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 more than 15 minutes 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 surgical mask when N-95 mask is not available), face shield, gloves, and, if direct contact is expected, gowns.
- A separate space away from other patients, families and visitors ("Fever" clinic) need 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 precautions (surgical mask, face shield or goggles, gown) need to be strictly implemented in the designated area for isolation.
- For details of the appropriate use of personal protective equipment and other infection control practices in fever clinics or elsewhere in the hospital, please refer to the most recent version of the Nepal Medical Council/MOHP "Interim Guidance on Infection Prevention and Control Practices when COVID-19 is suspected".

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

- Suspected COVID-19 cases with no symptoms or mild symptoms do not require hospital admission *for clinical reasons* unless other underlying risk factors for progression exist,

such as DM, immunocompromised patient, cardiovascular disease, chronic respiratory conditions, etc.

- 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.
- If the patient does not meet criteria for a suspected case for COVID-19, and there is no other reason for the patient to be admitted, they can be discharged from the hospital.
- Refer to Appendix 1 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 $3/4^{th}$ (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, 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.
- 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)".
  - 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.

- Higher risk of severe disease has not generally been noted in pregnant women. Children are not noted to be at higher risk except infants less than one year of age. (See section VI.J for details.)
- 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 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. **Molecular Tests**: RT-PCR is currently available and is the most widely available molecular test in Nepal. It is being done either by traditional RT-PCR method or GeneXpert technology at present. **Molecular methods are considered as the standard method for diagnosis of COVID-19 at present and should be used as the preferred method whenever available.**

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 current FDA EUA or FDA approval 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.

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

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 optimal 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 **should NOT be used** in the following situations:

i. Asymptomatic individuals
ii. To establish immunity against COVID-19
iii. To establish the presence or absence of SARS-CoV-2 infection or reinfection

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 in 24-48 hours.
- When repeated tests are negative but the suspicion for COVID-19 remains high, can consider doing a validated antigen- or antibody-based test, if available.
- 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.
- Collect blood cultures for bacteria that cause pneumonia and sepsis, ideally before antimicrobial therapy. DO NOT delay antimicrobial therapy to collect blood cultures.

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 offered to the non-hospitalized patients whose respiratory symptoms are worsening.
- CT scan of the chest can be performed in patients suspected of COVID-19; however, CT scan 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 patients with worsening conditions 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, 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, D-dimer level, lactate dehydrogenase level, quantitative C-reactive protein, troponin, ferritin, procalcitonin, etc.
- Samples should be sent for cultures of blood, sputum, and, if indicated, urine, before starting antibiotics for any reason or if bacterial sepsis suspected.

3. Depending on epidemiology and availability and indications for testing, other tests may be performed to rule out alternative causes of fever such as typhoid, tuberculosis, and tropical diseases such as scrub typhus, dengue, leptospirosis, 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) >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 ≤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 CKD
- Advanced liver disease
- Blood disorders (e.g., 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
- Surgery during incubation period

- Any one of the following clinical findings:
  - Oxygen saturation (SaO2) ≤93% on room air; <90% if known chronic hypoxic conditions or receiving chronic supplemental oxygen
  - Respiratory rate >24 breaths/min

  Note: Low socioeconomic status and being a victim of racism have been identified as risk factors for severe COVID-19 infection especially in the USA. While these findings have not been validated in the context of Nepal, these risk factors should be taken into account on a case by case basis while designing management plan in Nepal.
- 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, creatine phosphokinase, ferritin and IL-6, and prolonged prothrombin time.

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 or specific treatment is recommended for persons with asymptomatic or presymptomatic infection.
- 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* unless other underlying risk factors for progression exist, such as DM, immunocompromised patient, cardiovascular disease, chronic respiratory conditions, etc. 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 of these symptoms, they should return to designated 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.

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

- Patients with moderate COVID-19 should be admitted and closely monitored in a hospital.
- If the hospital doesn't have an intensive care facility, clinicians should consider referring patients with moderate illness to a hospital with an intensive care facility.
- Laboratory tests as listed above in [Section V. Diagnosis] should be performed, for assessment and monitoring of severity and for prognostic value.
- Chest X-ray or ultrasound should be performed.

