, LFT and monitor liver and renal function

POST EXPOSURE PROPHYLAXIS

Dosage-

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.

(NB -Remdesivir has been found to be effective against NIV-B in both vitro and in vivo , it may be preferred over favipiravir whose effectiveness was tested only in NIV-M)

IMMUNOMODULATORS

- Altered monocytic, Th1/Th2, as well as cytokines and chemokines balances.
- In diseases like COVID-19, Ebola virus disease, Nipah virus infection, SARS, and MERS etc
- These suggested to be considered for a novel immunological reclassification as acute onset immune dysrhythmia syndrome (n-AIDS)
- Present with Acute respiratory distress, Multi inflammatory syndromes Encephalitis etc
- Manipulate the inflammatory and immunological response including the interferon homeostasis .
- .

IMMUNOMODULATORS…

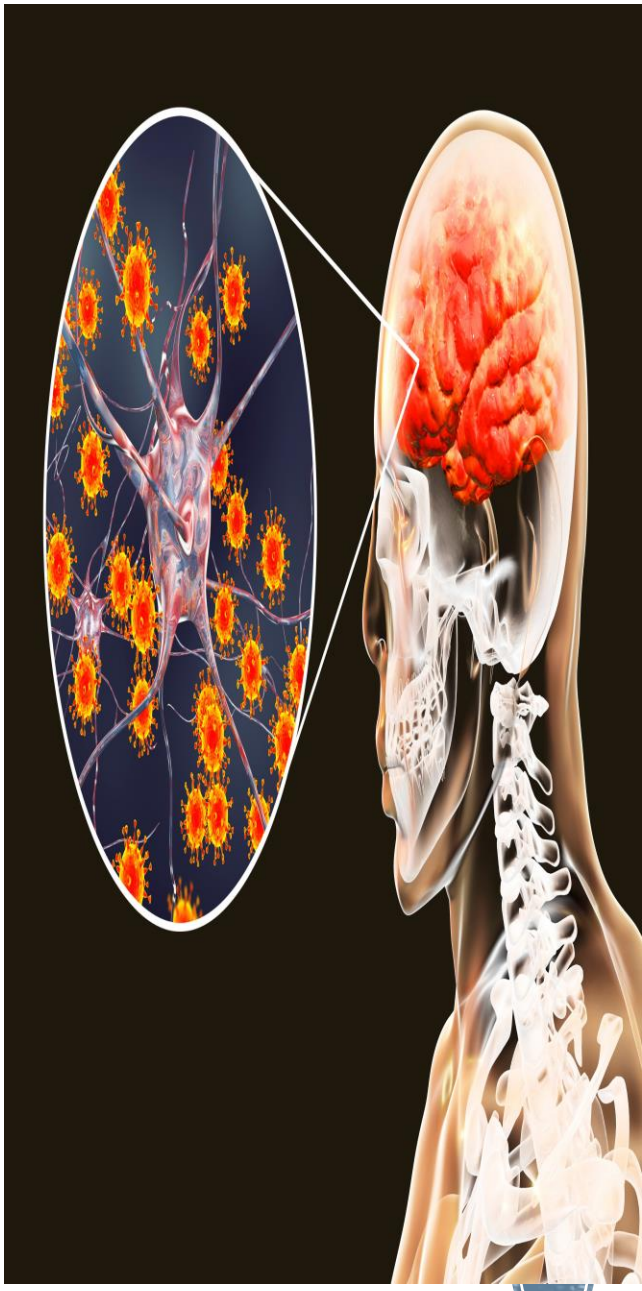
- Influence the proinflammatory agents and leucocyte attracting cytokines abnormally
- Induce a dysregulated immune recruitment
- In Nipah encephalitis early administration of immunomodulators [steroid pulse therapy] may be considered in patients with features of raised ICT, GCS ≤8 or rapid neurological deterioration. 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

Care for encephalitis

- Management of fever, pain, control of cough.
- Prevention of seizures
- Control of systemic hypertension
- Furosemide 0.5 to 1.0 mg/kg IV and / or mannitol 1 g/Kg IV over 30-60 minutes, Repeat dosing can be given as needed, generally every eight hours–provided circulatory volume is protected
- IV Sedation and mechanical ventilation

