INTERIM CLINICAL GUIDANCE FOR CARE OF PATIENTS WITH COVID-19 IN HEALTHCARE SETTINGS

NEPAL MEDICAL COUNCIL

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INTERIM CLINICAL GUIDANCE FOR CARING OF PATIENTS WITH COVID-19 IN HEALTHCARE SETTINGS

I. PURPOSE OF THE GUIDELINES

The purpose of these clinical guidelines document is to help physicians, other healthcare workers and healthcare institutions to properly manage persons with suspected or proven Coronavirus Disease 2019 (COVID-19). COVID-19 is a respiratory tract infection caused by the betacoronavirus SARS CoV-2 (SARS coronavirus type-2). These guidelines are based on current knowledge in the available literature, expert consultations, and recommendations from WHO, CDC and other authorities. These guidelines are not meant to replace clinical judgment based on individual patient needs and do not exclude expert consultation and are subject to change based on new knowledge.

II. TARGET GROUPS

The intended target audience are physicians, nurses, other healthcare personnel, healthcare administration and policy makers involved in management of COVID-19 infection.

III. TRIAGING AND TRANSPORTATION OF PATIENTS PRESENTING TO THE HEALTHCARE FACILITY

III.A. Who should be screened?

All persons including children and adults presenting to the outpatient clinics (OPD) and Emergency Room (ER) should be screened at the entrance of the healthcare facility in a triage area.

III.B. How will the patients presenting to outpatient clinics (OPD) and Emergency Room (ER) be screened and handled?

1. **SCREENING QUESTIONNAIRE**: All individuals presenting to the OPD or ER entrance should be screened with the following questions:

a. Symptoms:

Do you have any of the following new symptoms?

Cough? Fever? Shortness of breath? Chills? Muscle pain? New loss of taste or smell? Diarrhea? Sore throat?

b. Exposures:

Did you have exposure to any of the following?

- Close contact with anyone with the symptoms listed above, without alternative explanation
- Close contact with a person known or suspected to have C0VID-19

2. TEMPERATURE: All persons presenting to the OPD or ER should be screened for fever with thermometer on the temple of head following non-contact method. A core body temperature of 38°C (100.4°F) (corresponding to surface temperature 37.5°C or 99.5°F) or higher is considered as fever.
(If not a no-touch thermometer, it should be cleaned with 60-70% alcohol or an alcohol swab.)

III.C. Case Definitions

The criteria for treating someone as a suspected case is subject to change depending on the dynamics of the epidemic and prevalence of cases inside and outside the country. The case definitions for COVID-19 *for clinical purposes at hospitals* will be as follows:

Suspected case

A patient with fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, diarrhea or sore throat in the last 14 days
AND
Has no alternative explanation of the symptoms

Probable case

A suspected case for whom testing for the COVID-19 virus is inconclusive
OR
A suspected case for whom testing could not be performed for any reason.

Confirmed case

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Definition of Contact: A contact is a person who experienced any one of the following exposures during the infective period of a probable or confirmed case:

1. Being within 2 metres of a probable or confirmed case for 15 minutes or more over a 24-hour period without wearing proper personal protective equipment; OR
2. Having unprotected direct contact with infectious secretions or excretions of the patient (e.g., being coughed on, touching soiled handkerchief with a bare hand) and not washing hands immediately afterwards; OR
3. Additionally, for healthcare workers, not wearing eye protection if the person with COVID-19 was not wearing a cloth face covering or facemask, OR not wearing all recommended personal protective equipment (i.e. gown, gloves, eye protection, respirator) while performing an aerosol-generating procedure
4. Other situations as indicated by local risk assessments.

Definition of a confirmed case's period of infectivity to contacts:

For confirmed symptomatic cases, the period is considered to start from 48 hours before the onset of symptoms, and last until 10 days after the onset of symptoms.

For confirmed asymptomatic cases,

- If there is history of known exposure to a suspected or confirmed case or exposure to a situation potentially leading to the infection (such as attending a mass congregation), the period of infectivity will be considered to start at 2 days after such exposure and end 10 days after the test sample was taken.
- If there is no known history of such exposure, the period of infectiveness to contacts will be considered to start 2 days prior to taking the test sample, and end 10 days after the sample was taken.

III.D. How and where will a suspected case be handled and transported?

- All suspected cases should be given a surgical mask and asked to perform hand hygiene with hand sanitizer, and then escorted by a healthcare worker (HCW) to a separate designated area for isolation of suspect cases.
- The HCW should be wearing proper personal protective equipment (PPE) such as an N95 mask or an equivalent (or surgical mask with measures to improve fit when N-95 mask is not available), face shield, and, if direct contact is expected, gown and gloves.
- A separate space away from other patients, families and visitors ("Fever" clinic) needs to be designated for isolation and evaluation of symptomatic suspected cases. If necessary, a temporary structure such as a tent should be erected in a separate area away from the entrance of the emergency department or the outpatient clinics.
- If there are more than one suspected cases, they should be separated at least by 6 feet distance between them. A protective barrier should be placed between two suspected cases, when possible.
- Standard precautions (hand hygiene and use of gloves as necessary) and droplet and airborne precautions (N-95 or equivalent mask, face shield or goggles, gown) need to be strictly implemented in the designated area for isolation.

III.E. How will a suspected case be disposed after initial evaluation?

- Suspected COVID-19 cases with no symptoms or mild or moderate symptoms generally do not require hospital admission *for clinical reasons*.
- All suspected patients need to be on isolation, either self-isolation or in a designated isolation center, to contain virus transmission until the infection is ruled out.
  Please note that depending on the public health policy adopted by the government at a particular time, in the broader public health interest, even asymptomatic or mildly symptomatic suspected cases of COVID-19 may be admitted to isolation units in hospitals or elsewhere.

- During pandemic surges, if there is no availability of appropriate tests (antigen or NAAT) in an area, suspected symptomatic cases would need to be isolated and managed as true positive cases based on the level of suspicion on clinical assessment.
- Refer to Appendix 1(a) for initial triage, evaluation and management flow chart.

IV. CLINICAL PRESENTATION

IV.A. What is the clinical presentation of COVID-19?

- The incubation period for COVID-19 is estimated to be 2-14 days from the time of exposure, with median incubation period being 4-5 days.
- The illness spectrum ranges from asymptomatic infection to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction. (See Section VI.A below.)
- As per current best estimates by CDC, about 40% of the cases of COVID-19 remain asymptomatic. The infectiousness (potential to transmit infection) of asymptomatic patients is 3/4th (75%) compared to that of symptomatic patients.
    - The commonest symptoms are fever or chills, cough, shortness of breath, myalgia, fatigue, diarrhea and nausea. Although fever eventually occurs in close to 90% of those with symptoms, it may be absent in close to half of them at initial presentation.
    - Less common symptoms such as new loss of sensation to smell (anosmia) or taste (dysgeusia), sore throat, congestion or runny nose, sputum production, headache, dizziness, anorexia, etc. have been reported.
- Findings such as deep venous thrombosis including fatal pulmonary embolism, chilblain-like lesions on digits ("COVID toes"), etc. appear to be more common than in other respiratory viral illnesses.
- According to the *Report of the WHO-China Joint Mission on Coronavirus Disease 2019*, approximately 80% of (symptomatic) confirmed cases do not progress to severe disease or critical disease. In those who develop severe or critical COVID-19, the worsening from mild to moderate illness usually occurs after around 7-10 days from the onset of symptoms.
- In pregnant women with COVID-19, there is an increased risk of development of severe disease than in non-pregnant women of similar age at least in the context of Nepal. Presence of a higher body mass index, age ≥ 35 years or diabetes mellitus or hypertension pose an increased risk for severe disease.
- Children are not noted to be at higher risk except infants less than one year of age. (See section VI.J for details.)
- In some children and relatively younger adults, asymptomatic or symptomatic SARS-CoV-2 infection may be followed by a "multisystem inflammatory syndrome in children (MIS-C)".
- A significant number of recovering COVID-19 patients, mostly after severe or critical illness but some with milder illnesses, have been noted to experience persistent symptoms such as shortness of breath, fatigue, myalgia, joint pain, chest pain, palpitations, headache, tremors, cognitive impairment, and a poor quality of life, for up to 3 months after diagnosis of COVID-19. Also described

are anxiety, mood changes and psychological distress, which are more frequent in those <60 years of age.

V. DIAGNOSIS

V.A. Who should get tested for SARS CoV-2?

All of the following (both groups 1 and 2) should be tested for SARS CoV-2 with appropriate approved testing. However, in the absence of adequate testing resources, suspected cases in group 1 should receive priority for testing (See Appendix 1(a) Triage and Management Algorithm):

Testing Group 1:

- Hospitalized patients with symptoms of potential COVID-19 infection, including fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, diarrhea or sore throat without an alternative explanation of symptoms.
- Healthcare workers with symptoms
- Workers or residents in congregate living settings, such as prisons, with symptoms
- Symptomatic elderly ≥60 years of age
- Symptomatic individuals with underlying chronic conditions, such as diabetes mellitus, heart disease (congestive heart failure and coronary artery disease), lung disease, chronic kidney disease or immunocompromising conditions
- Symptomatic pregnant women
- All patients being admitted to the intensive care unit
- All patients undergoing procedures under general anaesthesia or other potentially aerosol generating procedures
- Pregnant women going into labor or undergoing Caesarian section

Testing Group 2:

- Individuals with less typical symptoms or presentations reported to be associated with COVID-19, such as deep venous thrombosis, stroke, myocardial infarction, “COVID toes”, etc. regardless of history of exposure to suspected or confirmed COVID-19 cases, depending on the clinician’s assessment of the need for such testing and the hospital infection prevention needs
- Symptomatic or asymptomatic contacts of confirmed cases or travelers from areas with reports of cases, who may or may not be in quarantine facilities
- All frontline workers such as HCWs, ambulance drivers, firefighters, security forces, cleaning persons and laundry workers at COVID hospitals, etc., who

are likely to get exposed to COVID-19 should be tested if there is a breach in infection control measures or significant exposure with infected patient.

- Individuals without symptoms, who have been referred for testing by clinicians or prioritized for testing by public health agencies for any reason, including but not limited to preoperative screening, sentinel surveillance, public health monitoring or screening of other asymptomatic individuals

Please note that the testing criteria can be expanded by the public health authorities depending on the dynamics of the epidemic and the available testing capacity nationally or locally.

V.B. What type of diagnostic tests will be performed for suspected cases?

The diagnostic tests for COVID-19 are rapidly being developed and variety of tests are rapidly expanding. They may be available in various forms in various hospitals, independent labs and clinics. However, these tests are not equivalent and should be used and interpreted in correct individual contexts. The following guidelines are provided as a general rule but in case of questions, expert consultation is recommended.

TESTS FOR SARS COV-2:

a. **Nucleic Acid Amplification Tests (NAATs)**: **NAATs such as RT-PCR are considered to be the standard method for diagnosis of COVID-19 at present and should be used as the preferred method whenever available.** RT-PCR is the most widely available molecular test in Nepal, done either by traditional RT-PCR method or GeneXpert technology. Other molecular tests such as LAMP and CRISPR/Cas9 may also be utilized when available following appropriate validation and quality assurance.

Indications for PCR test are listed in section V.A. above.

b. **Antigen Detection Methods**: Antigen testing has already been approved by the MoHP for use in Nepal within specified restrictions. An antigen test is usually based on immunoassay to detect presence of a specific viral antigen on a nasopharyngeal or nasal swab specimen. A positive test implies presence of current viral infection. Antigen tests are less expensive, do not require specialized labs, have a quick turnaround time, and can be done at the point-of-care. However, compared to the molecular tests (such as RT-PCR), the antigen tests for SARS-CoV-2 are generally less sensitive. The antigen tests that have received FDA emergency use authorization have demonstrated “technical” sensitivity ranges of 84%-97% and specificity of 98-100% compared to the RT-PCR, however there have been numerous reports of much higher rates of false negative (much lower “clinical” sensitivity than claimed) and significant false positive results with the same test kits. The positive predictive value of the antigen test is expected to be higher in symptomatic patients within first 5-7 days of symptom onset.

Therefore we recommend that SARS-CoV-2 antigen tests should only be utilized with the following restrictions:

i. Only the specific brand and test kit that has received emergency use authorization or full authorization by countries with stringent regulatory authorities (e.g. USA FDA) or have been listed by the WHO in its emergency use listing or prequalification listing for in vitro diagnostics for SARS-CoV-2 should be utilized.

ii. Antigen test may only be used

   a. In symptomatic patients suspected to have COVID-19 within 5-7 days of onset of symptoms, when nucleic acid amplification tests (NAAT) such as the RT-PCR tests are either not available or where prolonged turnaround times precludes clinical utility.

      All symptomatic patients with negative antigen test results must be tested as soon as possible with a NAAT and treated as positive until a negative NAAT result becomes available.

   b. To respond to suspected outbreaks of COVID-19 in remote settings, institutions and semi-closed communities where NAAT is not immediately available. Positive antigen test results from multiple suspects is highly suggestive of a COVID-19 outbreak and would allow for early implementation of infection control measures. All (or at least a subset) of samples giving positive antigen test results should be transported to laboratories with NAAT capability for confirmatory testing.

   c. To support outbreak investigations (e.g. in closed or semi-closed groups including care-homes, prisons, work-places and dormitories, etc) *in NAAT-confirmed COVID-19 outbreaks*. In such settings, antigen tests could be used to screen at-risk individuals and rapidly isolate positive cases (and initiate other contact tracing efforts) and prioritize sample collection from antigen test-negative individuals for NAAT.

   d. During extraordinary surges in the pandemic when the country's immediately available testing capacity is overwhelmed, antigen tests can be utilized to support mass testing and rapid identification and isolation of as many positive cases as possible. In such situations, antigen tests should preferably be used on symptomatic individuals only. When the antigen test is negative in symptomatic individuals, they should be tested with an NAAT, and kept in isolation while awaiting the NAAT result.

The antigen based rapid diagnostic tests should NOT be used:

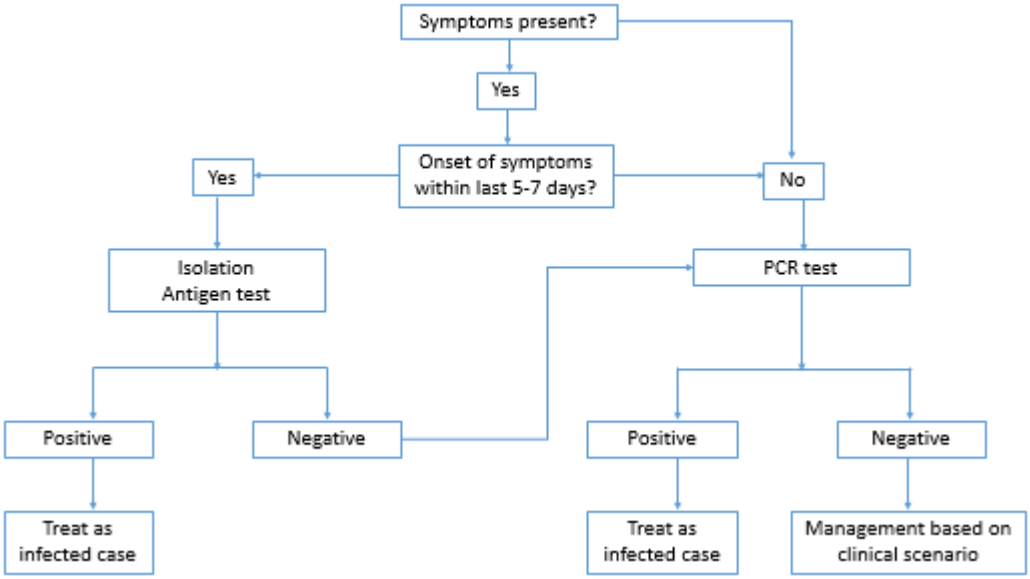
i. For asymptomatic individuals

ii. As a substitute for RT-PCR or other NAAT where NAAT is available

iii. For contact tracing

iv. For any setting other than the ones mentioned above where antigen testing has been suggested

The proposed workflow for use of antigen tests in mass testing during pandemic surge is as follows:



c. **Antibody Based Methods**: Certain antibody-based serological assays can be useful for certain specific situations. Currently, only approved serological assays detecting IgG alone or both IgM/IgG (total antibody) done in laboratories with CLIA, eCLIA or ELISA are considered as reliable tests. Only serological assays approved by authorities such as US FDA, and validated and registered by the NPHL should be used. Based on their performance, serological tests done by lateral flow methods (RDT) are not considered appropriate at present. Similarly, antibody tests using IgM or IgA alone are not considered optimal for testing in the absence of sufficient evidence. The following general situations are appropriate use of serological tests:

i. Providing support for diagnosis of acute COVID-19 illness for persons who present late (7–14 days) after onset of illness when RT-PCR is not positive and a high clinical suspicion remains
ii. Supporting diagnosis when patients present with late complications of COVID-19 illness, such as MISC (multisystem inflammatory syndrome in children)
iii. Determination of antibody titer of convalescent plasma donor
iv. For epidemiological studies and surveillance purposes

Antibody-based tests are not currently recommended to evaluate the level of immunity following COVID-19 vaccination. Most antibody tests available in clinical settings will report negative results in vaccinated persons who have not have natural infection, because those tests usually do not detect vaccine-induced antibodies that may be different from the ones induced by natural infection.

SAMPLE COLLECTION CONSIDERATIONS FOR MOLECULAR TESTS:

1. ALL SUSPECTED CASES:

- Collect upper respiratory tract specimen, preferably nasopharyngeal swab or, if nasopharyngeal swab cannot be collected, oropharyngeal swab, for RT-PCR.
- If initial testing is negative but the suspicion for COVID-19 remains high, resampling and testing from multiple respiratory tract sites (nasopharynx, oropharynx, turbinates, sputum if readily available) should be performed as soon as possible.
- When repeated tests are negative but the suspicion for COVID-19 remains high, may consider doing a validated antigen- or antibody-based test, if available. (treat as clinical COVID) → treatment chapter
- Infection control precautions for COVID-19 should continue while repeat evaluation is being performed.
- Patients who were initially screened while asymptomatic and reported negative and subsequently develop symptoms concerning for COVID-19 should undergo repeat RT-PCR testing.

