Health & Family Welfare Department,
Govt of Kerala.
Thiruvananthapuram, Kerala

2/NIPAH/H&FWD- NIPAH Treatment Protocol (Amendment- Sept 2021) – dated 5TH SEPT 2021

Ref: 1/NIPAH - Management plan for Nipah outbreak in Kozhikode – dated 5th Sept 2021

The Nipah outbreak in Kozhikode is reported on 4th September 2021 and received confirmation from NIV Pune. Accordingly, the guidelines cited in reference above were issued regarding management action plan, revised treatment guidelines and discharge guidelines for follow up in all Government and Private Hospitals in Kerala.

The amended detailed treatment guidelines are appended as Annexure 1.

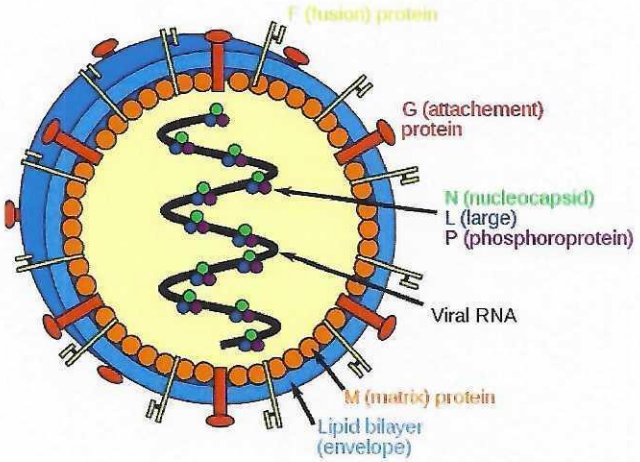
Principal Secretary

ANNEXURE 1

NIPAH Virus Infection

REVISED TREATMENT PROTOCOL

September 2021



Department of Health & Family Welfare

Government of Kerala

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 and no definite treatment or vaccine so far identified. So the management essentially involves infection control practices and triaging, isolation and management of patients including intensive supportive care. The Emergency Department must be strengthened 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 of all supplies including drugs, disposables and 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**
- Ensure strict adherence to proper Triaging
- **Proper infection control practices must be followed up.**
- 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 withfever or any symptoms suggestive of Nipah infection (*vide* clinical features)
- Health care provider who has come in contact with the patientwith 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 equipments (BP apparatus, Stethoscope, Thermometer, Pulse oximeter) for each room and use only disposable consumables to 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 treating clinician.

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. O_2 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 consenting.

Currently the available treatment options are very limited.

3.3.2 .1 Ribavirin

Ribavirin, 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 have 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 received 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 was ended by that time. In Kochi 2019 outbreak as there were no new confirmed cases and the patient was towards the recovery phase when the NiV infection was confirmed, the drug was not used. The protocols, the drug, facility and trainings were started in anticipation . 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 was 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 .

[Ref; 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.]

3.3.2.4 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 afer 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.

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 ofsystemic 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

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 with dopamine.
- 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 tachycardia. Can beused withdobutamine.
- 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 recruitmentmanoeuvre 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

No approved drug so far. 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 and there exist a strong history of contact with NiV infected patient/sample must have repeat testing in 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