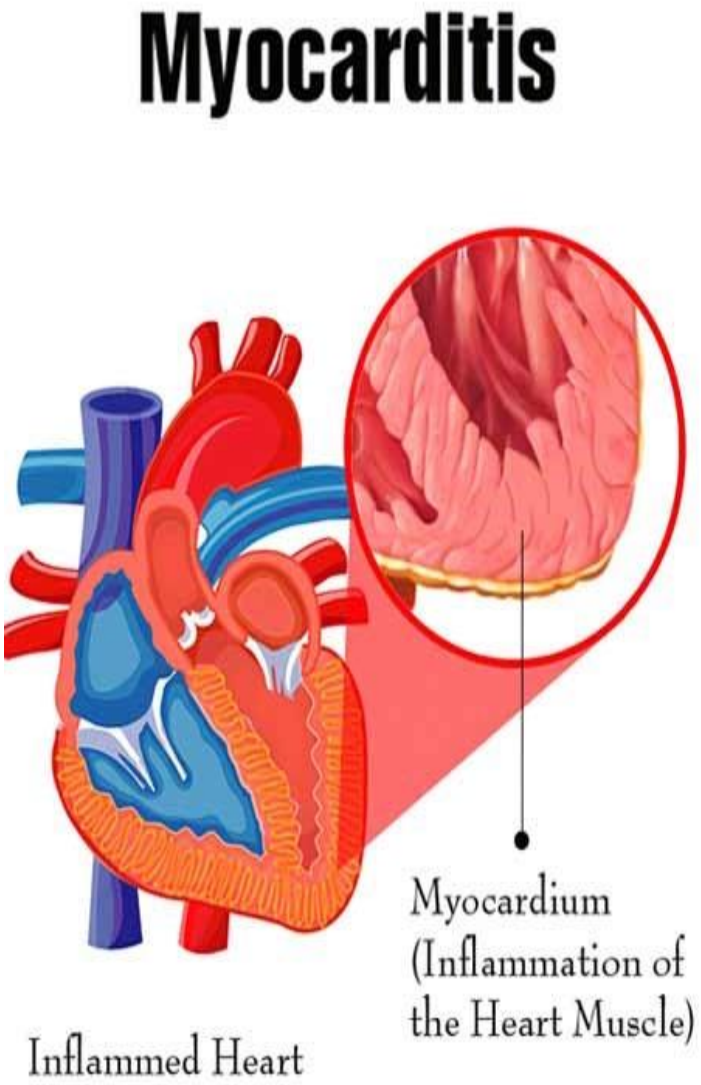
- Seizures
  - Lorazepam 4 mg IV or
  - Phenytoin 100mg IV q6-8h or
  - Fosphenytoin 150 PE q8h IV or
  - Levetiracetam 500mg q8-12h IV

- **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 15-30deg 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 sedation and analgesia



Care for myocarditis

- Supportive therapy for symptoms of acute heart failure - diuretics,nitroprusside, ACE inhibitors etc



INOTROPES

- **Dobutamine**
  - Dosage: - 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.
  - In patients with low systolic blood pressure use in combination with Noradrenaline

- **Dopamine**
  - Dosage :- 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 combined with Dobutamine