2. HOSPITALIZED PATIENTS:

- If upper respiratory specimens are negative and clinical suspicion remains, collect specimens from the lower respiratory tract when readily available (expectorated sputum or endotracheal aspirate in ventilated patient) for COVID-19 virus testing by RT-PCR and bacterial stains/cultures.
- However we recommend against doing sputum induction or bronchoalveolar lavage just for the purpose of getting specimen for testing for COVID19 because of high risk for healthcare worker infection.

V.C. **Should follow up molecular testing be performed for confirmed cases?**

- Molecular testing such as PCR does not differentiate a replication-competent virus from nonviable viral RNA fragments. Therefore, time-based strategy is recommended for discontinuation of isolation and discharge from hospitals and isolation centers. **Follow up PCR testing is NOT required**.
- See Discharge Criteria in Section VI.M for information regarding discontinuation of infection control precautions and isolation at home after discharge.

V.D. How will the specimens be collected and transported?

- Use appropriate PPE for specimen collection including droplet and contact precautions for upper respiratory specimens.
- Follow airborne precautions for obtaining lower respiratory tract specimens (PPE, eye shield, gloves & N-95).
- Avoid sputum induction to minimize risk of aerosol transmission.

- Follow the guidance from the National Public Health Laboratory regarding processing and transporting of the collected specimen.) See figure in Appendix 7.

V.E. What type of imaging study should be offered initially?

- Chest X-ray should be done in all hospitalized patients with fever and cough or shortness of breath. Ground glass opacities and patchy infiltrates are common findings in patients infected with COVID-19.
- Chest X-ray should also be considered for the non-hospitalized patients whose respiratory symptoms are worsening.
- CT scan of the chest is unlikely to give further useful information in most circumstances and **poses significant risk of transmission from floating aerosols to staff members and others** in the poorly ventilated CT scanner rooms. CT scan should only be done in selected patients with worsening conditions where additional or alternative diagnosis is suspected (e.g., pneumomediastinum, pneumothorax, pulmonary embolism or secondary bacterial or fungal coinfection), primarily in inpatient settings only, at the discretion of the clinicians.

V.F. What other routine tests should be ordered initially?

1. No additional tests are needed for patients with asymptomatic or mild cases of COVID-19.
2. For moderate COVID-19 cases, no specific laboratory test is of proven clinical utility, and management is unchanged in the majority of cases regardless of the test results. Clinicians should make decisions based on individual patient's past medical history, symptoms and clinical findings.
3. For severe or critical COVID-19 cases, the following tests are recommended:
    - complete blood count and differential count (Leukopenia and lymphopenia are expected in 85% of COVID-19 patients)
    - renal function and electrolyte tests to assess kidney injury
    - liver function tests
    - Where available troponin, quantitative C-reactive protein, etc. may have some clinical utility especially if the patient is worsening or critically ill. It should be noted that D-dimer, CRP or procalcitonin can all be elevated just due to the COVID-19 infection itself, without additional pathology.
    - Samples should be sent for cultures of appropriate specimen, before starting antibiotics for any reason or if bacterial sepsis suspected.
4. Depending on epidemiology, may need to consider other tests to rule out alternative causes of fever such as scrub typhus, dengue, tuberculosis, malaria, kala-azar, etc.

VI. TREATMENT

VI.A. How will the severity of illness be classified?

We recommend following the classification of COVID-19 patients as suggested by the National Institutes of Health (USA) COVID-19 Treatment Guidelines Panel:

1. **Asymptomatic or Presymptomatic Infection**: Individuals who test positive for SARS-CoV2 but have no symptoms.

2. **Mild Illness**: Individuals who have any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, chills, headache, muscle pain, diarrhea) without shortness of breath, dyspnea, or abnormal imaging.

3. **Moderate Illness**: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and the oxygen saturation (SpO_2) >92% on room air (>93% on room air at sea level).

4. **Severe Illness**: Individuals who have any of the following criteria- respiratory rate >30 breaths per minute, SaO2 ≤92% on room air (≤93% on room air at sea level), ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 (or if arterial blood gas test is not available, SpO2/FiO2 ratio ≤ 315).

5. **Critical Illness**: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

VI.B. Who is at high risk of developing severe illness?

Patients diagnosed with COVID-19 who are at high risk for poor outcomes, including ARDS and death, are those who meet any 1 of the following criteria:

- Age ≥60 years
- Any one of the following medical conditions:
    - Obesity
    - Cardiovascular disease, excluding hypertension as the sole cardiovascular diagnosis
    - Diabetes with HbA1c level >7.5%
    - Chronic pulmonary diseases, including asthma
    - Advanced chronic kidney disease
    - Advanced liver disease
    - Sickle cell disease
    - Cancer
    - Neurologic or neurodevelopmental disorders
    - Post-solid organ transplantation, on immunosuppressive therapy

  - Use of biologic agents for immunosuppression
  - Undergoing treatment with chemotherapy or immunotherapies for malignancy
  - Within one-year post-marrow transplant
  - Undergoing treatment for graft-versus-host disease
  - HIV infection, with CD4 cell count <200 copies/mm^3
  - Pregnancy
  - Surgery during incubation period
  - Low socioeconomic status
- Any one of the following clinical findings:
  - Oxygen saturation (SaO2) ≤92% on room air; <90% if known chronic hypoxic conditions or receiving chronic supplemental oxygen
  - Respiratory rate >24 breaths/min
- Laboratory findings: elevated D-dimer level (>1 µg/mL), admission absolute lymphocyte count of <0.8, elevated levels of lactate dehydrogenase, troponin, C-reactive protein, or ferritin.

VI.C. How will asymptomatic or pre-symptomatic infection with SARS-CoV-2 be managed?

- Those with asymptomatic and presymptomatic infection *need to be isolated* as transmission of the virus from asymptomatic or presymptomatic cases accounts for close to half of the transmission of SARS-CoV-2 in the community.
- Persons with asymptomatic or presymptomatic infection with SARS-CoV-2 do not need to be admitted to a hospital *for clinical reasons* however, given the tradition of relatively larger and multigenerational households in Nepal and the significant risk of household transmission of this particular virus, public health authorities may require such patients to be admitted to hospitals or isolation facilities if safe and appropriate arrangements for isolation cannot be made at their own homes.
- It is not clear what proportion of patients with asymptomatic or presymptomatic infection will develop clinical disease.
- Those with presymptomatic or asymptomatic infection will need to be monitored for onset of symptoms or rise in temperature. Psychosocial evaluation and support may be indicated. (See below in Section VI.K)
- No additional laboratory testing is recommended for persons with asymptomatic or presymptomatic infection.
- No specific treatment is recommended for persons with asymptomatic or presymptomatic infection. Specifically, we recommend against the use of hydroxychloroquine or chloroquine, antibacterials (azithromycin, doxycycline, or others), and dexamethasone or other systemic glucocorticoids in the absence of another clear indication.
- For criteria for discontinuation of isolation precautions, please see [section VI.M Discharge Criteria].

VI.D. How will mild COVID-19 be managed?

- Patients with mild COVID-19 infection generally do not require hospital admission *for clinical reasons*. However, they need to be monitored closely, including monitoring of oxygen saturation, since rapid worsening of clinical status can occur.
- Patients need to be kept in isolation. For criteria for discontinuation of isolation precautions, please see [section VI.M Discharge Criteria].
  Given the tradition of relatively larger and multigenerational households in Nepal and the significant risk of household transmission of this particular virus, patients with mild COVID-19 may need to be admitted to hospitals or isolation facilities if safe and appropriate arrangements for isolation cannot be made at their own homes.
- If the patient is kept in isolation at home or at another designated location, they should be counseled about signs and symptoms of progression and if they develop any indication for hospitalization, they should be transferred to hospital immediately.
- Psychosocial evaluation and support may be indicated. (See below in Section VI.K)
- No specific laboratory tests are indicated in patients that are otherwise healthy at baseline.
- Monitor vitals including SpO2 at least every 6 hours. Inform treating doctor if SpO2 drops by >2%.
- Use symptomatic treatment such as antipyretics (preferably paracetamol) as needed for fever.
- No specific antiviral or immunomodulatory therapy is recommended in mild COVID-19 disease.
- We specifically recommend against the use of hydroxychloroquine or chloroquine, antibacterials (azithromycin, doxycycline, or others), and dexamethasone or other systemic glucocorticoids in the absence of another clear indication.
- For adults with mild disease and aged over 50 with risk factors for severe disease, or aged over 65 years, treatment with inhaled budesonide 800 micrograms twice a day may be considered. The treatment can be discontinued upon resolution of symptoms, or if the patient is started on systemic corticosteroids.
- There is insufficient evidence to recommend for or against convalescent plasma in ambulatory patients with mild or moderate COVID-19.

VI.E. How will moderate COVID-19 be managed?

- Patients with moderate COVID-19 generally do not require hospital admission *for clinical reasons*. However, they need to be monitored closely, including monitoring of oxygen saturation, since rapid worsening of clinical status can occur.
- Patients need to be kept in isolation. For criteria for discontinuation of isolation precautions, please see [section VI.M Discharge Criteria].

- No specific laboratory test is of proven clinical utility, and management is unchanged in the majority of cases regardless of the test results. Clinicians should make decisions based on individual patient's past medical history, symptoms and clinical findings.
- Chest X-ray may be considered.
- Monitor vitals including SpO2 at least every 6 hours. Inform treating doctor if SpO2 drops by >2%.
- There are insufficient data to recommend any antiviral or immunomodulatory therapy in patients with moderate COVID-19. Remdesivir may be *considered* in selected patients with worsening moderate COVID-19 for 5 days or until hospital discharge, whichever comes first (200 mg on day 1, and 100 mg once daily on subsequent days), if within 10 days from onset of symptoms, and they have significant risk factors for developing severe illness, or rapidly progressing radiographic findings, and/or dropping oxygen saturation, even though the SpO2 may still be >92%. (See section VI.B above)

  However, if / when Remdesivir supplies are limited, they should be prioritized for use in selected cases with severe COVID-19.

  (See Appendix 8: "Annex to NMC treatment guidelines: Management of Patients during Shortage Created by COVID-19 Surge", published May 12, 2021)
- We recommend against the use of hydroxychloroquine or chloroquine and antibacterials (azithromycin, doxycycline, or others) in the absence of another clear indication.
- We recommend against the use of dexamethasone or other *systemic* glucocorticoids in the absence of another clear indication.
- For adults with moderate disease and aged over 50 with risk factors for severe disease, or aged over 65 years, treatment with inhaled budesonide 800 micrograms twice a day may be considered. The treatment can be discontinued upon resolution of symptoms, or if the patient is started on systemic corticosteroids.
- There is insufficient evidence to recommend for or against convalescent plasma in ambulatory patients with mild or moderate COVID-19.
- Avoid nebulization, if possible, or use dry nebulization protocol (See Appendix 4) or dry powder inhaler as a non-aerosol generating option.
- Patients should be advised to take plenty of fluids and ambulate at least every few hours when awake.
- Prophylactic dose anticoagulation or antiplatelet therapy is not recommended for prevention of deep venous thromboembolism in moderate COVID-19, unless the patient is hospitalized.
- Psychosocial evaluation and support may be indicated. (See below in Section VI.K)

VI.F. How will severe COVID-19 be managed?

- Patients who are hypoxemic (SPO2 <93% in room air) but not in respiratory distress (RR <30, not using accessory muscles of respiration), supplemental oxygen should be given via nasal cannulae (upto 4-6 litres/minute) or via Venturi mask or non-rebreathing mask with reservoir (10-15 litres/minute) to keep SpO2 between ~~93~~92 to 96% (or 88 to 92% if having chronic respiratory diseases).
- These patients need to be admitted to a hospital as soon as possible and closely monitored for worsening saturation or respiratory distress and planned to be shifted to ICU as early as possible.
- For modified thresholds for oxygen therapy and oxygenation targets during pandemic surge, please see Appendix 8: "Annex to NMC treatment guidelines: Management of Patients during Shortage Created by COVID-19 Surge", published May 12, 2021.
- FiO2 level from various oxygen delivery devices can be estimated using the FiO2 estimation chart. (See appendix 3a)
- Consider using facemask or venturi mask instead of nasal cannula when using >4 litres/minute oxygen.
- Patients should use a medical mask over the nasal cannula if they can tolerate it.
- **Ask for ICU review if oxygen requirement is >4 litres/minute or >28% FiO2 via venturi mask to keep Sp02 >92%. These patients need to be closely monitored for worsening saturation or respiratory distress and planned to be shifted to ICU as early as possible, depending on ICU doctor's assessment of the patient.**
- **Awake prone positioning:** For patients admitted to the ward, awake prone positioning should be considered if they require supplemental oxygen (SpO2< 93%). This should only be attempted in those who are alert, able to communicate and with stable hemodynamics. It is contraindicated in patients who are in respiratory distress and require immediate intubation. It is also contraindicated in those who had abdominal surgery recently, or those with spinal instability. Patients need to be monitored carefully to look for signs of deterioration.
  (See appendix 5)
- Patients should be advised to ambulate within the isolation unit at least every few hours when awake.
- Prophylactic dose anticoagulation is **recommended** in all hospitalized patients with severe COVID-19, unless anticoagulation is contraindicated such as presence of severe thrombocytopenia or active bleeding.
- For pharmacologic prophylaxis, one of the following may be used: Enoxaparin, Dalteparin, Fondaparinux or Unfractionated Heparin. (See Table 1)
- There is insufficient data to recommend for higher than prophylactic dose of anticoagulation at this point, and concern for safety and futility of the intervention have led to early termination of some clinical trials assessing therapeutic anticoagulation in hospitalized COVID-19 patients.
- When there is a strong suspicion for thromboembolic disease but imaging is not possible, therapeutic dose anticoagulation should be initiated.

- Based on studies documenting a low incidence of venous thromboembolism following discharge from hospital in these patients, post-discharge prophylaxis is not recommended. However, prophylactic anticoagulation may be considered post-discharge in selected patients with recent trauma or major surgery or history of venous thromboembolism.
- There is no role of antiplatelet therapy for DVT prophylaxis.
- Laboratory tests as listed above in [Section V Diagnosis] should be considered.
- Chest X-ray or ultrasound should be performed, preferably at bedside. CT scan may rarely be indicated, only if it changes the management significantly. Usually, CT scan evaluation may only be useful if there is concern for pulmonary embolism, or bacterial or fungal superinfection, or pneumothorax or pneumomediastinum that is not clearly identifiable by x-ray, or if there is an unexplained deterioration in the patient's status needing further evaluation. (See *Interim Guidelines for Radiology Practice During COVID-19 Pandemic* published by Nepal Radiologists' Association for infection control measures during radiological tests.)
- We **recommend** treatment with Dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, in patients with severe COVID-19. Prednisolone 40 mg once a day, or Methylprednisolone 32 mg given in 1-4 divided doses per day, or Hydrocortisone 160 mg per day (i.e. 50 mg every 8 hours or 100 mg every 12 hours), can be used as alternatives to Dexamethasone when it is not available.
- Remdesivir is **recommended** for use in patients who are **within 10 days from the onset of symptoms** and have severe COVID-19 **requiring low-flow oxygen.** It is given for 5 days or until hospital discharge, whichever comes first. It should be dosed at 200 mg on day 1, and 100 mg once daily on subsequent days. (See Section VI.J below.).
  If/when supplies of Remdesivir are limited, it should be prioritized for use in patients who are within the first 10 days from symptom onset, require supplemental oxygen but do not need invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), and either are immunocompromised or have rapidly progressing hypoxia in spite of systemic corticosteroid use. See "Annex to NMC treatment guidelines: Management of Patients during Shortage Created by COVID-19 Surge", published May 12, 2021. (See Appendix 8)
  During such circumstances, if the condition of a patient receiving Remdesivir while on supplemental oxygen worsens to needing oxygen through a high-flow device, noninvasive ventilation, mechanical ventilation or ECMO, the course of Remdesivir should be completed and duration possibly extended up to 10 days.
- Tocilizumab in single dose of 8 mg/kg (maximum 800 mg), when available, may be considered in patients with severe or critical COVID-19, who have rapidly increasing oxygen needs and systemic inflammation despite use of systemic corticosteroids, with or without Remdesivir. Those with CRP ≥ 75 mg/L and have required initiation of high-flow oxygen therapy, noninvasive ventilation or invasive mechanical ventilation in the previous 24 hours appear to benefit the most from addition of Tocilizumab.

There is insufficient data regarding the utility of Tocilizumab in patients who require supplemental oxygen but not oxygen through a high-flow device, non-invasive or invasive ventilation.

Tocilizumab should only be given in the presence of dexamethasone or another systemic corticosteroid. Since both drugs increase risk of disseminated strongyloidiasis, prophylactic treatment with Ivermectin (200 micrograms / kg / day for 2 days) may be considered.

- We recommend against using convalescent plasma in hospitalized patients with COVID-19.
- There are insufficient data so far to recommend any other antiviral or immunomodulatory therapy in patients with severe COVID-19. Such treatment should ideally be offered only in the setting of clinical trial.
- Empiric coverage with antibacterials or antifungals is NOT recommended in the absence of another indication in patients with severe or critical COVID-19. (See below in Section VI.K)
- Influenza activity was extremely low in the past year due to the preventive public health measures adopted worldwide, therefore even in winter the rates of influenza coinfection were negligible in both northern and southern hemispheres. Therefore empiric antiviral treatment for influenza is not recommended without clinical, laboratory or epidemiologic evidence suggesting the presence of influenza coinfection.