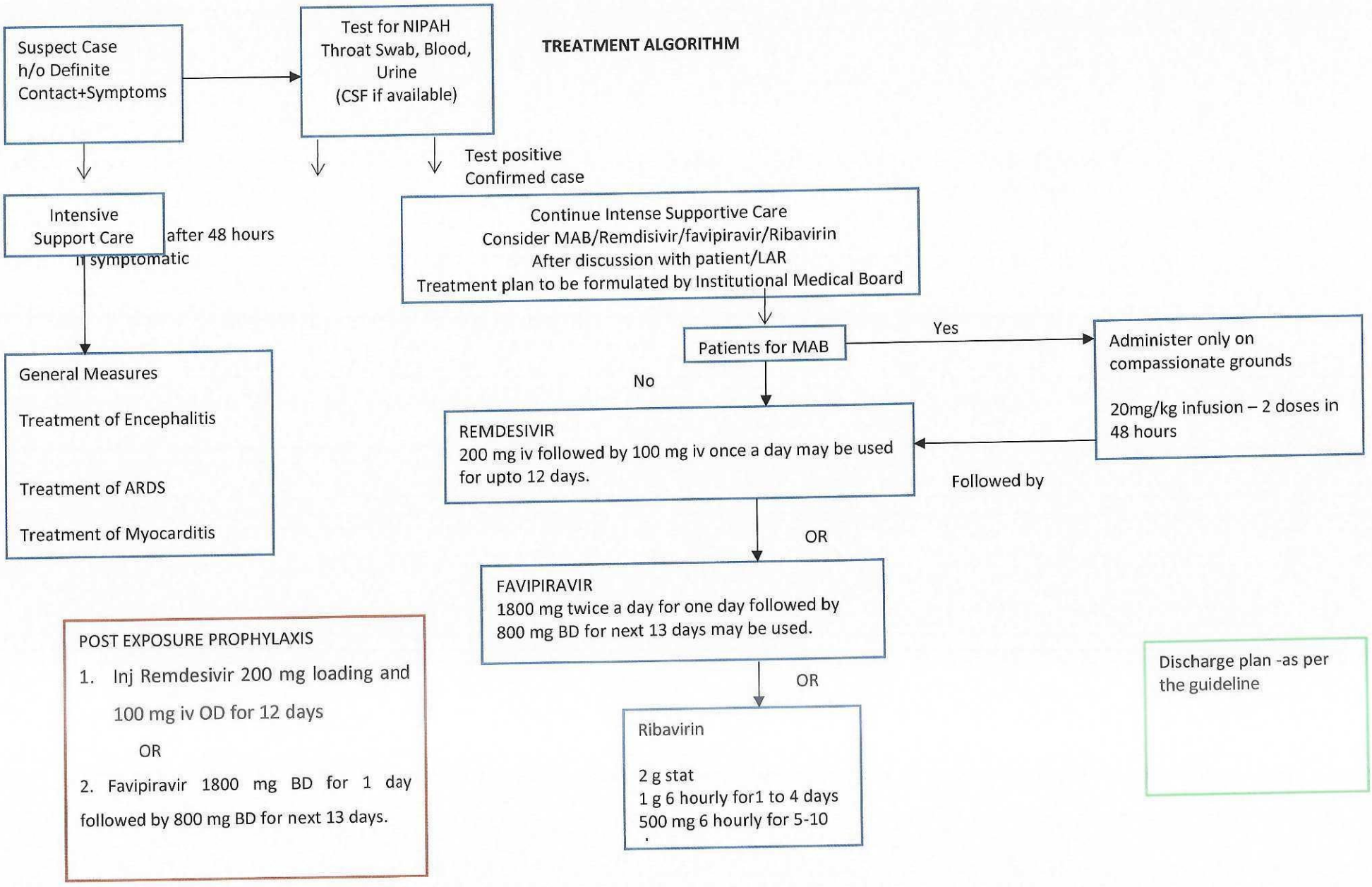
- Clinically stable
- Nipah RT-PCR from all three samples (Throat swab, Urine and blood)reported negative on two occasions at least 5 days apart.
- To be decided by the treating clinician and confirmed by the Medical board

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 were reports of relapse and late onset encephalitis in an earlier series.


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
after 48 hours
if symptomatic
Continue Intense Supportive Care
Consider MAB/Remdisivir/favipiravir/Ribavirin
After discussion with patient/LAR
Treatment plan to be formulated by Institutional Medical Board
Patients for MAB
Yes
Administer only on
compassionate grounds
20mg/kg infusion – 2 doses in
48 hours
No
General Measures
Treatment of Encephalitis
Treatment of ARDS
Treatment of Myocarditis
REMDESIVIR
200 mg iv followed by 100 mg iv once a day may be used
for upto 12 days.
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
500 mg 6 hourly for 5-10
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.
Discharge plan -as per
the guideline