- 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 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 >93%. (See section VI.B above)
  However, if / when Remdesivir supplies are limited, they should be prioritized for use in cases with severe COVID-19.
- We recommend against using dexamethasone for treatment of moderate COVID-19.
- When bacterial superinfection is suspected, appropriate empiric antibiotics should be started. (See below in Section VI.K)
- Deep vein thrombosis prophylaxis should be considered in all patients when there is no contraindication for anticoagulation.
- Patients should be advised to ambulate within the isolation unit at least every few hours when awake.
- For pharmacologic prophylaxis, one of the following may be used: Enoxaparin, Dalteparin, Fondaparinux or Unfractionated Heparin. (See Table 1 below)
- Avoid nebulization, if possible, or use dry nebulization protocol (See Appendix 4) as a non-aerosol generating option.
- Psychosocial evaluation and support may be indicated. (See below in Section VI.K)

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

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 via nasal cannulae (upto 4-6 litres/minute) or non-rebreathing mask with reservoir (10-15 litres/minute) should be given to keep SpO2 between 93 to 96% (or 88 to 92% if having chronic respiratory diseases). These patients need to be closely monitored for worsening saturation or respiratory distress and planned to be shifted to ICU as early as possible.
- 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 >93%. 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 self-proning or repositioning:** For patients admitted to the ward, 'awake self proning or repositioning' 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. Monitor patients carefully to look for signs of deterioration.
  (See appendix 5)
- Deep vein thrombosis prophylaxis should be considered in all patients when there is no contraindication for anticoagulation.
- Patients should be advised to ambulate within the isolation unit at least every few hours when awake.
- For pharmacologic prophylaxis, one of the following may be used: Enoxaparin, Dalteparin, Fondaparinux or Unfractionated Heparin. (See Table 1)
- Laboratory tests as listed above in [Section V Diagnosis] should be performed, for assessment and monitoring of severity and for prognostic value.
- Chest X-ray or ultrasound should be performed, preferably at bedside. CT scan may sometimes be indicated, only if it changes the management significantly. (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 once a day, or Hydrocortisone 160 - 200 mg in divided doses per day, can be used as alternatives to Dexamethasone when it is not available.
- Remdesivir is **recommended** for use in patients with severe COVID-19 who **require low-flow oxygen** 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 require supplemental oxygen but do not need oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). 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.
- There are insufficient data 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.

  An adult (≥18 years-old) patient with critical (severe or immediately life threatening) COVID-19 may be offered convalescent plasma therapy provided there are no contraindications. (See details below in "Section VI.J.2".)
- When bacterial superinfection or viral coinfection is suspected, appropriate empiric antimicrobials should be started. (See below in Section VI.K)

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.

<u>Indications for ICU admission</u> (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%. 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.

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:
  - 93% - 96% for patients without chronic respiratory disease
  - 88% - 92% for patients with chronic type II respiratory failure

Proning:

- Consider awake proning 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).
- Pre-requisites for awake proning- patient should be alert/ able to communicate, hemodynamically stable and not in respiratory distress.
- Monitor patient closely during awake proning 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, May 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 OD or methylprednisolone 32mg OD or Hydrocortisone 160-200mg per day 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.
- 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.
- When bacterial superinfection or viral coinfection is suspected, appropriate empiric antimicrobials should be started. (See below in Section VI.K)

Convalescent plasma therapy:

- An adult (≥18 years-old) patient with critical (severe or immediately life threatening) COVID-19 may be offered convalescent plasma therapy provided there are no contraindications. (See details below in "Section VI.J.2".)

Treatment of co-infections:

- At initial presentation, if bacterial pneumonia or sepsis is suspected, 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**.