VI.G. How will critical COVID-19 be managed?

- Critically ill patients have associated acute respiratory distress syndrome (ARDS), septic shock that may represent virus-induced distributive shock, cardiac dysfunction, elevations in multiple inflammatory cytokines that provoke a cytokine storm, and/or exacerbation of underlying co-morbidities
- They may also experience cardiac, hepatic, renal, and central nervous system disease in addition to pulmonary disease.

Indications for ICU admission (any one of the following):

- Respiratory failure requiring ventilatory support such as NIV / HFNC or mechanical ventilation
- Presence of shock or multi-organ failure
- PaO_2/FiO_2 < 200 mmHg, or SpO_2/FiO_2 ratio ≤ 235 if ABG not available, with worsening respiratory distress
- Ask for ICU review if oxygen requirement is >4 litres/minute or >28% FiO2 via venturi mask to keep SpO2<~~93~~92%. These patients need to be closely monitored for worsening saturation or respiratory distress and planned to be shifted to ICU as early as possible depending on ICU doctor's assessment of the patient.

Table 1: Parenteral Anticoagulation for adults with COVID 19 hypercoagulopathy

Anticoagulation Agent (AC)	VTE Prophylaxis		VTE Treatment	
	Cr Cl >30 ml/min	Cr Cl <30 ml/min	Cr Cl >30 ml/min	Cr Cl <30 ml/min
Enoxaparin	40 mg/day SC	30 mg/day SC	1mg/kg BD SC	1mg/kg OD SC
Dalteparin	5000 units OD SC	Use alternative AC	200 U/kg OD SC, or 100 U/kg BD SC	Use alternative AC
Fondaparinux	2.5 mg OD SC	Use alternative AC	<50kg: 5mg OD 50-100kg: 7.5mg OD >100kg: 10mg OD SC	Use alternative AC
Unfractionated Heparin (UFH)	5000 units 8-12 hourly SC		†80 units/kg bolus (maximum dose: 10,000 units), then 18 units/kg/hour IV (maximum initial infusion: 2,000 units/hour) APTT needs to be monitored within 6 hours of starting infusion and then regularly for dose adjustment. DO NOT USE treatment dose of UFH if there is no facility to measure APTT.	

†Enoxaparin is the preferred anticoagulant for prophylaxis and treatment of hypercoagulopathy. Avoid use of unfractionated heparin especially for VTE treatment if other options are available.
*In case of previous heparin-induced thrombocytopenia (HIT) or suspected HIT, use Fondaparinux.
*VTE- venous thromboembolism, SC- subcutaneous, IV- intravenous, Cr Cl- creatinine clearance

Oxygen Therapy and Monitoring:

- Monitor oxygen saturation continually during oxygen therapy
- Give supplemental oxygen therapy immediately to patients with severe acute respiratory infection (SARI) and respiratory distress, hypoxemia or shock.
- Target oxygen saturation:
  92% - 96% for patients without chronic respiratory disease
  88% - 92% for patients with chronic type II respiratory failure

For modified thresholds for oxygen therapy and oxygenation targets during pandemic surge, please see Appendix 8: "Annex to NMC treatment guidelines: Management of Patients during Shortage Created by COVID-19 Surge", published May 12, 2021.

Prone positioning:

- Consider awake prone positioning for >12-16 hours a day in patients who require supplemental oxygen but are not yet intubated. Awake proning can also be done in patients who are on high flow nasal cannula (HFNC) or non-invasive ventilation (NIV). It is contraindicated in patients who are in respiratory distress and require immediate intubation. It is also contraindicated in those who had abdominal surgery recently, or those with spinal instability.
- Pre-requisites for awake prone positioning patient should be alert and able to communicate, hemodynamically stable and not in respiratory distress.
- Monitor patient closely during awake prone positioning for signs of deterioration. (See Appendix 5)

High Flow Nasal Cannula (HFNC) or Non Invasive Ventilation (NIV):

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy and no indication of urgent intubation, use HFNC over conventional oxygen therapy. When HFNC is not available, NIV can be used with close monitoring and assessment for worsening respiratory failure at short intervals.
- Adopt airborne precaution when using HFNC/NIV as it can generate aerosols. Use viral filter or high efficiency particulate air (HEPA) filters wherever possible in NIV circuit.
- Patients should use surgical mask over the high flow nasal cannula or NIV mask if tolerated.
- Proceed to endotracheal intubation with airborne precaution if patient is not improving or has respiratory distress.
- **Note: NIV / HFNC should not be used or continued in patients who fulfill criteria for mechanical ventilation (e.g., respiratory distress, unable to protect airway, not improving on a trial of NIV / HFNC, etc.), because delayed intubation leads to increased mortality.**

Endotracheal Intubation:

- If worsening respiratory distress with SPO_2<90% despite oxygen supplementation with 10-15 litres/minute via non-rebreathing facemask, and/or failure of HFNC/NIV to achieve target oxygen saturation, AND
- PaO_2/FiO_2 <150

Mechanical ventilation:

- If patients have indications for mechanical ventilation, intubate them without delay with airborne precautions. Use Rapid Sequence Intubation (preoxygenation, sedation, neuromuscular blocking (NMB) agents, intubation) technique to minimize bag-mask ventilation and to minimize aerosol generation.
- In case of severe crisis and ventilator shortages in the country, anesthesia workstations can be used for ventilation of patients with COVID-19.
- Full airborne precautions measures should be adopted when performing Bag and Mask Ventilation or endotracheal intubation or any other aerosol generating procedures. Viral filters should be used when available. (Refer to NMC Interim Guidance for Infection Prevention and Control When COVID-19 is Suspected, June 2020)

Antiviral and immunomodulatory treatments:

- Dexamethasone 6mg once a day, through either intravenous or oral route, is **recommended** in patients with critical COVID-19. Prednisolone 40mg once a day, or methylprednisolone 32mg per day in 1-4 divided doses, or Hydrocortisone 160 mg per day (50 mg every 8 hours or 100 mg every 12 hours) can be used as an alternative to Dexamethasone when it is not available. Corticosteriods should be given for up to 10 days or until hospital discharge, whichever comes first.
- Given that the likely prevalence of Strongyloidiasis is high in Nepal, presumptive treatment with Ivermectin 200 micrograms/kg/day for 1-2 days can be considered for those being started on corticosteroids.
- Since corticosteroids lead to high blood glucose levels both in those with known or unknown preexisting diabetes mellitus as well as those without such history, close monitoring and management of blood sugar is important. Combined basal and bolus insulins regimen may be necessary to achieve adequate blood sugar control.
- There are insufficient data to recommend any other immunomodulatory therapy or any antiviral therapy in critically ill COVID-19 patients.
  Remdesivir may be **considered** in those needing oxygen through high flow devices or noninvasive or invasive ventilation on a case by case basis.
- Empiric coverage with antibacterials or antifungals is NOT recommended in the absence of another indication in patients with severe or critical COVID-19. (See below in Section VI.K)
- Tocilizumab in single dose of 8 mg/kg, when available, may be considered in patients with severe or critical COVID-19, who have rapidly increasing oxygen needs and

systemic inflammation despite use of systemic corticosteroids, with or without Remdesivir. Those with CRP ≥ 75 mg/L and have required initiation of high-flow oxygen therapy, noninvasive ventilation or invasive mechanical ventilation in the previous 24 hours appear to benefit the most from addition of Tocilizumab.

Tocilizumab should only be given in the presence of dexamethasone or another systemic corticosteroid. Since both increase risk of opportunistic infections, prophylactic treatment with Ivermectin (200 micrograms / kg / day for 2 days) is recommended.

Convalescent plasma therapy:

- We recommend against using convalescent plasma in hospitalized patients with COVID-19. (See details below in "Section VI.J.2".)

Treatment of co-infections:

- Empiric coverage with antibacterials or antifungals is NOT recommended in the absence of another indication in patients with severe or critical COVID-19. (See below in Section VI.K)
- However if there is strong suspicion for bacterial pneumonia or sepsis, start empiric antimicrobials to treat likely pathogens causing severe pneumonia and sepsis as soon as possible, preferably within 1 hour of initial assessment for patients with sepsis.
- When a viral etiology such as SARS-CoV-2 is identified, empiric antibiotic therapy should be deescalated or stopped on the basis of microbiology results and clinical judgement.
- A COVID-19 patient presenting after around a week of symptoms with clinical pneumonia, with or without hypoxia, may have negative RT-PCR and antigen tests. Clinical clues based on review of clinical course and progression, local epidemic patterns and pattern of imaging (possibly HRCT chest) findings should guide treatment with steroids and/or symptomatic management rather than empiric addition of antibacterial therapy in such cases.

Fluid management:

- Use restrictive fluid management strategy ensuring patient's tissue perfusion.
- In patients with severe acute respiratory illness, when there is no evidence of shock, aggressive fluid management may worsen oxygenation.
- Closely monitor fluid intake and output.

Deep Vein Thrombosis (DVT) prophylaxis:

- Pharmacologic DVT prophylaxis should be offered in all admitted patients where there is no contraindication for anticoagulation.
- One of the following may be used: Enoxaparin, Dalteparin, Fondaparinux or Unfractionated Heparin.

- Increased incidence of arterial and venous thrombosis has been noted in severe/ critical COVID 19 patients. In case of worsening hypoxia not fully explained by worsening chest x-ray or in case of high suspicion of DVT/ pulmonary embolism, therapeutic dose of anticoagulation may be needed. Consider venous Doppler ultrasound and echocardiogram to assess for right heart strain when available. If no alternative explanation, consider therapeutic anticoagulation.
  (See Table 1, for anticoagulant dosage)

VI.H. How will ARDS secondary to COVID-19 be managed?

(Refer to Appendix 6 for management of refractory hypoxemia and ventilator adjustment.)

- Recognize severe hypoxemic respiratory failure and prepare to provide advanced oxygen/ventilatory support when a patient has worsening respiratory distress and is failing to respond to standard oxygen therapy (PaO_2/FiO_2<150 mmHg).
- Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions and using full PPE.
- Implement mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight, PBW) and lower inspiratory pressures (plateau pressure < 30 cmH_2O)

Prone positioning:

- Early prone positioning without pulmonary vasodilator trial is recommended in adult patients with severe ARDS due to COVID-19, which is a departure from the typical practice for ARDS from other causes. In patients with severe ARDS (PaO2/FiO2 <150 mmHg), prone early, within 12 hours of FiO2 >75%, for 12–16 hours per day.
- Spinal cord injury and open chest are absolute contraindications to prone ventilation.
- Prone positioning may be associated with several complications; hence, experienced team should carry out or supervise the management of proned patients. Several sessions of prone positioning may be needed.
- Titrate PEEP and FiO2 as per ARDSnet's protocol. (Appendix 6)
- Adopt permissive hypercapnia (Target pH > 7.2)
- Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.
- Use in-line catheters (Closed Suction Catheter) for airway suctioning, and clamp endotracheal tube when disconnection is required. Consider paralysis during airway manipulation.
- Use Ventilator Bundle (Table 2) strictly.

Table 2: Ventilation Bundle
Head-of-bed elevation 30 - 45°
Daily sedation interruption
Daily spontaneous breathing trial
Deep vein thrombosis prophylaxis
Stress ulcer prophylaxis (in patients with high risk of gastrointestinal bleeding

Subglottic secretion drainage in patients likely to be ventilated for > 48 hours

Sedation and neuromuscular blockade:

- Avoid continuous sedation and neuromuscular blockade when possible.
- Sedation should be given in case of ventilator dyssynchrony.
- Intermittent boluses of neuromuscular blocking agents can be given if there are some ventilator dyssynchrony.
- If persistent dyssynchrony, high plateau pressures or if prone ventilation then continuous NMBA may be needed for upto 24 hrs.

Extracorporeal membrane oxygenation (ECMO) therapy:

- Consider ECMO if resources are available, in patients with refractory hypoxemia in spite of management including lung protective mechanical ventilation and prone positioning.

VI.I. How will Septic Shock secondary to COVID-19 be managed?

Recognition of septic shock

Recognize septic shock when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) ≥ 65 mmHg AND lactate is ≥ 2 mmol/L, in absence of hypovolemia. If lactate measurement is not available use clinical assessment for tissue perfusion status e.g. capillary refill time, change in mental status, urine output.

Resuscitation of patients with septic shock

a. Give 500 mL crystalloid fluid (such as Normal saline or Ringer's lactate) as rapid bolus in first 15 minutes and reassess for signs of fluid overload after each bolus.
b. Fluid resuscitation may lead to volume overload and respiratory failure, particularly with ARDS. If there is no response to fluids or if patient develops signs of volume overload (e.g. jugular venous distension, crackles on lung auscultation, pulmonary oedema on imaging, B lines on Lung USG, or hepatomegaly in children), then reduce or discontinue fluid administration.
c. Do not use hypotonic crystalloids, starches, or gelatins for resuscitation.

Vasopressors

a. Administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥ 65 mmHg in adults and improvement in markers of perfusion.
    - Norepinephrine is considered first-line treatment in adult patients; vasopressin and/or epinephrine can be added to achieve the MAP target. Because of the risk of tachyarrhythmia, reserve dopamine for selected patients with low risk of tachyarrhythmia or those with bradycardia.

b. Vasopressors (i.e. norepinephrine, vasopressin, epinephrine and dopamine) are most safely given through a central venous catheter at a strictly controlled rate, but it is also possible to safely administer them via peripheral vein (lower concentration solution) and intraosseous needle.

c. Monitor blood pressure frequently and titrate the vasopressor to the minimum dose necessary to maintain perfusion targeting MAP of 60-65 mmHg and also prevent side effects.

Antimicrobials

When bacterial superinfection is suspected, appropriate empiric antimicrobials should be started. (See below in Section VI.K)

VI.J. What antiviral or other COVID-19 specific treatment should be offered to COVID-19 patients?

1. Antiviral Drugs

- Except for remdesivir which is now recommended by some international expert groups and authorities such as the NIH and IDSA in certain COVID-19 patients, antivirals should be used under investigational settings only. Treatment decisions with antiviral drugs should be made by the health care provider based on their discussion with the patient and their legal guardians.

a. Remdesivir: Remdesivir is a direct acting antiviral drug that inhibits viral RNA synthesis of SARS-CoV, MERS-CoV, and SARS-CoV-2.

In a randomized placebo-controlled trial (ACTT-1), remdesivir resulted in a faster time to recovery, median 10 days, compared to 15 days with placebo, mainly in the subset of patients who were on low-flow oxygen at baseline. There was also noted a non-statistically significant improvement in overall 29-day mortality. In the subset of patients who were on oxygen but not on high-flow oxygen or ventilatory support, there was a statistically significant improvement in mortality at 29 days.

In another open-label trial of hospitalized patients with moderate COVID-19, patients were randomized in a 1:1;1 ratio to receive a 10-day course of remdesivir, a 5-day course of remdesivir, or standard care. By day 11, the 5-day remdesivir group had better clinical status according to a 7-point scale compared with standard of care. There was not a statistically significant difference at day 11 in clinical status between the 10-day remdesivir group and the standard care group.

In the large, open label randomized WHO-sponsored Solidarity trial of four repurposed antiviral medications, published in preprint server only at this time (awaiting peer review), no significant effect was noted in terms of overall in-hospital mortality, initiation of ventilation or duration of hospital stay. As this study suggests no utility of remdesivir even

in patients with moderate or severe COVID-19, contrary to the conclusions of the ACTT-1 study, some critiques of the study have questioned the quality of its evidence because of some weaknesses in design and the definitions used, as compared to the other trials.

Based on our review of the evidence available at this point, we **recommend** using remdesivir in the subgroup of severe COVID-19 patients requiring low flow oxygen supplementation if within 10 days from the onset of symptoms.

The evidence so far points towards lack of benefit in using Remdesivir in the following subgroups but it may be **considered** on a case by case basis:

i. the subgroup of patients with moderate COVID-19 who have significant risk factors for developing severe illness, or rapidly progressing radiographic findings, and/or dropping oxygen saturation, even though the SpO2 may still be ≥ 94%.
ii. critically ill patients requiring oxygen supplementation through high flow devices or invasive or noninvasive ventilation.

The US FDA has warned against using remdesivir alongside hydroxychloroquine or chloroquine because it may result in lower remdesivir's antiviral activity. Remdesivir has been associated with gastrointestinal side effects (nausea, vomiting), transient elevations in ALT or AST, and mild, reversible PT prolongation without change in INR. The drug vehicle has been associated with renal toxicity and known to accumulate in patients with moderate or severe renal impairment. Remdesivir is contraindicated in patients with hepatic dysfunction (ALT >5 times ULN) and renal impairment (creatinine clearance <30 mL/min).

b. Favipiravir (T-705 or Avigan): Favipiravir is an inhibitor of viral RNA-dependent RNA polymerase. Favipiravir has been approved in Japan and China for the treatment of novel influenza virus infections. It has also been used for postexposure prophylaxis and treatment for Ebolavirus infection. However, it is a mutagen and has potential for both teratogenicity and embryotoxicity in humans. An open-label trial in China comparing oral favipiravir plus inhaled interferon compared with a historical cohort of patients receiving lopinavir/ritonavir showed that patients receiving favipiravir+interferon had median shedding of virus of 4 days compared with 11 days in the lopinavir/ritonavir group. In a company-sponsored randomized, open-label trial in India involving asymptomatic, mild or moderate COVID-19 cases, lack of statistical significance was noted on the primary endpoint of time to the cessation of viral shedding, although median time to clinical cure was reported to be statistically significant (3 days vs 5 days), with those in the favipiravir arm observing more than 4 times the side effects compared to the standard care arm. A multicenter randomized open-label trial on moderate to severe cases performed in Iran, comparing favipiravir and lopinavir/ritonavir, showed no difference in in-hospital mortality, ICU admissions or mechanical ventilation, nor shortened the length of hospital stay or time to clinical recovery. Based on the above information, currently its use in COVID-19 can be recommended only as an investigational agent.

c. Chloroquine/Hydroxychloroquine: We do NOT recommend treatment with hydroxychloroquine or chloroquine for COVID-19, either alone or in combination with azithromycin. Reports from multiple randomized controlled trials including the WHO Solidarity trial have shown no benefit from use of hydroxychloroquine or chloroquine as pre- or post-exposure prophylaxis, nor as treatment in COVID-19. If chloroquine or hydroxychloroquine is used for another indication in patients with COVID-19, clinicians should closely monitor the patients for adverse effects, especially prolonged QTc interval. Hydroxychloroquine should NOT be used with azithromycin because of the increased potential for cardiac arrhythmias.

d. Lopinavir-ritonavir: Lopinavir-ritonavir cannot be recommended alone in the absence of supporting evidence.