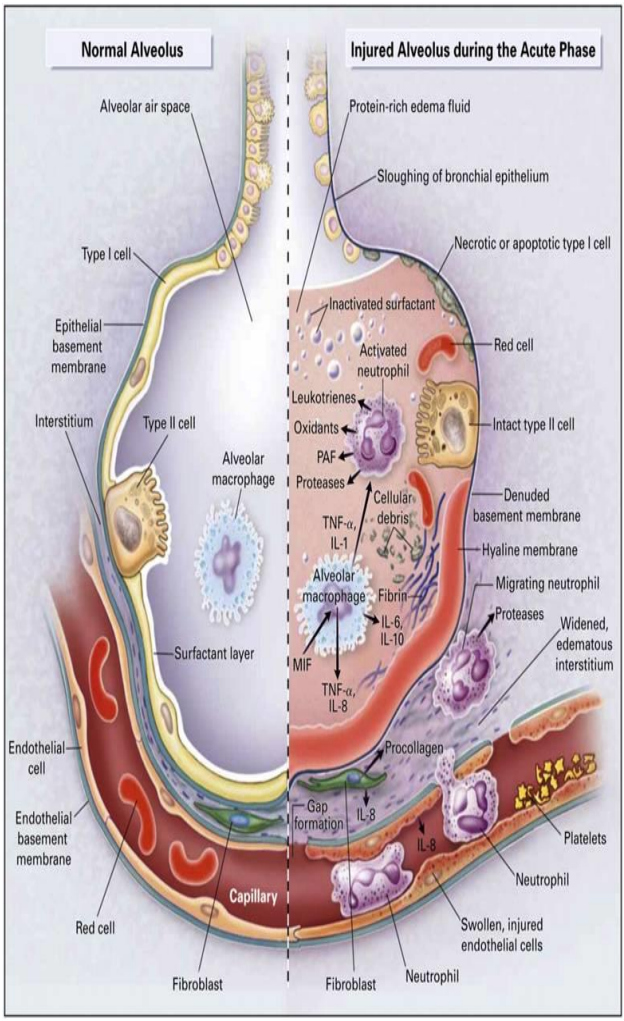
- **Norepinephrine**
  - Dosage :- 2 - 50 micrograms/min (0.02 – 2 micrograms/kg/minute) titrate to response
  - Vasoconstrictor and inotrope; preferred as a single agent over dobutamine if SBP <70.
  - Can use combined with dobutamine.

Care for ARDS

- **For mild ARDS**
  - 1st line treatment - non invasive ventilation .
  - Avoid in
    - diminished level of consciousness
    - Vomiting
    - upper GI bleed
    - other conditions that increase aspiration risk
    - hemodynamically unstable
    - Agitated
    - patients with inability to obtain good mask fit.

- **Severe ARDS**

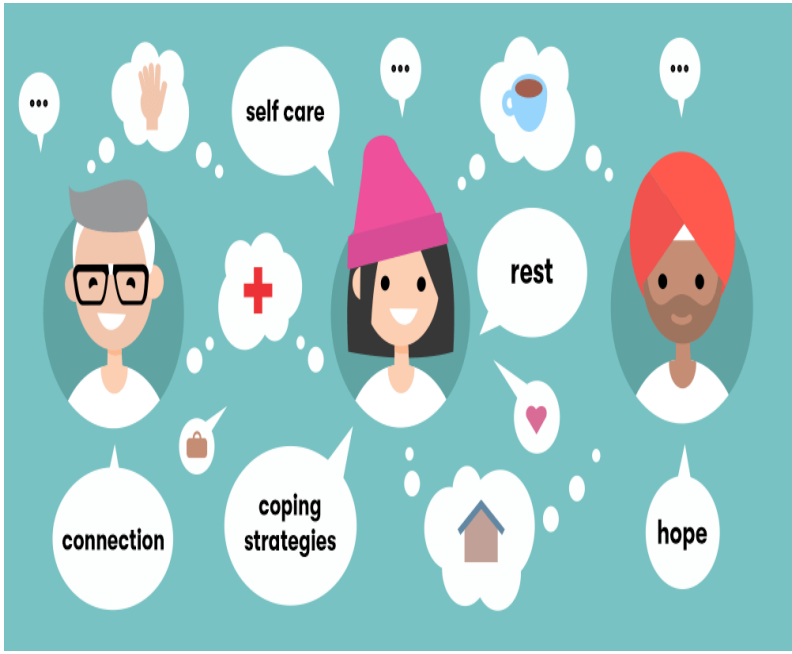
  - Associated with refractory hypoxemia ++.
  - Mechanical ventilation specific settings are recommended
  - Limitation of tidal volume (6 ml/kg predicted body weight)
  - Adequate high PEEP
  - A ‘balanced’ respiratory rate (20-30/min)for appropriate baseline minute ventilation.
  - Consider the use of incremental FiO2/PEEP combinations
  - Oxygenation goal (PaO2 55-80 mm Hg or SpO2 88-95 %)



Psychosocial support

Beneficiaries

- Patients
- Contacts kept in isolation facility for testing
- Family members
- Community contacts



Discharge and follow up

- **Criteria for discharge of a patient from isolation facility presented with suspected Nipah and tested negative**
  - Tested negative and totally symptom free can be discharged with observation at home for total of 21 days.
  - 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.
  - No need of repeat testing if tested negative on two occasions found negative and an alternate diagnosis is made.