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 rising D-dimer (>6 times the normal limit), worsening hypoxia not fully explained by worsening chest x-ray or in case of high suspicion of DVT/ pulmonary embolism or thrombosis of central venous or arterial line, treatment 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)

Proning:

- Early proning 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 or viral coinfection is suspected, appropriate empiric antimicrobials should be started. (See below in Section VI.K)

Table 3. Treatment Recommendations summary
Mild to moderate COVID-19 with no requirement for supplemental oxygen
Supportive care only Dexamethasone should NOT be used. For moderate COVID-19, additional consideration are: Pharmacologic DVT prophylaxis, if not contraindicated, in hospitalized patients *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 93%.*
Severe 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 Remdesivir* 200 mg x 1, then 100 mg for 5 days or until discharge from hospital, whichever comes earlier **in those needing low flow oxygen**

Pharmacologic DVT prophylaxis if no contraindications Awake proning *Convalescent Plasma* 200 mL over 1-2 hours from a matched donor may be* ***considered.***
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 Pharmacologic DVT prophylaxis 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.* *Convalescent Plasma* 200 mL over 1-2 hours from a matched donor may be* ***considered.***
* Convalescent plasma is available only as an investigational agent in Nepal at present.

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 early 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.

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. According to the early data released by Glenmark (manufacturer of favipiravir in India), 69.8% of participants in the favipiravir arm experienced clinical cure by day four compared to 44.9% in the control group, which was statistically significant (unpublished data). 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.

e. Umifenovir: Umifenovir is a licensed drug in some countries for prophylaxis and treatment of influenza. It is a broad-spectrum antiviral agent that inhibits fusion of virus with host cells. Although *in vitro* studies have suggested that umifenovir is an efficient inhibitor of SARS-CoV-2, human studies so far do not support its use against COVID-19.

f. Monoclonal antibodies: Monoclonal antibodies against specific viral proteins are new modalities of treatment being studied. One such therapy being tested is REGN-COV2 (by Regeneron Biotech) is a combination of two monoclonal antibodies (REGN10933 and REGN10987) which was designed specifically to block infectivity of SARS-CoV-2. It is undergoing Phase 3 clinical trial.

2. Convalescent Plasma Therapy (CPT)

- CPT is currently being evaluated 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.
- CPT should only be used as an investigational therapy only for patients with severe or immediately life-threatening COVID-19 infection. According to the protocol of the clinical study of convalescent plasma for treatment of severe and life threatening COVID-19 infection, conducted by the Nepal Health Research Council (NHRC), an adult (≥18 years-old) patient with critical (severe or immediately life threatening) COVID-19 may be offered convalescent plasma therapy provided there are no contraindications. Informed consent should be obtained prior to initiating therapy. Generally, 200 ml of ABO compatible COVID-19 convalescent plasma should be administered over 1-2 hours. The patient should be closely monitored for possible transfusion related adverse events such as fever, pruritus, haemolytic and nonhaemolytic transfusion reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), delayed posttransfusion purpura, etc. and managed accordingly.

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, methylprednisolone 32 mg, or hydrocortisone 160 mg) may be used in severe or critically ill patients.

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

- We recommend against the use of anti-IL6 monoclonal antibody siltuximab or anti-IL6 receptor monoclonal antibodies sarilumab or tocilizumab, 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.

4. Vaccines

- Currently there is no proven vaccine against COVID-19. Multiple potential COVID-19 vaccines are under development and being evaluated in clinical trials.

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 requiring supplemental oxygen. 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 low (10-20%), 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 drug-resistance, as well as the possibility that antibiotics may become a limited resource.

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. The initial antibiotic regimens should be chosen based on the type of patients.

c. Empiric antimicrobial coverage of a presumed pulmonary source of infection:

In patients **without** risk factors for MRSA or *Pseudomonas* (i.e., community acquired infection, no prior multi-drug resistant organisms): Ceftriaxone or Amoxicillin-clavulanic acid +/- Azithromycin or doxycycline

(If the patient is getting treatment with chloroquine or hydroxychloroquine, doxycycline should be preferred to azithromycin to avoid QTc prolongation.) - If proven or suspected influenza, add oseltamivir.

In patients **with** risk factors for *Pseudomonas* or MRSA (i.e., hospital-acquired infection, recent courses of antibiotics): Cefepime or Piperacillin/tazo +/- Teicoplanin or Vancomycin.

Consider adding Meropenem or Imipenem-cilastatin if high concern for multidrug resistant organism infection.

d. Give oral antibiotics when possible to reduce volume load, unless concerns for poor oral absorption.

e. **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

c. Such decisions regarding withholding access to intensive care unit interventions or withdrawing of active life sustaining treatment of patients (including mechanical ventilation) need to be made by a separate team or committee formed by the hospital (Ethics Committee, Triage Committee, or a similar entity) with at least three members (as stipulated in the Nepal Medical Council Guidelines "Professional Ethics During COVID-19 Pandemic"). Treating clinical team members should not be a part of this committee. The Ethics Committee's decision has to be documented in writing and signed by all members.

d. Communication about such decisions should be done to the patient's family or concerned parties by the Ethical Committee members and not by the treating critical care team.