2. Convalescent Plasma Therapy (CPT)

- CPT has been evaluated in multiple clinical trials as a treatment option under clinical trials for patients with severe COVID-19.

  A multicentered study conducted by Mayo Clinic (USA), which included over 35,000 patients, showed 7-day mortality rate of 8.7% in patients transfused within 3 days of COVID-19 diagnosis vs. 11.9% in patients transfused 4 or more days after diagnosis ($p<0.001$), and 30-day mortality of 21.6% vs. 26.7%, respectively ($p<0.0001$). Studies have also established safety of COVID-19 CPT with reported incidence of adverse events of <1% among plasma recipients.

  Since the last update, more data from randomized controlled trials on convalescent plasma in hospitalized and non-hospitalized patients were published. The RECOVERY trial, a randomized, controlled, open label, platform trial, showed that high-titer convalescent plasma improved neither the 28-day survival, nor the proportion of patients discharged from hospital, nor, among those not on mechanical ventilation, decrease in progression to invasive mechanical ventilation. The lack of survival benefit was evident among recipients with no detectable SARS-CoV-2 antibody at baseline. A number of other randomized trials have supported similar conclusions regarding futility of use of convalescent plasma in hospitalized patients.

  A randomized, double-blind, placebo-controlled trial using high titer convalescent plasma was performed in outpatient setting in Argentina. Participants included ambulatory COVID-19 patients who were either either 65-74 year old and had ≥1 comorbidity, or were >75-year old. Although the trial had to be prematurely terminated because of lack of COVID-19 cases at study site, the primary endpoint of progression to severe respiratory disease by day 15 was shown to be significantly lower in the convalescent plasma arm compared to the placebo arm. Further evidence is awaited on the possible utility of high-titer convalescent plasma therapy on those with mild or moderate COVID-19, especially among those at higher risk of having poor outcomes.

In light of the above, CPT is NOT recommended in hospitalized patients with COVID-19. There is insufficient evidence to recommend for or against convalescent plasma in ambulatory patients with mild or moderate COVID-19.

3. Host Modifiers/Immune-Based Therapy

- **Dexamethasone and other corticosteroids:** A metaanalysis of 7 trials that included 1703 critically ill patients with COVID-19, glucocorticoids reduced 28-day mortality compared with standard care or placebo (32% vs 40%). The majority of the data on the efficacy of glucocorticoids is derived from the RECOVERY trial in the UK, where oral or intravenous dexamethasone reduced 28-day mortality among hospitalized patients compared with usual care alone. The survival benefit was more remarkable on patients on invasive mechanical ventilation or ECMO at baseline (4.1% absolute mortality reduction), but were still statistically significant on patients on noninvasive oxygen therapy including noninvasive ventilation (4.1% absolute mortality reduction). The benefit was not seen among patients not requiring oxygen, and there was actually a nonstatistically significant trend towards higher mortality.

  Based on the findings of RECOVERY trial and other studies using corticosteroids, dexamethasone, 6 mg daily for up to 10 days, is recommended for patients with severe and critical COVID-19. However, corticosteroids are not recommended for patients with COVID-19 without hypoxemia requiring supplemental oxygen.

  It is not clear if use of other corticosteroids for the treatment of COVID-19 provides the same benefit as dexamethasone. If dexamethasone is not available, equivalent doses of other corticosteroids (Prednisolone 40 mg once a day, Methylprednisolone 32 mg in 1-2 divided doses per day, or Hydrocortisone 160 mg in 2-4 divided doses per day) may be used in severe or critically ill patients.

  Given that the likely prevalence of Strongyloidiasis is high in Nepal, preemptive treatment with Ivermectin 200 micrograms/kg/day for 1-2 days should be considered for those being started on corticosteroids.

  Patients being treated with glucocorticoids should be monitored for adverse effects including hyperglycemia, delirium, and increase risk for bacterial, fungal and Strongyloides infection.

- **Tocilizumab:**

  Since our last update, two large randomized controlled trials have shown significant benefit from the use of the IL-6 inhibitor Tocilizumab in selected patients with severe and critical COVID-19.

  The open-label, randomized controlled platform trial in the UK, RECOVERY, assessed the utility of Tocilizumab in severe or critical COVID-19 patients with CRP ≥75. Patients with active non-SARS-CoV-2 infection were excluded. 82% of the participants were also being treated with corticosteroids. The Tocilizumab arm had lower mortality (29%) vs the usual care arm (33%) by day 28. The mortality difference was not noted in the subgroup who required mechanical ventilation at baseline.

In the "Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia" (REMAP-CAP) trial, a multinational open-label, randomized controlled trial in critically ill ICU-admitted patients with COVID-19, 28-day mortality were treated with tocilizumab plus standard care, or sarilumab plus standard care, or standard care alone. 90% of the patients in this trial were also treated with corticosteroids. Those admitted to the ICU more than 24 hours earlier, those under immunosuppression, and those with ALT >5 times the upper limit of normal range were excluded. Very few patients ended up being randomized to Sarilumab. The in-hospital mortality was significantly lower in those receiving tocilizumab compared those receiving standard of care (28% vs 35.8%; adjusted OR 1.64; 95% CI, 1.14-2.35). Among those who were not mechanically ventilated, 41.3% progressed to intubation or death in the tocilizumab arm vs 52.7% in the standard care arm.

Earlier, several randomized controlled clinical trials had failed to show significant benefit with tocilizumab. The important difference between the clinical trials that showed no benefit and the RECOVERY and REMAP-CAP trials is that in the latter, the majority of the patients received tocilizumab in addition to corticosteroids, while only a minority of patients in the earlier trials were on corticosteroids.

Based on the data above, a single dose of Tocilizumab 8 mg/kg, when available, may be considered in patients with severe or critical COVID-19, who have rapidly increasing oxygen needs and systemic inflammation despite use of systemic corticosteroids, with or without Remdesivir. Those with CRP ≥ 75 mg/L and have required initiation of high-flow oxygen therapy, noninvasive ventilation or invasive mechanical ventilation in the previous 24 hours appear to benefit the most from addition of Tocilizumab.

Tocilizumab should only be given in the presence of dexamethasone or another systemic corticosteroid. Since both increase risk of opportunistic infections, prophylactic treatment with Ivermectin (200 micrograms / kg / day for 2 days) is recommended.

- We recommend against the use of anti-IL6 monoclonal antibody siltuximab or anti-IL6 receptor monoclonal antibodies sarilumab, or in severe or critically ill CoVID-19 patients, interferon beta.
- There are insufficient clinical data to recommend either for or against the use, in mild and moderate COVID-19, interferon alfa or beta.

VI.K. What other adjunct treatment considerations are there?

- Systemic corticosteroids: Based on the findings of RECOVERY trial and other studies using corticosteroids, dexamethasone or alternatively, methylprednisolone or hydrocortisone, are recommended for patients with severe COVID-19. However, corticosteroids are not recommended for patients with COVID-19 *without* hypoxemia. Please see above in section VI.J.3 regarding discussion on the use of dexamethasone in COVID-19. Systemic corticosteroid can be considered in patients with severe ARDS with high ventilatory

support or if required for septic shock, adrenal crisis or comorbidities such as COPD exacerbation or asthma exacerbation.

- Antimicrobials:
  a. The rates of bacterial superinfection of COVID-19 appear to be very low, but when present increase mortality risk. Anecdotal reports suggest less MRSA superinfection than is often seen with influenza. Unnecessary antibiotics carry risks of fluid overload and, most importantly, drug-resistance, that leads to significantly higher morbidity and mortality especially in severe or critical COVID-19 patients, as well as the possibility that antibiotics may become a limited resource. Empiric coverage with antibacterials or antifungals is NOT recommended in the absence of another indication in patients with COVID-19.
  b. In patients who meet the definition of sepsis/septic shock, antibiotics should be started within an hour of presentation or recognition of signs of sepsis.

     One of more of the following findings may prompt consideration of primary or secondary bacterial infection:
     - the patient starts to have fever spikes after initial improvement on systemic corticosteroids, or
     - there is profuse production of purulent sputum, or
     - there is development of hypotension or shock
     - the x-ray of the chest shows a lobar involvement or other patterns not usually seen in COVID-19 pneumonia, or
     - if the WBC count is very high (beyond the range of mild or moderate leukocytosis)

     When bacterial infection is suspected, local antibiotic sensitivity pattern when reliable, should guide the choice of empiric antibiotics, especially if the patient is in shock or critically ill, with further modifications in the regimen performed depending on lower respiratory tract specimen culture findings.
  c. Antibiotics should be discontinued or deescalated if cultures are reported as negative or if bacterial infection ruled out clinically.

- Antihypertensive medications: Patients already on anti-hypertensive medications of the groups angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) can continue to use these medications. They should be stopped only when they develop hypotension or CKD. Switching to other groups of antihypertensives is not recommended.

- Management of myocarditis: Patients may develop cardiogenic shock secondary to myocarditis, in which case check ECG and trends of BNP and troponin. Refer these patients to cardiologist for appropriate management.

- Nonsteroidal anti-inflammatory drugs: There is no clear evidence to recommend stopping or avoiding NSAIDs when clinically indicated. However, it is advised to use Paracetamol as the preferred temperature-lowering agent and analgesic, and when NSAIDs are needed, to use the lowest effective dose.

- Nutritional Support:
  a. Start enteral feeding early.
  b. Nasogastric or orogastric tube feeding in intubated patients.
  c. Consider parenteral nutrition if enteral feeding is not tolerated despite prokinetic use or if enteral feeding is contraindicated.

- Psychosocial Support:
  a. Patients with COVID-19 are at risk of developing fear and worry about their own health and the health of their loved ones, changes in sleep or eating patterns, insomnia, worsening of chronic health problems or preexisting mental health conditions, or increased use of alcohol, tobacco or other drugs.
  b. Those with higher risk for severe illness such as older adults, along with those with disabilities are at increased risk for increased stress, or even depression.
  c. Clinicians should have a higher suspicion for development of psychological disturbances in patients with COVID-19.
  d. Such patients can be helped by connecting them with family and loved ones, by acknowledging their distress, and with psychological or psychiatric evaluation and support if needed.

VI.L. What are the possible ethical issues that need to be considered?

1. End-of-life care and care of the dying patient
   a. Patients who are terminal because of COVID–19 may be allowed to be visited by only a limited number closest family members at their wish but with appropriate PPE. If appropriate PPE is not available, hospitals may refuse such visits considering the risk of transmission of the virus.
   b. If the patient's outcome seems grim and the treatment offered may be futile as evidenced by multiple organ failures, refractory shock or refractory hypoxia, this should be conveyed to family members and opted for a DNR status as providing CPR to the patient won't be helpful and will increase the risk of transmission of disease.
2. Resource utilization during crisis
   a. In case of rapid significant increase in the number of cases requiring critical care and mechanical ventilation beyond the effectively available critical care capacity, such increase may give rise to a situation when criteria for access to (and discharge from) intensive care resources and ventilators may need to be set up, based not

only on clinical appropriateness and proportionality of care, but also on likelihood of therapeutic success, while also aspiring towards distributive justice. Principles of justice, transparency, non-abandonment of patient, and, non-restriction of autonomy of the patient except for compelling public health concern, should be followed while designing such criteria.

b. Parameters indicating likelihood of therapeutic success may include:
   i. the type and severity of the disease
   ii. the compromise of other organ systems and their reversibility
   iii. the presence of hypoxic brain Injury
   iv. types, numbers and severity of underlying comorbidities
   v. age

3. Prioritization of resources to healthcare workers:
   a. Critical Covid-19 interventions such as lab tests, personal protective equipment, intensive care unit interventions such as ventilators, therapeutics, and vaccines should preferentially be made available to front-line health care workers and others who care for ill patients and who keep critical infrastructure operating, particularly those who face a high risk of infection.

   Whether healthcare workers who need ventilators will be able to return to work is uncertain, but providing preferential access to appropriate interventions as indicated recognizes the significant risks they have willingly exposed themselves to while taking care of suspected or confirmed COVID19 patients.

VI.M. What are the criteria for discharge of confirmed COVID-19 patients?

1. Criteria for stepdown from the ICU to isolation ward:
   a. Hemodynamically stable and no vasopressor support required for > 8 hours, AND
   b. Off ventilator for > 24 hours, AND
   c. SaO2 >92% with FiO2 requirement <35%

2. Criteria for discharge from isolation:
   a. **Patients with confirmed COVID-19 who have NOT had any symptoms:** Patients who have not had symptoms can be discharged to home if the following time-based criteria are met.

   Time-based criteria are used.
   a) At least **10 days** have passed since the first positive COVID-19 diagnostic test
   b) No symptoms have developed subsequent to the first positive test
   c) The patient does NOT have an underlying severe immunocompromising condition such as human immunodeficiency virus infection with CD4 count <350 cells/mm^3, treatment with immunosuppressive medications including high dose steroids (prednisolone >20 mg), cancer chemotherapy, leukemia, transplant, etc.

Note: If the asymptomatic patient or HCW is immunocompromised, they will need at least one negative SARS CoV-2 test result by a molecular method (e.g. PCR).

b. **Symptomatic patients with mild or moderate COVID-19:** Patients who meet the following criteria may be discharged to home.

Time-based criteria are used.

a) Resolution of fever >72 hours without antipyretics, and
b) Improvement in respiratory signs and symptoms (cough, shortness of breath and oxygen requirement), and
c) At least **10 days** have passed since the initial onset of symptoms
d) The patient does not have an underlying severely immunocompromising condition such as human immunodeficiency virus infection with CD4 count <350 cells/mm^3, leukemia, post-transplant, treatment with immunosuppressive medications including high dose steroids (prednisolone >20 mg/day), cancer chemotherapy, etc. (See recommendation for this group of patients below.)

A test-based strategy is no longer recommended except for immunocompromised hosts or severely infected patients as noted below. In the majority of cases, test-based strategy results in unnecessary prolonged isolation of patients who continue to shed SARS-CoV-2 RNA which are no longer infectious.

c. **Symptomatic patients with severe COVID-19:**
The time based criteria above will hold except that the duration from initial onset of symptoms will be 14 days.

d. **Symptomatic patients with critical COVID-19** and **symptomatic patients with immunocompromising conditions:** All of the 3 criteria below should be met:
a) Resolution of fever >72 hours without antipyretics, and
b) Improvement in respiratory signs and symptoms (cough, shortness of breath and oxygen requirement), and
c) At least **20 days** have passed since the initial onset of symptoms, OR
2 consecutive negative SARS CoV-2 test result by a molecular method (e.g. PCR) after 14 days from onset of symptoms

Table 3: Criteria for discharge from isolation for those with COVID-19

	Improvement in respiratory signs & symptoms + No fever for 72 hours	Number of days completed since swab collection	Number of days completed since symptom onset	At least 1 -ve PCR report

	without antipyretics	for +ve PCR		
Asymptomatic, NO severe IC	N/A	10	N/A	-
Asymptomatic, severe IC	N/A	10	N/A	Yes
Mild or moderate COVID, NO severe IC	Yes	-	10	-
Mild or moderate COVID, severe IC	Yes	-	10	Yes
Severe COVID, NO severe IC	Yes	-	14	-
Severe COVID, severe IC	Yes	-	14	Yes
Critical COVID, NO severe IC	Yes	-	20*	-
Critical COVID, severe IC	Yes	-	20*	Yes*
IC = immunocompromised state. Severe IC defined as having human immunodeficiency virus infection with CD4 count <350 cells/mm^3, leukemia, post-transplant, or treatment with immunosuppressive medications including high dose steroids, cancer chemotherapy, etc * = Or, 2 consecutive negative SARS CoV-2 test result by a molecular method (e.g. PCR) is acceptable after 14 days from symptom onset				

VII. SPECIAL POPULATIONS WITH COVID-19

VII.A Pregnant Women and Lactating Mothers

- Studies performed in the USA and the UK have suggested that pregnancy may increase the risk of ICU admission or mechanical ventilation but the absolute increase for ICU admission or mechanical ventilation is low compared to nonpregnant women with COVID-19. There was no significant increase or only slight increase in risk of death compared to nonpregnant women. Age ≥ 35, obesity, diabetes mellitus and hypertension increase risk of maternal death. The risk of preterm and caeserian delivery have been reported to increase in some studies, but miscarriage has not been noted to increase significantly.
  However, in the context of Nepal, with the compartmentalization of care for those with COVID-19, stigma, overall lower quality of healthcare services in general, the difficulty posed by various types of travel restrictions, and the consequent possibility of significantly

poorer quality of care for those identified to have SARS-CoV-2 infection, pregnancy is likely to lead to poorer outcomes.

- Few cases of likely vertical transmission have been reported. Cases of possible congenital infection, especially when mother has acquired an infection in late third trimester in the 2 weeks prior to delivery, have been reported.
- Pregnant women who need hospitalization should ideally be admitted to a facility that can conduct maternal and fetal monitoring.
- The safety of pregnant women should be prioritized over potential theoretical concern regarding the safety of potentially effective medications in pregnancy, and such treatment should not be withheld from them.
- SARS-CoV-2 has not been identified in breastmilk of infected mothers.
- All recently pregnant women with COVID-19 should be counseled on safe infant feeding and appropriate infection prevention measures to prevent COVID-19 virus transmission.
- Infants born to mothers with suspected, probable, or confirmed COVID-19 should be fed according to standard infant feeding guidelines, while applying necessary precautions for infection prevention and control
- Symptomatic mothers who are breastfeeding or practicing skin-to-skin contact or kangaroo mother care should practice respiratory hygiene, including during feeding (for example, use of a medical mask when near a child if with respiratory symptoms), perform hand hygiene before and after contact with the child, and routinely clean and disinfect surfaces which the symptomatic mother has been in contact with.