- **Discharge criteria for Confirmed case**

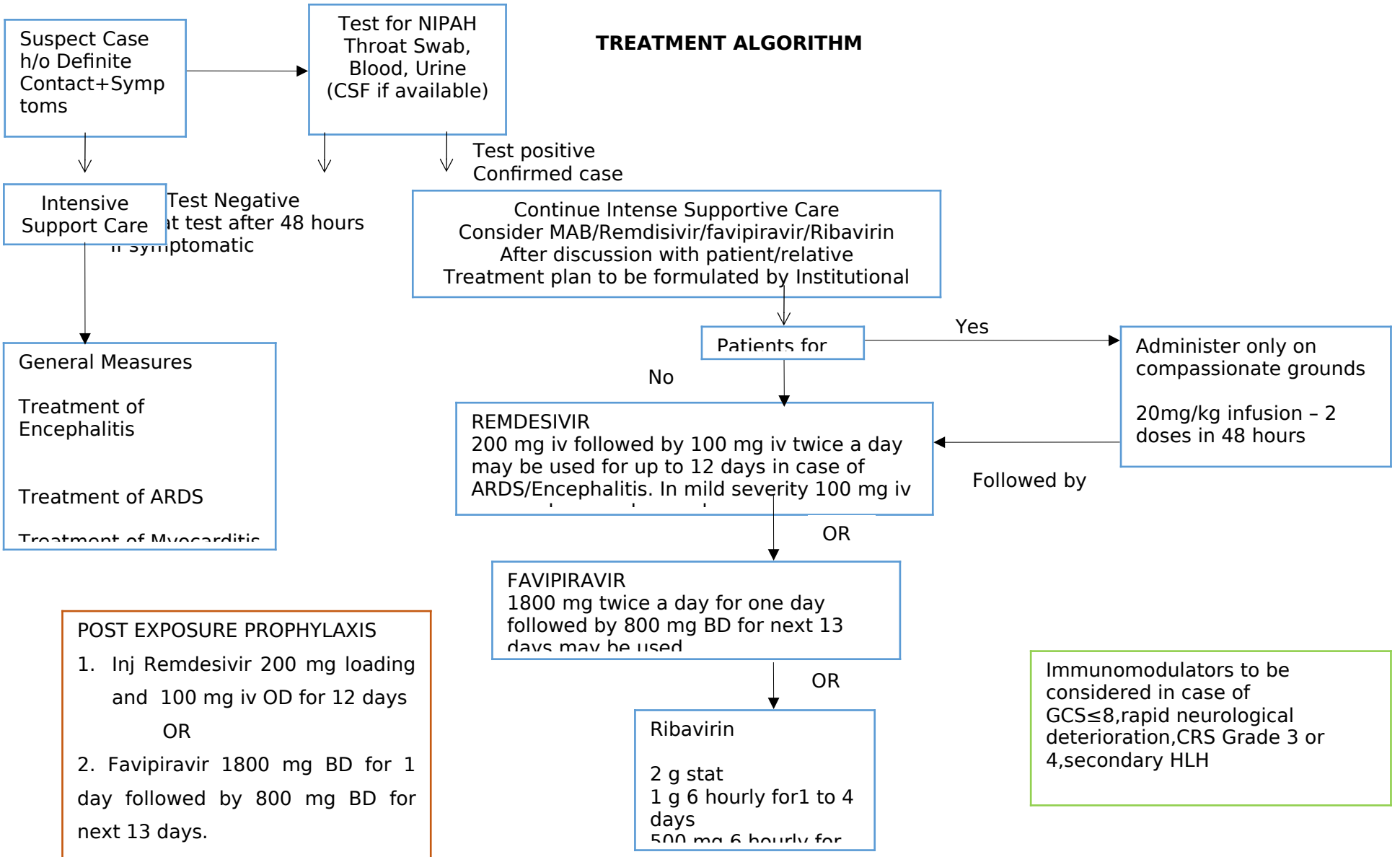
  - Clinically stable
  - Nipah RT-PCR from all three samples (Throat swab, Urine and blood) reported negative on two occasions at least 5 days apart.
  - To be decided by the treating clinician and confirmed by the Medical board