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, treatment with immunosuppressive medications including high dose steroids (prednisolone >20 mg/day), cancer chemotherapy, leukemia, transplant, 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)

VII. SPECIAL POPULATIONS WITH COVID-19

VII.A Pregnant Women and Lactating Mothers

- Based on currently available information, there is no evidence that pregnant women are at higher risk or at risk of severe illness. However, there may be increased risk for asymptomatic infection, preterm delivery, and stillbirth, especially with a pre-pregnancy obesity and/or diabetes.
- So far, there is little evidence of mother-to-child transmission when infection occurs in the third trimester.
- 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 the appropriate sections above for other management (e.g. Testing and Laboratory work-up, general treatment including antimicrobials, management of respiratory failure and septic shock.)*

- **Can children get COVID-19?**
  Children of all ages can get the COVID-19, although only 1 to 5% of diagnosed COVID-19 cases are seen in children. This may be due to the fact that rate of hospitalization is much lower in children.
- **How do they present?**
  Most common presenting symptoms are fever or cough. Other manifestations may include myalgia, shortness of breath, headache, sore throat, runny nose, diarrhea, nausea/vomiting, abdominal pain, new loss of taste or smell, and chills. Some children may present with just gastrointestinal symptoms. Infants may present with fever without any source and minimal or no respiratory symptoms.
  Children can also show stress associated symptoms. Younger children may develop excessive crying or irritation. Older children may show regression to previously outgrown behaviors such as bedwetting, excessive worry or sadness, irritability, poor ability to concentrate, unexplained headaches or body pain, etc.

- **What are the findings in laboratory tests and imaging?**

The recommended test for confirming diagnosis is RT-PCR, and nasopharyngeal, oropharyngeal or nasal swab samples can be collected for the test.

In newborns, testing should be performed at approximately 24 hours of age for both symptomatic and asymptomatic newborns born to mothers with confirmed or suspected COVID-19, regardless of the mothers' symptoms. If initial test results are negative, or not available, testing should be repeated at 48 hours of age.

Similar to adults, children may demonstrate leukopenia, lymphopenia, elevate procalcitonin and C-reactive protein. Chest radiographs may be unremarkable or show bilateral consolidation.

- **What is the range of severity of illness in children?**

Most children are asymptomatic or have mild or moderate disease and recover within a week or two. There have been reports of pediatric patients requiring invasive ventilation or even extracorporeal membrane oxygenator (ECMO) or but these are very rare and mainly occur in children with chronic co-morbid conditions.

- **What is Pediatric Multisystem Inflammatory Syndrome (PMIS)?**

There are recent reports of a rare but serious condition associated with COVID-19 in children. PMIS is also referred to as multisystem inflammatory syndrome in children (MIS-C), pediatric hyperinflammatory syndrome, and pediatric hyperinflammatory shock. The pathogenesis may be an antibody or immune complex mediated postinfectious inflammatory syndrome.

- Its presentation may be varied:

1. Refractory vasodilatory shock (toxic shock syndrome) with normal cardiac function
2. Septic and /or cardiogenic shock state with impaired cardiac function (mainly LV-failure)
3. Kawasaki-like illness (not all patients requiring ICU care) with prolonged persistent fever (>101.3 ºF), sore throat, headache, abdominal pain and vomiting, rash, conjunctivitis
4. Some combination of the above

World Health Organization's preliminary case definition of PIMS

1. Children and adolescents 0–19 years of age with fever for ≥3 days
2. **AND** two of the following:
   i. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
   ii. Hypotension or shock.
   iii. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
   iv. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
   v. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).

3. **AND**
   Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.
4. **AND**
   No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
5. **AND**
   Evidence of COVID-19 **(**RT-PCR, antigen test or antibody positive), or likely contact with patients with COVID-19.

- **How are children with COVID-19 managed?**

  Management is mainly supportive. The management specific to children is discussed here.