VII.B Pediatric Population

Please refer to Appendix 8 for evaluation and management of COVID-19 in pediatric population and multisystem inflammatory syndrome in children (MIS-C).

VIII. INFECTION PREVENTION AND CONTROL

Please refer to the separately published *Nepal Medical Council Interim Guidance for Infection Prevention and Control When COVID-19 Is Suspected – Update 1* for guidance regarding infection prevention and control in hospitals.

Please refer to this document's section VI.M.2 for updated guidance for the criteria for discharge from isolation.

IX. VACCINES

Multiple potential COVID-19 vaccines are under development and being evaluated in clinical trials. As of this update (June 5, 2021), Department of Drug Administration of Nepal (DDA) has given approval under EUA (Emergency Use Authorization) for the following vaccines in Nepal:

- ChAdOx1-S ("Covishield" or "Oxford-AstraZeneca"): a non-replicating chimpanzee adenovirus-vectored vaccine, administered intramuscularly, two doses 8-12 weeks apart, approved for over 18 years old; WHO listed for EUA. In pooled analyses of clinical trials, single dose of the vaccine offered 76% protection against symptomatic COVID-19 in the first 3 months. The vaccine had different efficacy in protecting against symptomatic COVID-19, depending on dosing interval between two doses: 54.9 %(CI 32.7-69.7%) when given less than 6 weeks apart vs 82.4 % (CI 62.7 - 91.7 %) when given 12 weeks or more. As per data from AstraZeneca (March 25, 2021; yet to be peer-reviewed), the vaccine is 100% effective in preventing severe or critical COVID19 or hospitalization after two doses. However, real world data analyzed and published by Public Health UK showed that efficacy against symptomatic disease 3 weeks after 1 dose of vaccine was 50% against the Alpha (B.1.1.7) variant but only 33% efficacy against the Delta (B.1.617.2) variant; and 3 weeks after 2 doses of the vaccine, the efficacy against symptomatic disease was 66% against the Alpha variant and 60%% against the Delta variant.
- Sinopharm/ BBIBP-CorV vaccine: inactivated SARS-CoV-2 vaccine (cultured in Vero cells), administered IM, 2 doses, 3-4 weeks apart, approved for 18 years & older; WHO listed for EUA. As per WHO, the vaccine has overall efficacy of 79 % against symptomatic SARS-CoV-2 infection & hospitalizations.
- Sputnik V vaccine (Gamaleya): An heterologous prime-boost adenovirus-vectored vaccine (non-replicating human adenovirus, rAd26-S and rAd5-S), administered IM, two doses 3 weeks apart, approved for over 18 years old. Reportedly, the vaccine was 91.6 % effective in preventing symptomatic COVID-19 infection.
- BBV152 / Covaxin (by Bharat Biotech): an inactivated SARS-CoV-2 vaccine (cultured in Vero cells), administered IM, two doses, 4 weeks apart, over 18 years old. Reportedly, the vaccine is 80.6 % effective in preventing PCR-confirmed symptomatic SARS-CoV-2 infection, as per interim data released by Bharat Biotech on March 3, 2021.
- Sinovac-CoronaVac: an inactivated SARS-CoV-2 vaccine (cultured in Vero cells), administered IM, two doses, 2-4 weeks apart, over 18 years old; WHO listed for EUA.. As per WHO, the vaccine has efficacy of 51% against symptomatic SARS-CoV-2 infection, 100% against severe COVID-19 infection & 100% against hospitalizations.

Please also refer to Appendix 9: Frequently Asked Questions on Vaccines against SARS-CoV-2.

X. REFERENCES

- Operational Planning Guidelines to Support Country Preparedness and Response. WHO, Feb 2020.
- Global surveillance for COVID-19 caused by human infection with COVID-19 virus: interim guidance WHO. March 2020.
- Comparative accuracy of oropharyngeal and nasopharyngeal swabs for diagnosis of COVID-19. Oxford COVID-19 Evidence Service Team, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford. March 26, 2020. https://www.cebm.net/covid-19/comparativeaccuracy-of-oropharyngeal-and-nasopharyngeal-swabs-for-diagnosis-of-covid-19/
- Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19) Guo et al. Clin Inf Dis.https://doi.org/10.1093/cid/ciaa310
- Infectious Diseases Society of America (IDSA) Guidelines on the Diagnosis of COVID-19. IDSA Panel. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/ Accessed May 9, 2020.
- WHO Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays Interim guidance, 11 September 2020: https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays
- CDC (USA). Interim Guidelines for COVID-19 Antibody Testing in Clinical and Public Health Settings. Updated March 17, 2021. Accessed June 1, 2021. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
- CDC (USA). Interim U.S. Guidance for Risk Assessment and Work Restrictions for Healthcare Personnel with Potential Exposure to COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidancerisk-assesment-hcp.html. Accessed May 23, 2020.
- CDC (USA). Public Health Recommendations for Community-Related Exposure. https://www.cdc.gov/coronavirus/2019-ncov/php/public-health-recommendations.html. Accessed May 24, 2020.
- CDC (USA). Interim Guidance: Discontinuation of Isolation for Persons with COVID -19 Not in Healthcare Settings Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html Accessed May 9, 2020.
- COVID-19 Treatment Guidelines Panel. Coronavirus Diseases 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed June 1, 2021.
- Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Aylward et al. Feb 2020.
- Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). CDC (USA). Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-managementpatients.html Accessed May 9, 2020.
- Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Wichmann et al. Ann Int Med. doi: 10.7326/M20-2003
- Foot Manifestations in a COVID-19 Positive Patient: A Case Study. Niremberg et al. J Am Podiatr Med Ass. doi: https://doi.org/10.7547/20-088
- Moriarty LF, et al. Public Health Responses to COVID-19 Outbreaks on Cruise Ships — Worldwide, February–March 2020. MMWR Morb Mortal Wkly Rep 2020;69:347-352. DOI: http://dx.doi.org/10.15585/mmwr.mm6912e3
- Li R et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). *Science* 2020: Vol. 368, Issue 6490, pp. 489-493 DOI: 10.1126/science.abb3221
- SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. Zou et al. PMID: 32074444 DOI: 10.1056/NEJMc2001737

- WHO. COVID-19 clinical management: living guidance. 25 January 2021. Accessed June 1, 2021. https://app.magicapp.org/#/guideline/j1WBYn
- Elharrar et al. Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. JAMA. May 2020.
- Sartini et al. Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit. JAMA. May 2020
- Telias et al. Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19? JAMA. May 2020.
- Prone Positioning in Severe Acute Respiratory Distress Syndrome. N Engl J Med. Guerin et al. PMID: 23688302.DOI: 10.1056/NEJMoa1214103
- KC et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. Lancet Glob Health. 2020 Oct;8(10):e1273-e1281. doi: 10.1016/S2214-109X(20)30345-4. Epub 2020 Aug 10.
- Sankar et al. COVID-19 in Children: Clinical Approach and Management. Indian J Pediatr 87, 433–442 (2020). https://doi.org/10.1007/s12098-020-03292-1
- American Academy of Pediatrics. Critical Updates on COVID-19. https://services.aap.org/en/pages/2019novel-coronavirus-covid-19-infections. Accessed May 17, 2020
- CDC (USA). Evaluation and Management Considerations for Neonates At Risk for COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/hcp/caring-for-newborns.html. Accessed June 14, 2020.
- World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID19. Scientific Brief. 15 May 2020, https://www.who.int/news-room/commentaries/detail/multisysteminflammatory-syndrome-in-children-and-adolescents-with-covid-19 Accessed May 17, 2020
- RCPCH Guidance - Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporallyassociated-covid-19 Accessed May 17.2020
- Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. www.thelancet.com Published online May 13, 2020 https://doi.org/10.1016/S0140-6736(20)31103-X
- HFSA/ACC/AHA. Using RAAS Antagonists in COVID-19. 2020. https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addressesconcerns-re-using-raas-antagonists-in-covid-19. Accessed March 30, 2020
- Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) March 20, 2020
- The RECOVERY collaborative group. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021; 384:693-704 DOI: 10.1056/NEJMoa2021436
- Tomazini et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19The CoDEX Randomized Clinical Trial. JAMA. 2020;324(13):1307-1316. doi:10.1001/jama.2020.17021
- European Commission Guidance on the collection and transfusion of convalescent COVID-19 plasma. Available at: https://ec.europa.eu/health/blood_tissues_organs/covid-19_en
- The Recovery Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet. 2021 May 14;S0140-6736(21)00897-7 DOI: https://doi.org/10.1016/S0140-6736(21)00897-7
- Li et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19 - A Randomized Clinical Trial. JAMA. June 3, 2020. doi:10.1001/jama.2020.10044
- Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Gallagher J, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society

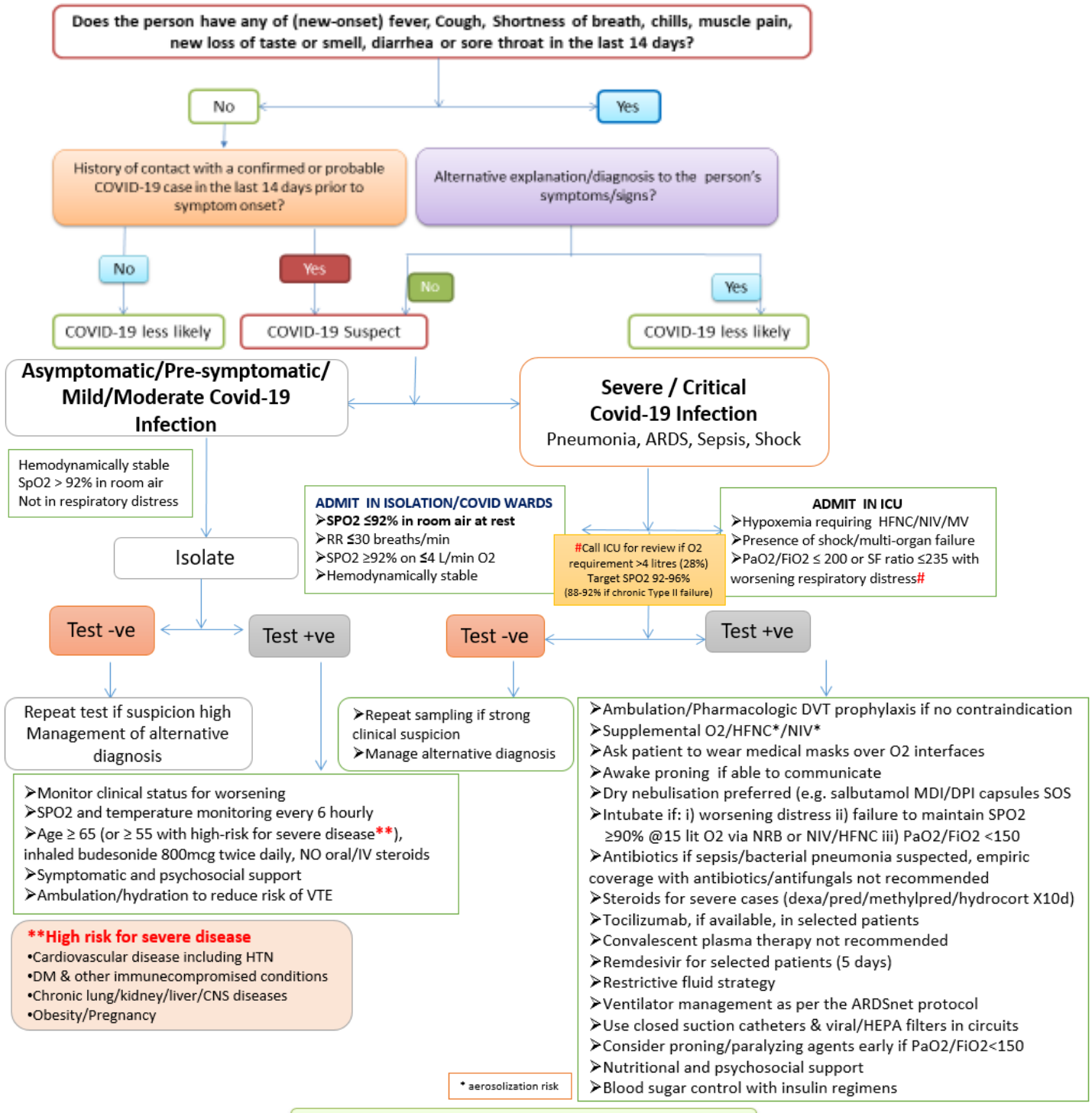
of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 4.2.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed May 10, 2021

- The RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.
- medRxiv preprint doi: https://doi.org/10.1101/2021.03.09.21252736
- Libster et al. Early High-Titer Plasma Therapy to Prevent Severe COVID-19 in Older Adults. N Engl J Med. 2021 Feb 18;384(7):610-618. doi: 10.1056/NEJMoa2033700.
- The RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0.
- The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med 2021; 384:1491-1502 DOI: 10.1056/NEJMoa2100433
- Tang et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020; 369 doi: https://doi.org/10.1136/bmj.m1849
- Boulware et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med. June 3 2020. DOI: 10.1056/NEJMoa2016638
- Rosenberg et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA. Published online May 11, 2020. doi:10.1001/jama.2020.8630.
- Grein et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19 [published online ahead of print, 2020 Apr 10]. N Engl J Med. 2020.
- Beigel JH et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. N Engl J Med. Oct 2020. DOI: 10.1056/NEJMoa2007764
- Spinner CD et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA. Sep 2020. DOI: 10.1001/jama.2020.16349.
- WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19; interim WHO SOLIDARITY trial results. Oct 2020 Preprint available at doi: https://doi.org/10.1101/2020.10.15.20209817.
- Goldman et al. Remdesivir for 5 or 10 Days in Patients with Severe COVID-19. N Engl J Med. May 27, 2020. DOI: 10.1056/NEJMoa2015301
- Kai Duan, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences Apr 2020, 117 (17) 9490-9496.
- Shen C, et al. Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma [published online ahead of print, 2020 Mar 27]. JAMA. 2020;323(16):1582-1589.
- Hung IF, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020 May 8. pii: S0140-6736(20)31042-4.
- Chen et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. BMJ. doi: https://doi.org/10.1101/2020.03.17.20037432
- Udwadia et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. Int J Infect Dis. 2021 Feb;103:62-71. doi: 10.1016/j.ijid.2020.11.142. Epub 2020 Nov 16.
- Solaymani—Dodaran et al. Safety and efficacy of Favipiravir in moderate to severe SARS-CoV-2 pneumonia. Int Immunopharmacol. 2021;95:107522. Epub 2021 Mar 11.
- Managing the Respiratory Care of Patients with COVID-19. Italian Thoracic Society. 2020
- Interim Guidance for Infection Prevention and Control When COVID-19 Is Suspected. Nepal Medical Council COVID-19 Treatment Guidance Committee. June 2020.

- Allotey J et al for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320. Epub 2020 Sep 1.
- Zambrano LD et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. MMWR Morb Mortal Weekly Rep. 2020;69(44):1641. Epub 2020 Nov 6.
- CDC (USA). Mental Health and Coping During COVID-19. 2020.
- Inter-Agency Standing Committee's Mental Health and Psychosocial Support Reference Group. Basic Psychosocial Skills: A Guide for COVID-19 Responders. https://interagencystandingcommittee.org/system/files/2020-05/Basic%20Psychosocial%20Skills-%20A%20Guide%20for%20COVID-19%20Responders.pdf
- CDC (USA). Coronavirus Disease 2019 (COVID-19): 2020 Interim Case Definition, Approved April 5, 2020 https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/
- CDC Coronavirus Disease - Healthcare Workers: Pandemic Planning Scenarios. Updated- July 10, 2020.
- CDC Coronavirus Disease- Laboratories: Using Antigen Tests. Updated Sept. 4, 2020.
- Huang D, et al. Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis [published online ahead of print, 2020 Jul 3]. J Med Virol. 2020.
- Joyner et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three Month Experience. MedRxiv, August 2020.
- Joyner et al. Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clin Proc. 2020 Sep;95(9):1888-1897.
- WHO Draft landscape and tracker of COVID-19 candidate vaccines, (updated: 7 May 2021); available at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines
- Voysey et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomized trials. Lancet. Feb 2021. DOI: https://doi.org/10.1016/S0140-6736(21)00432-3
- Voysey et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. Dec 2020. DOI:https://doi.org/10.1016/S0140-6736(20)32661-1
- WHO. Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience). April 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1
- AstraZeneca Press Release. AZD1222 US Phase III primary analysis confirms safety and efficacy. March 2021. https://www.astrazeneca.com/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html
- Public Health England. Press Release. Vaccines highly effective against B.1.617.2 variant after 2 doses. May 22, 2021. https://www.gov.uk/government/news/vaccines-highly-effective-against-b-1-617-2-variant-after-2-doses
- WHO. Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm. May 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-COVID-19-vaccine-BIBP
- Logunov et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet. February 2021. DOI:https://doi.org/10.1016/S0140-6736(21)00234-8
- Ella et al. Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine, BBV152 (a phase 2, double-blind, randomised controlled trial) and the persistence of immune responses from a phase 1 follow-up report. Lancet Inf Dis. March 2021. DOI:https://doi.org/10.1016/S1473-3099(21)00070-0
- Thiagarajan K. What do we know about India's Covaxin vaccine? BMJ. 2021 Apr 20;373:n997. doi: 10.1136/bmj.n997.