- **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
  - Reports of relapse and late onset encephalitis ++

PREVENTION

- Proper handwashing regularly with soap and water
- Raise awareness among population about high risk behavior, signs, symptoms, and complications of Niv.
- Monitor animals for features of outbreak and isolate the area if required.
- Avoid consumption of freshly collected date sap
- Thorough washing and peeling of fruits before consumption
- Discard fruits with signs of bat bite
- Use of mask , gloves and other protective equipment's especially in healthcare institutions
- Suspected cases and their contact isolation and regular monitoring and evaluation
- Implement standard infection control precautions in all health care institutions and their regular monitoring
- Continuous surveillance of people and animals of the high risk areas,


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

NIPAH: LOCAL BATTLE. GLOBAL RECOGNITION

EXPRESS NEWS SERVICE
@TPunam

KERALA has received international recognition for its effective prevention measures against Nipah virus outbreak. The Institute of Human Virology in Baltimore honoured Chief Minister Pinarayi Vijayan and Health Minister K K Shylaja for the government's efforts in curbing the outbreak.

Noted bio-medical scientist and co-founder of the institute Dr Robert C Gallo presented awards to the Chief Minister and the Health Minister.

Dr Robert Gallo, who was part of the scientific team that discovered the HIV, along with other scientists in the institute held talks with the Kerala delegation. The team discussed the scope of research association with Kerala in addition to the International Virology Institute proposed to come up in Thiruvananthapuram. Dr M V Pillai and Dr Sarngadharan took part in the discussions.

On the occasion, the Chief Minister said Kerala has been taking up healthcare to international standards. He also expressed the state's willingness to associate with the Institute of Human Virology in mutually beneficial research areas.

"The IHV can associate with the state in setting up [illegible] Advanced Virology Institute in Thiruvananthapuram. The IHV's honour is a major recognition to Kerala's public health system," Pinarayi said while adding that the state has given major stress to the public health system.

The state has decided to set up an international ayurveda centre. Once proper scientific research is being carried out in the traditional medicines, this can lead to the production of major medicines. The new ayurveda centre can contribute in this regard.

Institute of Human Virology co-founder Dr Robert C Gallo presents awards to Chief Minister Pinarayi Vijayan and Health Minister K K Shylaja in Baltimore

The Chief Minister said the state was able to provide free treatment to its citizens. As far as health indices are concerned, Kerala has been ranked along with developing countries. "The changing lifestyle and new food habits have been posing some challenges in the state's health sector. The attempt is to find a solution to these issues through the Aardram Mission," he said.

He also elaborated on how the state waged a war against the Nipah virus. When the first patient was identified with Nipah, all those who came in contact with him were brought under strict monitoring. Special guidelines were issued and a coordinated effort by all government machinery was ensured. Special training was given to the medical and paramedical staff. A collective and cautious effort helped reduce the number of casualties, he said.

In addition to the Health Minister, Dr Robert Gallo and Dr Syamsundar Kottilil, Director Clinical Virology, IHV, spoke on the occasion.

The reception accorded to the Chief Minister and the Health Minister is the biggest recognition that the state has ever received in the health sector. It's for the first time the institute is honouring a people's representative. The globally-acclaimed institution decided to honour the state after detailed analysis on the measures taken by Kerala following Nipah virus attack.

The Chief Minister will return to Kerala after a two-week-long visit to the US, on July 18.

Thank you