1. Ventilator: A lower level of plateau pressure (< 28 cmH_2O) is targeted, and lower target of pH is permitted (7.15–7.30). Tidal volumes should be adapted to disease severity: 3–6 mL/kg PBW in the case of poor respiratory system compliance, and 5–8 mL/kg PBW with better preserved compliance. Early proning for extended duration (24-48 hours) may be needed in children. Use restrictive fluid strategy. Aim for euvolemia. If signs of volume overload are present consider diuresis with furosemide. Strict intake and output with Foley catheter monitoring is recommended.
2. Septic shock and Decreased cardiac output:
   a. Recognize shock in children with any hypotension (systolic blood pressure [SBP] < 5th centile or > 2 SD below normal for age) or two or more of the following: altered mental state; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.
   b. Give 10–20 mL/kg crystalloid fluid as a bolus in the first 30 minutes and reassess for signs of fluid after each bolus.
   c. Administer vasopressors if
      i. Signs of shock including altered mental state; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and H R < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 seconds) or feeble pulses; oliguria persists after two repeat boluses; or
      ii. age-appropriate blood pressure targets are not achieved; or
      iii. signs of fluid overload are apparent but child is on shock
   d. Epinephrine is considered first-line treatment, while Norepinephrine can be added if shock persists despite optimal dose of epinephrine or if patient is in warm shock with vasodilatation, wide pulse pressure and near normal cardiac function.
3. Specific treatment of PMIS:

Patient may deteriorate rapidly. Close cardiorespiratory monitoring is indicated.

a. Kawasaki Syndrome:
    i. Intravenous immunoglobulin 2 g/kg. May need to be repeated.
    ii. Aspirin 50-80 mg/kg per day for 5 days. Then continue for 48 hours after defervescence then decrease dose to 3-5 mg/kg per day for 8 weeks.
b. Toxic shock syndrome
    i. Intravenous immunoglobulin 2 g/kg

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.