- WHO. Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac. May 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Sinovac-Coronavac
- Allotey et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m3320
- https://www.who.int/news-room/feature-stories/detail/the-sinovac-covid-19-vaccine-what-you-need-to-know?fbclid=IwAR2M8ZxQyMH3yGJ3UIZjHbGI7rze0fmW_RRdIwR1JC-K5vBCxkXqfAfSYmI
- WHO. Getting the COVID-19 vaccine. https://www.who.int/news-room/feature-stories/detail/getting-the-covid-19-vaccine

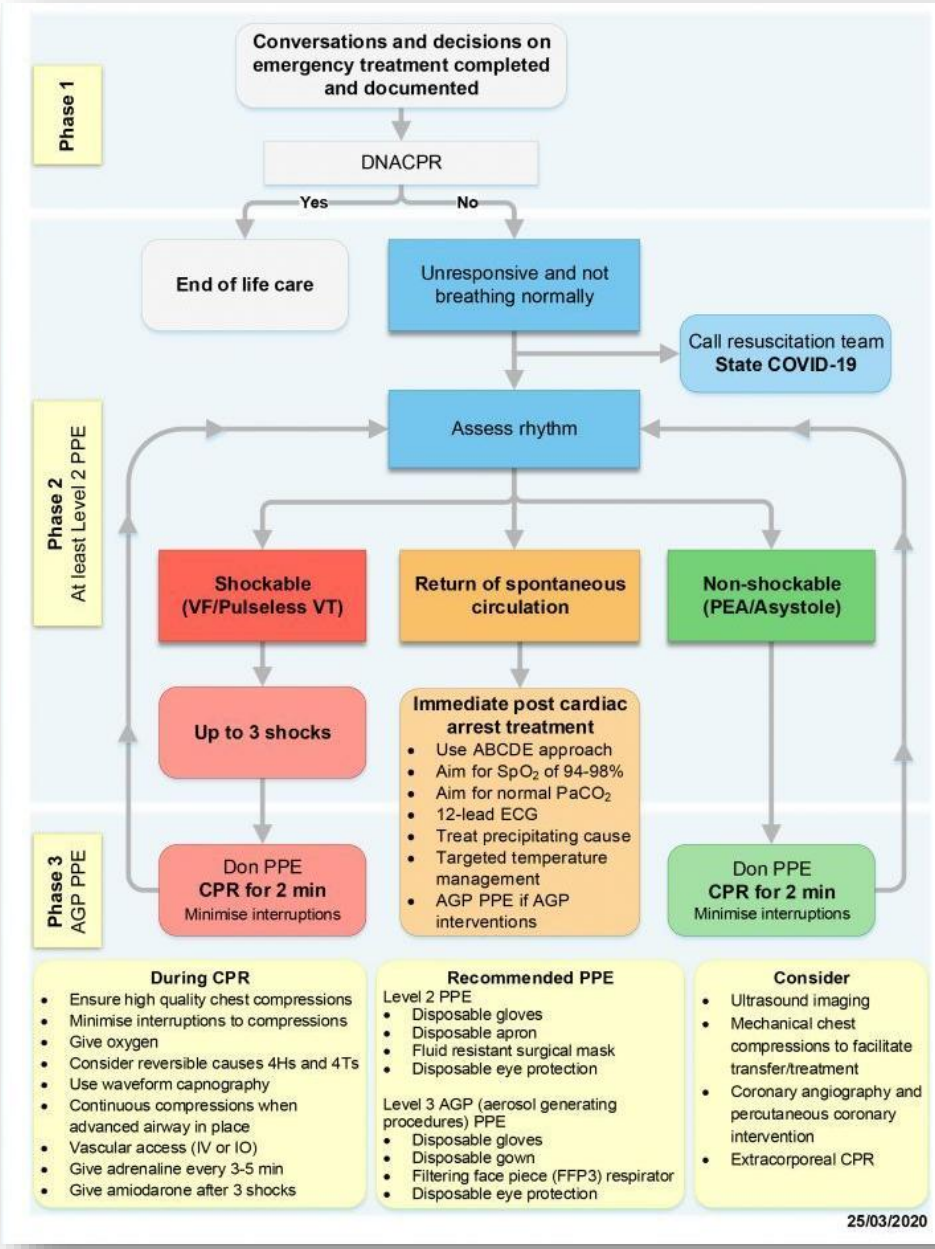
XI. APPENDIX 1(a): Patient triage and management flow chart



Appendix 1(b): Treatment Recommendations Summary According to the Stage of COVID Illness

Mild to moderate COVID-19 with no requirement for supplemental oxygen
Supportive care only No hospital admission In those aged over 50 with risk factors for severe disease, OR those aged over 65 years, may consider inhaled Budesonide 800 micrograms twice a day. Systemic corticosteroids should NOT be used. Empiric antibiotics should NOT be used. Pharmacologic DVT prophylaxis not recommended, unless the patient is hospitalized *Remdesivir may be **considered** if there are significant risk factors for developing severe illness, or rapidly progressing radiographic findings, and/or dropping oxygen saturation, albeit above 92%.*
Severe COVID-19
Dexamethasone 6 mg/day (or Prednisolone 40mg once a day, or Methylprednisolone 32mg in 1-4 divided doses per day, or Hydrocortisone 160-200 mg in 3-4 divided doses per day) for up to 10 days or until discharge from hospital, whichever comes first Remdesivir* 200 mg x 1, then 100 mg for 5 days or until discharge from hospital, whichever comes earlier in those not needing high flow oxygen therapy, non-invasive or mechanical ventilation within 10 days from onset of symptoms Consider Tocilizumab in single dose 8 mg/kg if rapidly increasing O2 need and systemic inflammation in spite of systemic corticosteroids. Also consider prophylactic treatment with Ivermectin (200 micrograms/kg/day for 2 days for such patients. Pharmacologic DVT prophylaxis recommended if no contraindications Awake prone positioning Convalescent plasma therapy NOT recommended. Empiric coverage with antibacterials or antifungals NOT recommended.
Critical COVID-19
Dexamethasone 6 mg/day (or Prednisolone 40mg once a day, or Methylprednisolone 32mg once a day, or Hydrocortisone 160 - 200 mg in divided doses per day) for up to 10 days or until discharge from hospital, whichever comes first Consider Tocilizumab in single dose 8 mg/kg if rapidly increasing O2 need and systemic inflammation in spite of systemic corticosteroids. Also consider prophylactic treatment with Ivermectin (200 micrograms/kg/day for 2 days) for such patients. Pharmacologic DVT prophylaxis recommended if no contraindications *Remdesivir may be **considered** in those needing oxygen through high flow devices, or noninvasive or invasive ventilation on a case by case basis.* Empiric coverage with antibacterials or antifungals NOT recommended. Convalescent plasma therapy NOT recommended.

APPENDIX 2: Advanced Cardiovascular Life Support Flowchart in Healthcare Settings (Source: Resuscitation Council, UK)



Key Points

Ensure all members of the resuscitatio team have full personal protective equipment protection (PPE) for aerosol generating procedure before starting BLS and ACLS.

Do not do mouth-to-mouth ventilation or use a pocket mask. Place face mask, preferably non-rebreathing mask, with oxygen on the patient's face during chest compressions to limit aerosol spread during compressions.

Avoid bag and mask ventilation prior to intubation. Use "viral" filter while bagging after intubation.

Airway interventions (e.g. supraglottic airway insertion or tracheal intubation) must be carried out by experienced medical personnel to minimise delay

APPENDIX 3: FiO2 estimation

Method	O_2 flow (l/min)	Estimated FiO2 (%)
Nasal cannula	1	24
	2	28
	3	32
	4	36
	5	40
	6	44
Face mask (non Venturi mask)	5	40
	6-7	50
	7-8	60
Face mask with reservoir	6	60
	7	70
	8	80
	9	90
	10	95
Venturi mask (color code)		
Blue	2	24
White	4	28
Orange	6	31
Yellow	8	35
Red	10	40
Green	15	60

APPENDIX 4: "Dry nebulization" protocol metered-dose inhaler (MDI) with spacer/valvedholding chamber (VHC) (Adapted from the protocol of National University Hospital, Singapore)

"Dry nebulization" protocol using metered-dose inhaler (MDI) with spacer/ valved-holding chamber (VHC)

- Jet nebulization is associated with aerosol generation and can facilitate the transmission of viruses e.g. SARS and possibly 2019-nCoV.
- To reduce the risk of disease transmission, we recommend the use of "dry nebulization" in the treatment of acute airflow obstruction.
- This is clinically equivalent to nebulization therapy in patients with moderate to severe airflow obstruction.

Instructions

1. Selection of spacer or VHC

Choose one with a mouthpiece of facemask depending on your patient's ability to maintain effective seal (e.g. children, elderly with cognition, acute breathless patients)
Prime the new spacer by firing ~ 10 puffs of Salbutamol to reduce the static build-up inside (check product information sheet).

2. Preparation

Remove the cap of MDI
Shake the inhaler 5-10 times
Insert into back of spacer or VHC.

3. Ensure an effective seal

Face mask: Place mask over the mouth and nose and ensure minimal gaps
Mouthpiece: Put mouthpiece in mouth between teeth and close lips around it.

4. Slow breathing

Instruct the patient to breathe in and out slowly.
Tell patient to slow down breathing if the spacer/VHC whistles.

5. Administer 1 puff at a time (to reduce clumping of particles)

Press the canister once at the beginning of a slow inhalation.
Instruct patient to take in 5 slow breaths ("Breathe in and out slowly, 5 times")

6. Breath-hold for 5 to 10 seconds *(optional)*

Instruct patient to hold breath for 5 to 10 seconds, if he/ she is able to cooperate.
This allows the medication time to deposit in the airways.
Resume normal breathing

7. Repeat steps 2-6 when more than 1 puff is prescribed.
Initial treatment: repeat order every 10-20 min for 1st hour
Subsequent treatment: Reduce frequency to every 4-8 hourly-prn
Reduce/ stop ipratropium after initial 24 hours*

8. Escalate in event of poor response:

Severe features	Life-threatening features
- Talks in words only, agitated - Respiratory rate > 30/ min - Pulse rate > 120/min - SpO2 < 90% (room air)	- Drowsy, confused - Silent chest on auscultation

Medication prescription for "dry nebulization"

Salbutamol (100mcg) 4 puffs
Ipratropium (20mcg)* 4 puff (if available, if not available then use salbutamol only)

Every 10-20 minute for 1st hour
Every 4-8 hours-prn, subsequently

**Ipratropium is administered in combination with short-acting beta-agonist (SABA), if there is poor response to initial SABA nebulization, during acute moderate to severe exacerbations. Though the 2007 NAEPP guidelines suggest that Ipratropium can be dosed up to maximum of 8 puffs every 20 minutes for the first 3 hours in an emergency setting. This is an off-label recommendation. Both GINA 2019 and SIGN 2019 do not explicitly state the recommended dose in an acute setting. As the recommended maximal total daily dose of Ipratropium is 204 mcg, we recommend stopping/ reducing the dose after the initial 1-3 hours.*

For patients with preexisting airway disease like asthma/COPD, regular long acting inhalers can be continued using MDI with spacer.
If patient is unable to use or has poor response to dry nebulization, switching to conventional nebulization may be needed. Airborne precaution must be applied and patient should preferably be in isolation room.
Use mesh nebulizer rather than jet nebulizer for mechanically ventilated patients where available. Since disconnecting the ventilator circuit and nebulization generates aerosols, Healthcare workers must use airborne precaution and use appropriate PPE while caring for such patients with COVID19

APPENDIX 5: Instructions for "Awake Proning" (Adapted from: Self-positioning guide, Elmhurst Hospital Center, New York City, USA)

Instruction for patients with cough or trouble breathing

अक्सिजनको कमी देखिएका कोभिड बिरामीलाई अधोमुख (घोप्टो) आसनको उपचार विधि:

Please try to not spend a lot of time lying flat on your back! Laying on your stomach and in different positions will help your body to get air into all areas of your lung

कृपया उत्तानो परेर सकेसम्म कम समय सुत्नु होला। घोप्टो पर्दा वा दाहिने वा देब्रे कोल्टो फेर्दा फोक्सोको सबै भागमा हावा पुग्न सजिलो हुन्छ।

Your healthcare team recommends trying to change your position every 30 minutes to 2 hours and even sitting up is better than laying on your back. If you are able, to please try this

कृपया हरेक ३० मिनेट देखि २ घन्टापछि आफ्नो आसन फेर्ने प्रयास गर्नुहोला। उत्तानो सुत्नु भन्दा बरू ठाडो बस्नु फाइदाजनक हुन्छ। कृपया सकेसम्म तल सिकाइएअनुसार गर्ने कोशिश गर्नुहोला।

1. **30 minutes-2 hours: lying on your belly**
१. **३० मिनेट देखि २ घन्टा: घोप्टो परेर सुत्ने वा घोप्टो परेर कुइनो, घुँडा र टाउकोले टेकेर बस्ने**
2. **30 minutes-2 hours: lying on your right side**
२. **३० मिनेट देखि २ घन्टा: दाहिने कोल्टो फर्केर सुत्ने**
3. **30 minutes-2 hours: sitting up**
३. **३० मिनेट देखि २ घन्टा: ठाडो बस्ने**
4. **30 minutes-2 hours: lying on your left side, then back to position #1**
४. **३० मिनेट देखि २ घन्टा: देब्रे कोल्टो फर्केर सुत्ने अनि फेरि शुरुको (घोप्टो) आसनमा फर्कने**

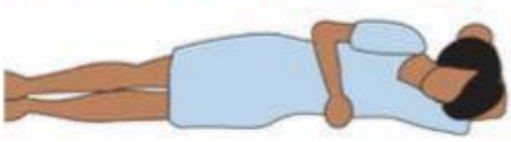
Note: As long as tolerated, you may lay on your belly and you don't need to switch to lying on your side or to sit up.

याद गर्नुहोस्: सकेसम्म लामो समय घोप्टो परेर सुत्ने कोसिस

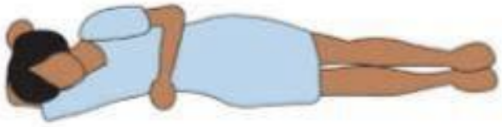
PHOTOS BELOW TO DEMONSTRATE THIS

1. **30 minutes-2 hours: lying on your belly**
१. **३० मिनेट देखि २ घन्टा: घोप्टो परेर सुत्ने वा घोप्टो परेर कुइनो, घुँडा र टाउकोले टेकेर बस्ने**

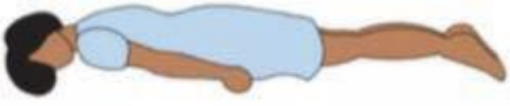
4. **30 minutes-2 hours: lying on your left side**
४. **३० मिनेट देखि २ घन्टा: देब्रे कोल्टो फर्कने**



2. **30 minutes-2 hours: lying on your right side**
२. **३० मिनेट देखि २ घन्टा: दाहिने कोल्टो फर्कने**



Then back to position #1. Lying on your belly
अनि फेरि शुरुको (घोप्टो) आसनमा फर्कने



3. **30 minutes-2 hours: sitting up**
३. **३० मिनेट देखि २ घन्टा: ठाडो बस्ने**

Self Positioning Guide. Elmhurst Hopsital_SB
आफैं आसन बदल्ने निर्देशिका (एल्महर्स्ट अस्पताल, अमेरिका)

APPENDIX 6: Critical care management including ventilator adjustment (Adapted from Brigham and Women's Hospital COVID-19 Critical Care Clinical Guidelines)

Ventilator adjustment and daily management

Changing ventilation parameters

1. Follow ARDSnet ventilation recommendations where possible:
   Tidal volumes should be 4-6 cc/kg using IBW to minimize volumes (and thus ventilator-associated injury).
2. Minute ventilation (respiratory rate x tidal volume) typically drives pH and PCO2: Titrate ventilator parameters to pH, not PCO2.

- To achieve low tidal volumes, tolerate hypercapnia (functionally no limitation unless clinical sequelae) and acidemia (pH > 7.2).
- Because tidal volumes are low, the respiratory rate often has to be high to accommodate; typical RR is 20-35 breaths/minute.

3. pH goal is normally 7.25-7.45:

- If pH > 7.45, decrease respiratory rate
- If pH 7.15-7.30, then increase respiratory rate until pH > 7.30, or PaCO2 < 25 (maximum RR= 35 breaths/minute)
- If pH < 7.15, then increase respiratory rate to 35 breaths/minute. If pH still < 7.15, then perform the following:
  a. Tidal volume may be increased by 1 mL/kg until pH > 7.15 (until plateau pressure reaches 30 cm H2O or tidal volume reaches 8 ml/kg)
  b. Deep sedation advancing to RASS -5 if needed
  c. If no improvement, initiate continuous paralysis
  d. If still no improvement, initiate prone ventilation (may improve V/Q matching and better ventilation)

Changing oxygenation parameters

1. Minimize oxygen toxicity: PEEP and Fi02 drive oxygenation
   - The goal is to deliver a partial pressure of oxygen to perfuse tissues (PaO2 > 75, Sp02 >92%) while limiting lung injury from high distending pressures (Ppl< 30) and hyperoxia (FiO2 < 75, SpO2 < 96%)
   - Lower limit goals for PaO2 / SpO2 are widely debated; PaO2 > 55 and SpO2 >88% are also commonly used.
2. Optimize PEEP:
   - Initial PEEP should be set as explained in the PEEP table below.
3. Adjust Fi02:
   - Adjust Fi02 after optimizing PEEP.
   - Goal FiO2 < 75%; if FiO2 > 75%; patient requires ventilator optimization.
   - It is reasonable to put a desaturating patient temporarily on 100% Fi02, but remember to wean oxygen as rapidly as possible
4. Check plateau pressure:
   - Check plateau pressure with every change in tidal volume, PEEP, or clinical deterioration (worsening oxygenation) but not as part of routine practice
   - If plateau pressure is > 30 cm H20, then decrease tidal volume by 1 ml/kg (minimum 4 mL/kg).
   - If plateau pressure is < 25 H20 and tidal volume < 6 mL/kg, then increase tidal volume by 1 mL/kg until plateau pressure is > 25 cm H2O or tidal volume = 6 mL/kg.
   - If plateau pressure is < 30 cm H20 and patient is breath stacking or dyssynchronous, then increase tidal volume in mL/kg increments to 7 mL/kg or 8 mL/kg so long as plateau pressure is < 30 cm H20.

Refractory hypoxemia pathway

If patient is hypoxic (Pa02 <55) on Vt = 6 ml/kg, ideal PEEP and Fi02 >75%, perform the following in this order:

1. Optimize volume status by diuresis or RRT if possible.

If no improvement, then:

2. Deep sedation, advancing to RASS -5 if needed.

If no improvement, then:

3. Initiate continuous paralysis using available paralyzing agents, titrated to patient-ventilator synchrony).

If no improvement then:

4. Initiate prone ventilation (see below); high consideration for use early in severe ARDS (<36 hours from ARDS onset, start discussion of proning when P:F< 150, prone within 12 hours of FiO2 > 75%)

If no improvement then:

5. Consider ECMO if available

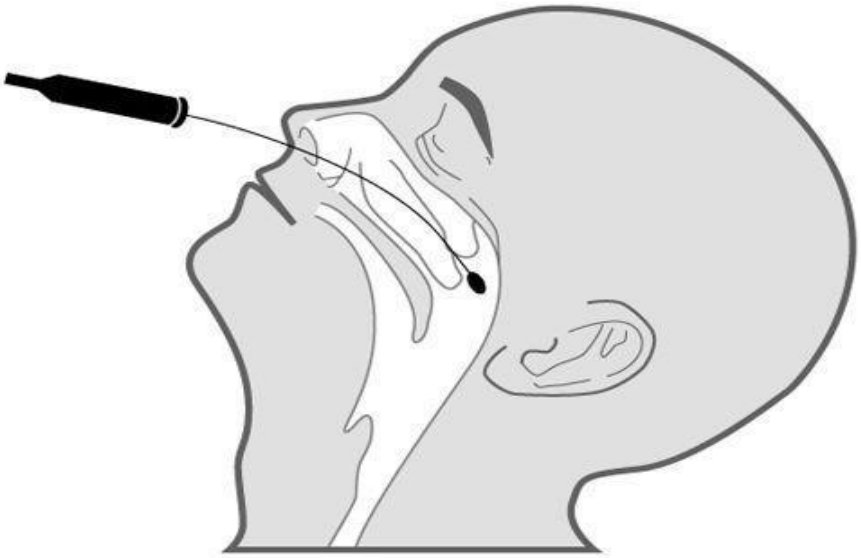
Titrate FiO2 and PEEP for oxygenation for BMI<35 as per the ARDSnet LOW PEEP table

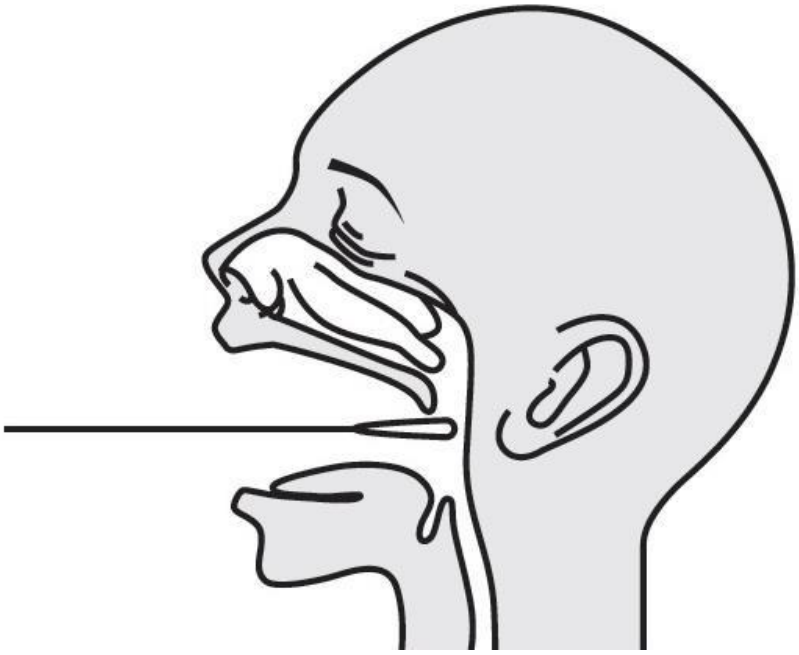
FiO2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Titrate FiO2 and PEEP for oxygenation for BMI>35 as per the ARDSnet HIGH PEEP table

FiO2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5-0.8	0.8	0.9	1.0	1.0
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22	24

APPENDIX 7: Nasopharyngeal and oropharyngeal swab specimen collection





Source for images: www.stanfordlab.comand another online source that could not be verified on the internet

APPENDIX 8a: COVID-19 in paediatric population

With the rapid rise of SARS-CoV-2 infections in Nepal and children being particularly vulnerable to the newer variants, this guideline aims to help providers triage and manage pediatric patients. Similarly, it isnecessary to distinguish between acute COVID-19 and MIS-C since the management of the 2 are different and both may be currently prevalent in Nepal.

COVID-19 prevention strategies, including mask (surgical, N95), gown, gloves, eye protection, and physical distancing need to be practiced at all times when examining any child with suspected and/orconfirmed COVID-19.

Management is based on 4 categories according to severity of illness:

1. **Mild:** Mild respiratory or other symptoms not requiring hospital admission; and withoutsupplemental oxygen requirement
2. **Moderate**: Respiratory (increased work of breathing) or other symptoms requiring hospitaladmission; but without supplemental oxygen requirement
3. **Severe**: Requiring supplemental oxygen (Oxygen saturation < 94%, or below patient baseline inthe presence of chronic lung disease)
4. **Critical**: New or increased requirement for invasive or noninvasive mechanical ventilation, sepsis, multiorgan failure, or rapidly worsening clinical trajectory that does not yet meet thesecriteria

Distinguishing Acute COVID-19 from MIS-C

Acute COVID-19 and MIS-C have overlapping features. Some differentiating factors:

ACUTE COVID-19	MIS-C
COVID exposure within 2 weeks	2-6 weeks after infection or exposure
May be negative for COVID antibodies	More likely positive for COVID antibody
More likely to be positive for COVID PCR	May be negative for COVID PCR
Upper and/or Lower respiratory symptoms more common	Oral mucosal changes
Acute loss of taste and/or smell	Swollen hands/feet
	Erythema palms/soles
	Extremely elevated ferritin (>10K)
	Coronary artery aneurysm
	Elevated BNP/ Cardiac dysfunction

COVID PCR positive or H/O exposure

SYMPTOMATIC: No symptoms ascribed to COVID

MILD: Mild runny nose/cough or other symptoms not requiring hospital admission; and without supplemental oxygen requirement

→ Specific COVID treatment not recommended

Monitor and follow-up

MODERATE: Respiratory (Increased work of breathing) or other symptoms requiring hospital admission; but without supplemental oxygen requirement

→ Supportive care for all patients:

- Close monitoring
- **Do NOT administer** dexamethasone or remdesivir
- Provide nutrition and encourage ambulation
- **AVOID overhydration**
  - NO fluid boluses
  - IV fluids only if not drinking and/or voiding well
- Paracetamol, antihistamine, dry albuterol inhaler with spacer as needed
- **Avoid antibiotics**
- Recommended Labs: CBC with differential, CMP, CRP OR ESR

SEVERE: Requiring supplemental oxygen (Oxygen saturation < 94%, or below patient's baseline in the presence of chronic lung disease)

→ Supportive care for all patients

- Close monitoring
- **AVOID overhydration**
  - NO fluid boluses if voiding well
- Paracetamol, antihistamine, albuterol inhaler (with spacer) as needed
- **Dexamethasone** 0.15 mg/kg/dose (max 6 mg/dose) IV/PO once daily x 10 days. Alternately IV/PO once daily: prednisolone 0.8 mg /kg (max 32 mg/d) or prednisone 1 mg/kg (max 40m mg/d) may be administered.
  - Consider risks vs. benefits of steroids in relationship to underlying conditions (e.g. prior immunosuppression, metabolic disease, etc.) especially in patients with less severe respiratory illness
  - Therapy can be discontinued if patient is well enough to be discharged
- **Consider Remdesivir** (**see below for dosing**) illness duration <10 days only
- **DVT prophylaxis** for >12 years old, <12 years if risk factors (**see below**)
- **Avoid antibiotics** if bacterial pneumonia not strongly suspected
- **Recommended labs**: CBC with differential, CMP (LFT, RFT), CRP or ESR
  - Tier 2 labs to consider: BNP, Troponin, D-dimer, Ferritin, Fibrinogen, INR/PT/PTT, Blood Culture if indicated
- **Oxygen** by NC or venturi mask- HHFNC may be required (1-2L /kg)
- Awake proning if tolerated by patient.
- **Encourage ambulation** at least 3 times a day

CRITICAL: New or increased requirement for invasive or noninvasive mechanical ventilation, sepsis, multiorgan failure, or rapidly worsening clinical trajectory that does not yet meet these criteria

Supportive care for all patients

- Close monitoring
- **Dexamethasone** 0.15 mg/kg/dose (max 6 mg/dose) IV/PO once daily for 10 days. Alternately IV/PO once daily prednisolone 0.8 mg /kg (max 32 mg/d) or prednisone 1 mg/kg (max 40m mg/d) may be administered.
    - Consider risks vs. benefits of steroids in relationship to underlying conditions (e.g. prior immunosuppression, metabolic disease, etc.) especially in patients with less severe respiratory illness
    - Therapy can be discontinued of patient is well enough to be discharged.
- Remdesivir **not recommended** but may consider in illness duration <10 days (**see below for dosing**)
- **DVT prophylaxis** for all >12 years old, and <12 years if risk factors present **(see below)**
    - Consider early initiation of therapeutic heparin/enoxaparin in critically ill children with risk factors or patient with S/S of sudden thromboembolic events
- **AVOID Overhydration**
    - 5-10ml/kg bolus ONLY if not voiding or in septic shock
- **Avoid antibiotics** if bacterial pneumonia is not strongly suspected
    - If needed, ceftriaxone 50 mg/kg/d IV (max 2000mg) daily and azithromycin 10 mg/kg PO x 1 dose (max 500mg) on Day 1, followed by 5 mg/kg PO (max 250 mg) x 4 more days.
- **Respiratory support**
    - HFNC 1-2L/kg
    - NIV: RAM cannula if available,
    - NIV: BIPAP if solitary/negative pressure room, complete PPE for providers.
    - Awake proning
    - Intubation and invasive ventilation only for refractory hypoxemia despite aforementioned measures.
        - Most experienced provider should perform intubation.
        - Lung protective ventilation: TV 4-8ml/kg, Plateaupressure <30cm H20, higher PEEP
        - Prone for 12-24 hours alternate with supine position.
- **Recommended labs:** CBC with differential, CMP (electrolytes, LFT,RFT), CRP or ESR
- Tier 2 labs to consider: BNP, Troponin, D-dimer, Ferritin, Fibrinogen, INR/PT/PTT, Blood Culture if indicated

Remdesivir Therapy:

1. Treat with Remdesivir **only if all criteria** are fulfilled:
    a. COVID -19 RT-PCR or antigen test positive
    b. Hospitalized
    c. Illness duration ≤ 10 days
    d. O2 saturation ≤ 94% or requiring supplemental O2
    e. **NOTE:** Remdesivir should be prioritized for patients who require supplemental O2 but who are NOT on HFNC, noninvasive or invasive ventilation.
2. Dose:
    a. Weight > 40 kg: 200 mg IV x 1, then 100 mg daily
    b. Weight < 40 kg: 5 mg/kg/dose (max 200 mg) IV x1, then 2.5 mg/kg/dose (max 100 mg)IV daily
3. Duration: 5 days or until discharge whichever comes sooner.
4. **NOTE:** As per FDA (USA) guidelines**- for children <40 Kg weight or <12 years old**:
    a. **Not approved**- use only under Expanded Use Authorization
    b. **Must** use lyophilized powder NOT liquid which contains higher amount of cyclodextrin(SBECD) https://www.fda.gov/media/137566/download
5. Monitor daily LFT, RFP- Discontinue if increased ALT >10 x upper limit of normal and/or GFR <30.

Anticoagulation (DVT prophylaxis):

1. All severe and critical hospitalized children > 12 years.
2. Use in High risk and <12 years old, if:
    a. Mechanical ventilation, sedation/ms relaxant use
    b. Obesity (>95 percentile)
    c. D-dimer 2.5 mcg/ml
    d. History of thrombosis or acquired or inherited thrombophilia
    e. First degree family history of unprovoked VTE
    f. Active malignancy, nephrotic syndrome, flare of underlying inflammatory disease
    g. Any cardiac disease or rhythm abnormalities (consult cardiology)
3. Dose:
    a. Enoxaparin 0.5 mg/kg/dose SubQ q12h (max 30 q12h)
    b. May administer UFH in unstable patients 10-15 units/kg/hour IV
4. Contraindications: Platelet count <25,000 or actively bleeding
5. Relative contraindications: Platelet count <50,000; Fibrinogen <100 mg/dL; patient is receiving Aspirin >5mg/kg/d; Underlying bleeding disorder.
6. Discontinue at discharge or earlier if patient clinical status improves and risk factors resolved.

References:

1. NIH. COVID treatment guidelines. Children. https://www.covid19treatmentguidelines.nih.gov/special-populations/children/
2. NIH. Care of critically ill. https://www.covid19treatmentguidelines.nih.gov/critical-care/
3. IDSA guidelines on the treatment and management of patients with COVID-19. Updated 4/14/21.

APPENDIX 8b: Multisystem inflammatory syndrome in children (MIS-C)

DEFINITION

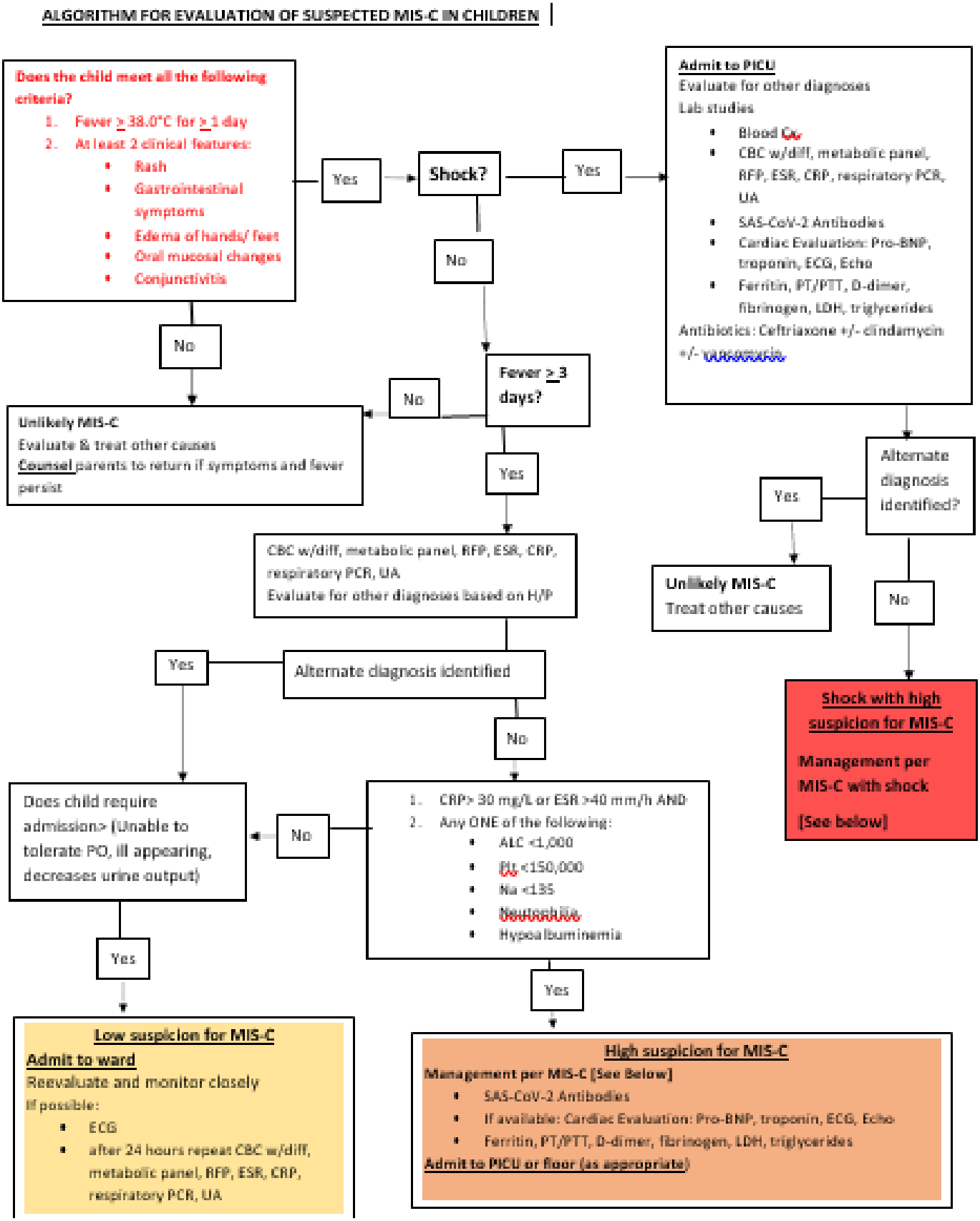
CDC Case Definition: https://www.cdc.gov/mis-c/cases/index.html
• An individual aged <21 years presenting with **fever**[i], laboratory evidence of **inflammation**[ii], and evidence of clinically severe illness requiring hospitalization, with **multisystem (≥2) organ involvement** (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND • **No alternative plausible diagnoses**; AND • **Positive for current or recent SARS-CoV-2 infection** by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms [i]Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours [ii]Including, but not limited to, one or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, elevated neutrophils, reduced lymphocytes, and low albumin

GENERAL PRINCIPLES FOR EVALUATION AND MANAGEMENT:

1. MIS-C is still rare. **Always consider other diagnoses such as:**
    a. Bacterial sepsis,
    b. Toxic shock syndrome,
    c. Staphylococcus Scalded Skin Syndrome,
    d. Kawasaki Disease,
    e. Myocarditis,
    f. Serum Sickness,
    g. Viral Infections (EBV, CMV, adenovirus, enterovirus)
    h. Scrub typhus,
    i. Dengue.