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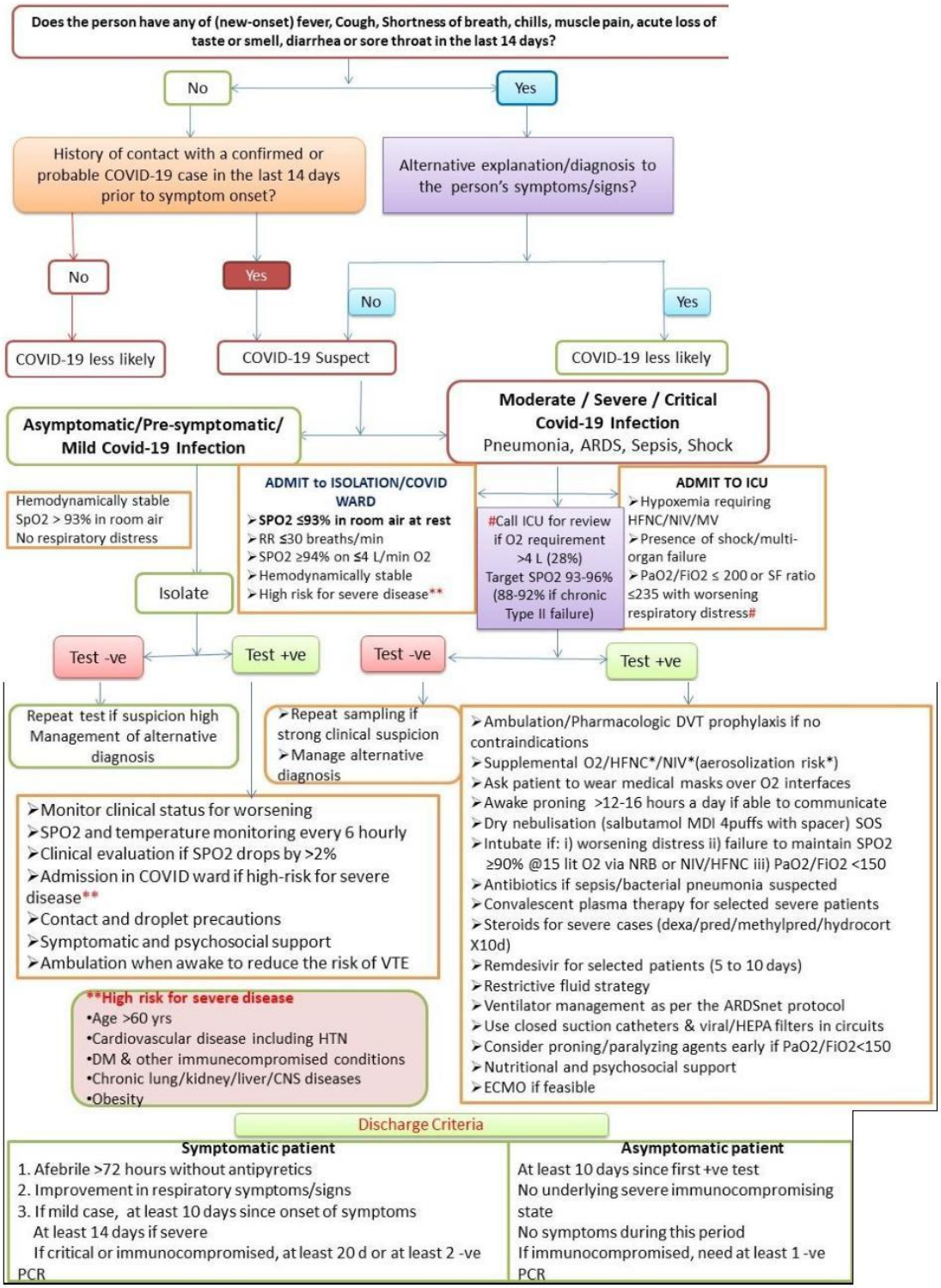
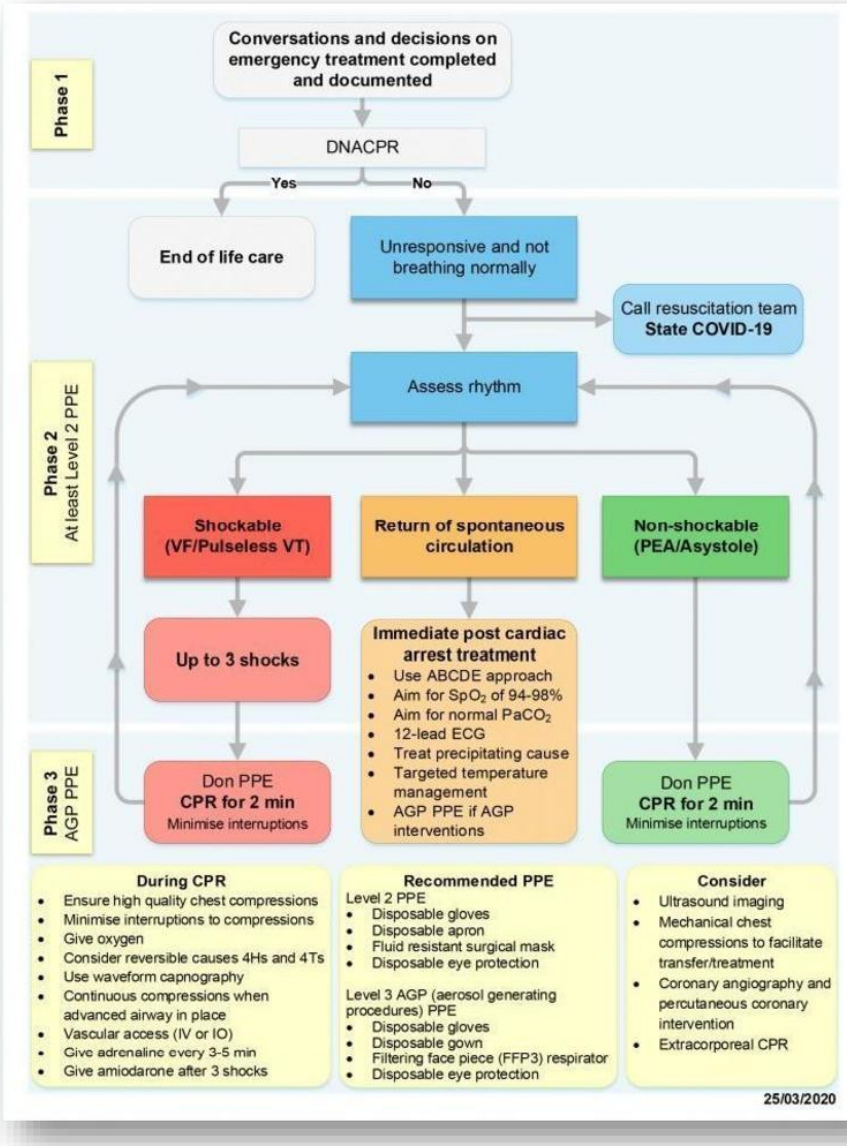
X. APPENDIX 1: Patient triage and management flow chart