2. **Majority may require PICU admission,** especially those with cardiac manifestations.

3. **The following algorithm will assist in triaging MIS-C**
    a. **Low suspicion for MIS-C, no evidence of shock**
    b. **High suspicion of MIS-C without shock**
    c. **Shock with high suspicion of MIS-C**


ALGORITHM FOR EVALUATION OF SUSPECTED MIS-C IN CHILDREN
Does the child meet all the following criteria?
1. Fever ≥ 38.0°C for ≥ 1 day
2. At least 2 clinical features:
Rash
Gastrointestinal symptoms
Edema of hands/ feet
Oral mucosal changes
Conjunctivitis
Yes
Shock?
Yes
Admit to PICU
Evaluate for other diagnoses
Lab studies
Blood Cx
CBC w/diff, metabolic panel, RFP, ESR, CRP, respiratory PCR, UA
SAS-CoV-2 Antibodies
Cardiac Evaluation: Pro-BNP, troponin, ECG, Echo
Ferritin, PT/PTT, D-dimer, fibrinogen, LDH, triglycerides
Antibiotics: Ceftriaxone +/- clindamycin +/- vancomycin
No
No
Fever ≥ 3 days?
No
Unlikely MIS-C
Evaluate & treat other causes
Counsel parents to return if symptoms and fever persist
Yes
CBC w/diff, metabolic panel, RFP, ESR, CRP, respiratory PCR, UA
Evaluate for other diagnoses based on H/P
Alternate diagnosis identified?
Yes
Unlikely MIS-C
Treat other causes
No
Shock with high suspicion for MIS-C
Management per MIS-C with shock
[See below]
Yes
Alternate diagnosis identified
No
1. CRP> 30 mg/L or ESR >40 mm/h AND
2. Any ONE of the following:
ALC <1,000
Plt <150,000
Na <135
Neutrophilia
Hypoalbuminemia
No
Does child require admission> (Unable to tolerate PO, ill appearing, decreases urine output)
Yes
Yes
Low suspicion for MIS-C
Admit to ward
Reevaluate and monitor closely
If possible:
ECG
after 24 hours repeat CBC w/diff, metabolic panel, RFP, ESR, CRP, respiratory PCR, UA
High suspicion for MIS-C
Management per MIS-C [See Below]
SAS-CoV-2 Antibodies
If available: Cardiac Evaluation: Pro-BNP, troponin, ECG, Echo
Ferritin, PT/PTT, D-dimer, fibrinogen, LDH, triglycerides
Admit to PICU or floor (as appropriate)

High suspicion for MIS-C

1. Consult Cardiology, Infectious Diseases, Haematology if available
2. Treat Shock according to shock protocol
3. Labs (if available) repeated every 48 hours: CBC w/diff, CRP, Ferritin, D-dimer, troponin, pro BNP

	MIS-C	MIS-C with shock
Intravenous immunoglobulin (IVIG)	IVIG 2 g/kg once Consider second dose of IVIG if febrile 24-36h after initial IVIG, especially for patients who meet criteria for Kawasaki disease (KD) or incomplete KD	
Steroids	Patients who do not respond to 1-2 doses of IVIG: Methylprednisolone 2 mg/kg/day IV dividedq12h Duration: 1-3 days Taper over 2-3 weeks	All: Methylprednisolone 2-4 mg/kg/day IV divided q12h Hypotension refractory to resuscitation: consider high dose methylprednisolone 10-30 mg/kg/day divided q12h Duration: 1-5 days Taper over 4-8 weeks
Aspirin	For patients meeting KD criteria or with coronary artery changes. Not routinely recommended for others. Dosing per AHA KD guideline: initial high dose aspirin 80-100 mg/kg/day divided q6h, max dose 1000mg q6h (max 4g/day). Transition to low dose aspirin (3-5 mg/kg/day, max 81 mg) once afebrile for 48h	
Anticoagulation	<12 years: early ambulation & SCDs if tolerated >12 years: Consider prophylactic enoxaparin for patients with 2 or more additional VTE risk factors and for patients with coronary artery aneurysms. Anti-Xa goal 0.1-0.3 units/mL	Prophylactic enoxaparin Anti-Xa goal 0.1-0.3 units/mL
Antibiotics	Not routinely indicated	Due to overlap with toxic and septic shock, empiric antibiotics recommended for 48h while blood cultures are pending: ceftriaxone +/- clindamycin (if signs of toxic shock) +/- vancomycin (history/concern for MRSA)
Antivirals	Remdesivir may be considered only for patients with positive PCR for SARS-CoV-2 according to COVID-19 protocol	

IVIG will lead to increase in ESR, which should not be repeated after administration of IVIG

Cardiac function and fluid status should be assessed in MIS-C patients before IVIG treatment is provided. Patients with depressed cardiac function may require close monitoring and diuretics with IVIG administration.
In some patients with cardiac dysfunction, IVIG may be given as in divided doses (1 gm/kg daily over 2 days).

VTE risk factors: obesity, presence of central venous catheter, chronic inflammatory illness, use of estrogen-containing contraception, personal history of VTE or thrombophilia trait, family history of VTE in 1st degree relative, altered mobility30 days prior to admission (major surgery, significant trauma)

Relative contraindications for VTE prophylaxis: platelet count <50k/dL, fibrinogen <100 mg/dL, elevated PT/aPTT, hepaticor renal failure, recent or ongoing bleeding, recent surgery

ISOLATION PRECAUTIONS

- Full COVID-19 precautions are recommended at the time of presentation for patients with suspected MIS-C.Duration of isolation precautions will be determined based on the patient's clinical course and SARS-CoV-2 testing results.

DISCHARGE AND OUTPATIENT FOLLOW UP

MIS-C

1. Discharge preparation and criteria:
    a. If more than 2 days since last echocardiogram, obtain echocardiogram prior to discharge
2. Minimum discharge criteria:
    a. 48 hours without fever, vasoactive medications, and supplemental oxygen
    b. Minimum of 48 hours downtrending CRP, ferritin, and d-dimer
    c. Troponin downtrending (if previously elevated)
    d. ECG without arrhythmia
    e. Latest echocardiogram improved/stable
    f. QT interval improved (if previously prolonged)

Follow-up:

1. All patients should follow up with primary care clinician 48-72 hours and 2 weeks after discharge.
2. All patients should follow up with cardiology 2 weeks and 6 weeks after discharge.
    a. 2 weeks follow up to include ECG, Echo, labs
3. Children should not participate in sports until evaluated by primary care clinician and cardiology.
    a. Children with concerns for myocarditis may be excluded from sports for 3-6 months.

MIS-C vs Kawasaki disease unrelated to SARS-C0V-2:

Both may share overlapping clinical features, including conjunctival injection, oropharyngeal findings (red and/or cracked lips, strawberry tongue), rash, swollen and/or erythematous hands and feet, and cervical lymphadenopathy.

	MIS-C	**KD unrelated to SARS-CoV-2**
Age	Older children and adolescents	Infants and young children
GI symptoms (abdominal pain)	Very common	Less prominent
Shock/ myocardial dysfunction	Common	Less common
COVID testing	Positive	Negative

Adapted from:

Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. Arthritis Rheumatol 2020; 72; 1791-1805. doi: https://onlinelibrary.wiley.com/doi/10.1002/art.41454.

Appendix 9: Frequently Asked Questions on Vaccines Against SARS-CoV-2

Q > WHO SHOULD BE VACCINATED?

All of the vaccines approved by Nepal's DDA have been approved for 18 years & older; priority has been given to older age, people with comorbidity & frontliners. (Please refer to vaccination guideline from MoHP).

As of now, no vaccine has been approved for children in Nepal.

Q> IS THE VACCINE SAFE FOR:

- Those older than 60 years of age? YES

These vaccines have been well studied among the adult population of a wide range.

There have been some public concerns, especially among the Chinese vaccines (Sinopharm & Sinovac) which don't have much data on populations above 60 years due to the small number of participants in clinical trials. Nevertheless, there is no difference in safety profile expected among older adults as compared to younger. So, WHO has recommended use of these vaccines even in people more than 60 years, while maintaining active safety monitoring.

- Pregnant women? YES > No

There is insufficient data on efficacy & vaccine-associated risks in pregnancy, while trials have been underway. Among the vaccines which are EUA approved by WHO, generally the recommendation has been to vaccinate in pregnant women only if the benefits outweigh the risks of vaccination. Also, WHO does not recommend pregnancy testing prior to vaccination. WHO does not recommend delaying pregnancy or terminating pregnancy because of vaccination.

Generally, pregnant females are at higher risk of developing severe COVID-19 infection compared to non-pregnant females. Pregnant women who are aged 35 years or older, or have high body mass index, or an existing comorbidity such as diabetes or hypertension, are at particular risk of serious outcomes from COVID-19.

To help pregnant females make informed decisions, they should be provided information about the risk of COVID-19 infection during pregnancy, the likely benefit of vaccination in context of current epidemiology & the relative lack of data on safety in pregnancy.

No official recommendation has been made for or against vaccination with Sputnik V & Covaxin among pregnant females by the WHO so far.

- Lactating mothers? YES

There is limited data of safety & efficacy of COVID19 vaccines among lactating females. However, it's a known fact that vaccinated females pass antibodies (IgA & IgG) to their babies. On this ground, WHO has recommended vaccination among lactating females if they fall within the priority list. WHO does not recommend discontinuing breastfeeding after vaccination.

Similar recommendations can be made for other vaccines awaiting WHO's EUA approval (Sputnik V & Covaxin).

- Persons with comorbidities or immunosuppression? YES

People with certain comorbidities (heart diseases, Diabetes, Hypertension) or immunosuppression (e.g. cancer patients, transplant patients) are at higher risk of severe COVID19 infection, so they should be given very high priority. The vaccines are safe among these people just like others. However, since the efficacy of the vaccine is also dependent on immunity of the individual, people with comorbidities or immunosuppression may get efficacy similar or slightly less than expected compared to the healthy adults of the same age group.

- People taking "blood thinners"? YES

People on blood thinners (like Aspirin, Clopidrogel, Warfarin, etc) have no contraindication to vaccination. Due to increased risk of bleeding, pressure should be applied at the injection site for approximately 5 minutes & it should be watched for excessive bleeding. The medications need not be held prior to the vaccination & can be continued without stopping after the vaccination.

Q > IF ONE CAN STILL GET INFECTED DESPITE VACCINATION, WHY SHOULD HE/SHE GET VACCINATED?

Based on studies so far, most COVID-19 vaccines are highly effective in preventing severe/critical COVID-19 infections & mortality. Also, fully vaccinated people are less likely to have asymptomatic infection or transmit SARS-CoV-2 virus to others. Hence, vaccination not only helps to prevent death, but also helps to break the chain.

To prevent possible disease transmission, it is recommended that strict preventive measures (using masks, maintaining 6 feet distance, etc.) be strictly followed by all people, regardless of vaccination status, during the pandemic.

Q > CAN A RECENTLY COVID-19 INFECTED PERSON GET VACCINATED? YES

Once infected, available data show that symptomatic reinfection is uncommon for the first 6 months. However, due to variants of concerns with evidence of immune escape circulating around the world, there is possibility of re-infection earlier than expected.

There is no optimum wait-time based on data. Generally, it is recommended that a person waits 2-4 weeks from symptom onset, until full recovery is attained, before getting vaccinated. WHO does not recommend checking for prior infection by any viral or serological method.

Q> HOW LONG TO WAIT FOR VACCINATION AMONG PEOPLE TREATED WITH CONVALESCENT PLASMA THERAPY OR MONOCLONAL ANTIBODY ?

There is no data regarding this scenario. However, WHO recommends waiting at least 90 days to avoid interference of the antibody treatment with vaccine-induced immune response.

Q> CAN ONE SWITCH TO A DIFFERENT VACCINE FOR THE SECOND DOSE ?

There is not enough data on safety & efficacy of switching between different vaccines. However, one can generally wait 2-4 weeks before switching to another vaccine for second dose.

Q > IN WHOM IS VACCINATION NOT RECOMMENDED ?

- people with history of severe allergy to vaccines
- people with fever or active COVID19 infection

Q> WILL THE VACCINES WORK AGAINST THE NEW VARIANTS IN NEPAL ?

As SARS-CoV-2 virus undergoes constant mutations, there is always a chance of new variants associated with higher transmissibility, worse severity or immune/vaccine escape. So, we need constant vigilance of disease epidemiology & need to follow evolving knowledge regarding vaccine efficacy against newer variants.

APPENDIX 10: Use of combination monoclonal antibody products in selected groups of COVID-19 patients in Nepal

Monoclonal antibodies against SARS-CoV-2 have been assessed in covid-19 patients in outpatient settings in randomized controlled clinical trials. Three combination monoclonal antibody products have been used in in different countries in select groups of non-hospitalized mild and moderate disease patients that are at high risk for progression to severe disease. These are:

a. Casirivimab 1200 mg + Imdevimab 1200 mg, single dose iv infusion
b. Strovimab 500 mg, single dose iv infusion
c. Bamlanivimab 700 mg + Etesevimab 1400 mg, single dose iv infusion

Based on clinical trial data, some yet to be published in a peer reviewed journal, all 3 of these medications have been shown to reduce viral loads, shorten duration of symptoms and reduce the risks for hospitalization or death related to COVID-19, in individuals with mild or moderate COVID-19 disease (in the case of the former two, onset of symptoms within 5-7 days from enrollment to trial) and at least one or more risk factors for developing severe disease.[1-6] At a higher dose, the combination Casirivimab 4 g + Imdevimab 4 g has also been shown to significantly reduce mortality in hospitalized severe-COVID patients who are seronegative at study entry.[7]

The adverse events reported during the use of these products include nausea, dizziness, fever and hypersensitivity events including rash, pruritus and infusion-related reactions. Anaphylactic reaction was reported in one among >850 participants treated with bamlanivimab according to an FDA review. In a clinical trial of Casirimab + Imdevimab, one recipient had an anaphylaxis reaction.

The US FDA has given EUA for Casirivimab + Imdevimab combination and Strovimab for use in non-hospitalized patients with mild and moderate disease with increased risk of disease progression, while the UK MHRA has given approval for use of Casirivimab + Imdevimab. Of note, even though the US FDA had previously given EUA for the combination Bamlanivimab + Etesevimab, its use has been paused due to concerns regarding its efficacy against emerging variants. Although some studies, including an industry-led study, have reported retained activity of the combination of Bamlanivimab + Etesevimab against the delta variant[8] that is the predominant variant in Nepal, there is concern raised for reduced efficacy in other studies[9].

Given that the utility of these drugs is seen in those with mild or moderate disease with median duration of symptoms being 3-4 days in the clinical trials, it needs to be noted that potentially hundreds of thousands of patients in Nepal could meet the criteria for these medications during the pandemic. The cost of these drugs would be prohibitively high for average citizens of Nepal, if they are to be purchased at current international market prices. As mentioned above, data on the efficacy of these medications against the emerging variants, especially those prevalent in Nepal, is inadequate.

In light of the above, it may be considered appropriate to use certain monoclonal antibody products in certain high-risk individual patients with COVID-19 in Nepal on a case by case basis, and the corresponding government authorities may provide appropriate authorization for their import and use. However, the NMC COVID-19 treatment guidance committee is awaiting further clarity on the issues of cost, availability and the efficacy against the predominant variants able to make formal recommendations on the use of specific monoclonal antibody products against COVID-19.

References:

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: https://www.fda.gov/media/143892/download
2. Food and Drug Administration. Fact Sheet for Health Care Providers: emergency use authorization (EUA) of Bamlanivimab and Etesevimab. 2021. Available at: https://www.fda.gov/media/145802/download.
3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of sotrovimab. 2021. Available at: https://www.fda.gov/media/149534/download

4. Gottlieb RL, et al. Effect of Bamlanivimab as Monotherapy or in Combination with Etesevimab on Viral Load in Patients with Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2021;325(7):632–644.
5. Dougan M, Nirula A, Gottlieb RL, et al. Bamlanivimab+etesevimab for treatment of COVID-19 in high-risk ambulatory patients. Presented at: Conference on Retroviruses and Opportunistic Infections. 2021. Virtual. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/resources/2021/vCROI-2021-Abstract-eBook.pdf.
6. Weinreich DM, et al; Trial Investigators. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med. 2021 Jan 21;384(3):238-251.
7. RECOVERY collaborative group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1
8. Planas et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021 Aug;596(7871):276-280. doi: 10.1038/s41586-021-03777-9. Epub 2021 Jul 8
9. Tada et al. The Spike Proteins of SARS-CoV-2 B.1.617 and B.1.618 Variants Identified in India Provide Partial Resistance to Vaccine-elicited and Therapeutic Monoclonal Antibodies. Preprint on bioRxiv **doi:** https://doi.org/10.1101/2021.05.14.444076
10. Bhimraj A, Morgan RL et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America **2021**; Version 4.3.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed August 21, 2021
11. National Institutes of Health COVID-19 treatment guidelines. www.covid19treatmentguidelines.nih.gov Accessed August 21, 2021

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