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

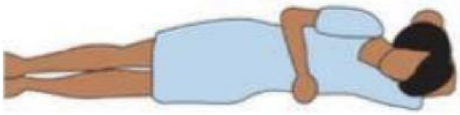
3. 30 minutes-2 hours: sitting up
३. ३० मिनेट देखि २ घन्टा: ठाडो बस्ने

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

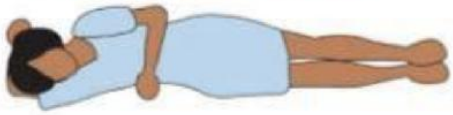
PHOTOS BELOW TO DEMONSTRATE THIS

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

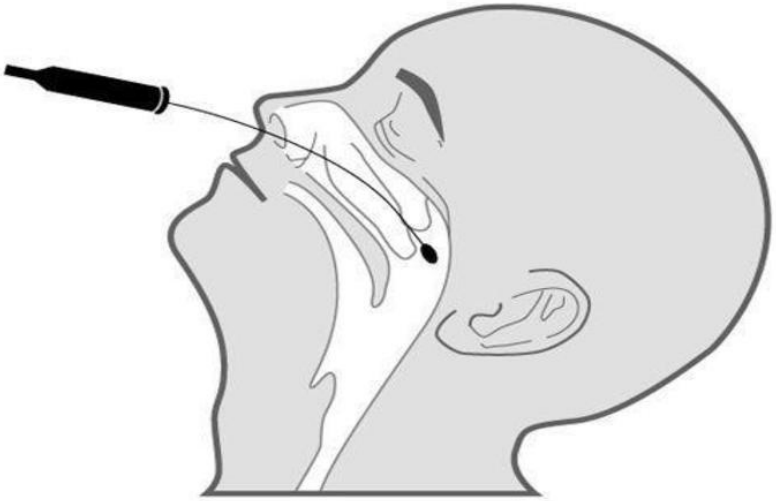
Titrate FiO2 and PEEP for oxygenation for BMI<35 as per the ARDSnet LOW PEEP table

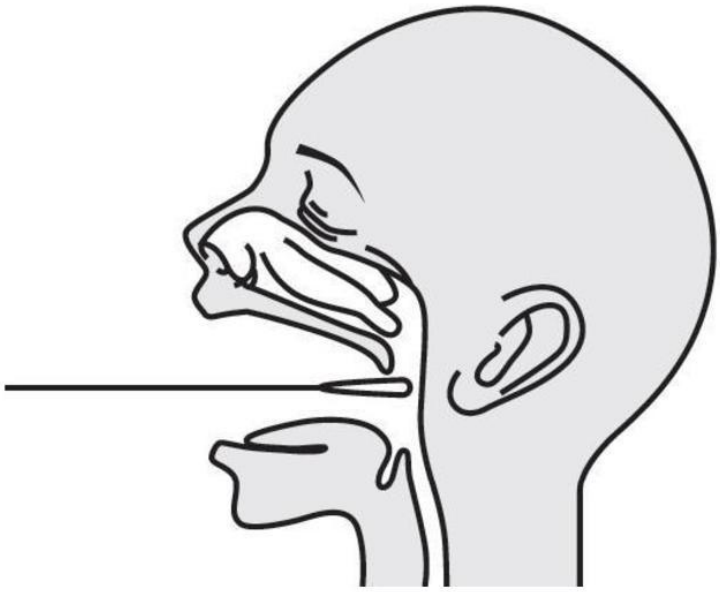
FiO2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

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

XI. CONTRIBUTORS

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