NMC COVID-19 Guidelines Update Statement

(January 2022)

As the pandemic caused by SARS CoV-2 has evolved, the prevention and management strategies have also evolved. These living NMC COVID-19 Guidelines are updated as necessary to address these changes appropriately in Nepal's context. The followings summarize the updates based on currently available literature including scientific publications, abstracts, and guidelines by widely recognized authorities.

Except for the updates mentioned in this statement, readers may refer to and follow the last version of the guidelines (Clinical Guidance for COVID-19 – Update 3) available at *https://nmc.org.np/files/4/NMC_Clinical_Guidelines_COVID19_update_3.pdf*

The recommendations made in this statement are pertinent to the ongoing pandemic wave in which Omicron variant is expected to remain the dominant variant, and may have to be adjusted if/when newer variants with different characteristics may become dominant.

A. EPIDEMIOLOGY AND TRANSMISSION

1. Nepal is currently in the midst of the third wave of the pandemic. Omicron variant was identified at the beginning of the current wave by genome sequencing (Source: Press statement, Ministry of Health and Population, 7 January 2022), and appears to be the driving force for the exponential surge at this time.
2. The Omicron variant (B.1.1.529) of SARS CoV-2 has a higher rate of replication and is transmitted at a higher rate than the Delta variant. It has a shorter incubation period (median 3 days) as compared to Delta variant (4-6 days).

B. CLINICAL FEATURES

The Omicron variant has mutated spike proteins with higher affinity to the upper respiratory tract epithelium resulting in predominantly upper respiratory symptoms. Similar to the other variants, it also causes systemic illness including fever, myalgia, and headache. Reports from other countries have showed that there were lower rates of hospitalization, oxygen requirement, ICU admission, and overall mortality during the Omicron variant wave compared to the previous wave with delta variant. Median duration of symptoms and hospitalization are shorter among patients with Omicron variant compared to Delta variant.

C. DIAGNOSIS

1. Molecular testing for SARS CoV-2: Omicron variant has mutated spike proteins (30 amino acid substitutions, three small deletions, and one small insertion) which may not be detected by PCR assays. If a PCR or another type of nucleic acid amplification test (NAAT) shows absence of spike protein gene (S-gene target failure or SGTF) but presence of other target genes of SARS CoV-2, the test is considered as a suspect case of Omicron variant. The characteristic features of Omicron variant is described as the Δ69-70 amino acid deletion in the spike protein gene (S-

gene) whereas the Orf1ab and nucleocapsid (N) targets are retained. The confirmation of a variant requires gene sequencing. However, gene sequencing is expensive, time consuming, not readily available, and has more epidemiological significance than clinical significance.

2. Antigen-based tests: Laboratory-based studies have shown that the rapid antigen-detection tests for SARS CoV-2 have lower sensitivity for Omicron compared to the previous variants, especially in the early days of infection. If an antigen detection test is negative in a patient who is suspected to have COVID-19, the patient should get tested with a molecular method to detect SARS CoV-2. On the other hand, because of the close correlation of antigen based tests with infectiousness, while massive numbers of essential frontline workers are getting infected within a short period of time in the Omicron wave, antigen-based tests have proven useful in designing alternative approaches to safely bring essential workers with recent infection or exposure to cases back into the workforce.

D. CLINICAL MANAGEMENT

Please see **Appendix 1** for a summary of management recommendations based on severity of illness.

Mild to moderate disease:

Based on current literature, following new agents may be considered for treatment of mild to moderate COVID-19 in individuals with high risk of disease progression.

1. The following antiviral agents are active against Omicron as well as previous variants including Delta, but they are currently neither approved nor available in Nepal.
   a. Neutralizing antibodies: Sotrovimab
   b. Nirmatrelvir/ritonavir
   c. Molnupiravir

   The use of monoclonal antibodies Bamlanivimab + Etesevimab, Casirivimab + Imdevimab and Regdanvimab is not recommended because of their expected efficacy being significantly reduced against the Omicron variant.

2. Antiviral agent currently available in Nepal
   a. Remdesivir:
      Remdesivir was studied in a randomized control trial (PINETREE study) in unvaccinated patients with mild to moderate disease who were within 7 days from onset of symptoms and had age ≥60 or at least one risk factor for development of severe disease. It was administered as daily infusions for 3 days. The risk of COVID-19 related hospitalization (HR 0.13; 95% CI 0.03-0.59) and all cause hospitalization (HR 0.28; 95% CI 0.10 – 0.75) were reduced by 87% and 72% respectively compared to the placebo group. No deaths were seen in either study group at day 28. Remdesivir is expected to maintain its activity against the Omicron variant.

      Since the study was completed prior to the Omicron wave, in which far less proportion of cases are noted to progress to severe or critical illness, the groups of patients that would benefit from this treatment would likely be smaller.

Remdesivir 200 mg on day 1, followed by 100 mg iv daily on days 2 and 3, should be considered for individuals who meet the following criteria:
1. Aged ≥12 and weighing ≥40 kg, and
2. Within 7 days from onset of symptoms (the treatment should be started as soon as possible after symptom onset), **and**
3. Moderate COVID-19
Or, mild COVID-19 with age ≥75,
Or, mild COVID-19 with a severe immunocompromising condition*,
Or, mild COVID-19 with 2 or more risk factors for progression to severe disease.*
(* See appendix 2.)
The infusions can probably be administered without requiring hospital admission, however should be given where appropriate infection prevention practices can be followed, patients can be monitored during and at least 1 hour after the infusion, and severe hypersensitivity reactions can be managed.
For patients who end up being hospitalized and require oxygen supplementation but not ventilator or ECMO, same dose should be extended to complete 5 days total.

Severe or Critical COVID-19

Corticosteroid therapy (e.g. dexamethasone) is the preferred immunomodulatory treatment for all patients who need oxygen supplementation. We have previously recommended the IL-6 inhibitor Tocilizumab if there is rapidly increasing oxygen need and systemic inflammation despite the use of corticosteroids. The following immunomodulatory medications have also been found to be potentially useful, though they are not currently approved for COVID-19 in Nepal.

a. Baricitinib: This Janus-kinase inhibitor was studied in combination with Remdesivir (without steroids) in severe or critical COVID-19 illness in ACTT-2 trial, and showed improved time to recovery in patients who required supplemental oxygen but not mechanical ventilation (10 vs 18 days, R 1.51, 95% CI 1.10 - 2.08) In the multinational, randomized controlled COV-BARRIER trial, Baricitinib was studied in addition to the standard of care corticosteroids, with or without Remdesivir, among unventilated patients with pneumonia and at least 1 elevated inflammatory marker. Adding Baricitinib was shown to reduce 28 day mortality (8.1% vs 13.1% with placebo; HR 0.57, 95% CI 0.41 – 0.78) and in the subgroup of patients on high-flow oxygen or noninvasive ventilation at baseline, the mortality was 17.5% with baricitinib vs 29.4% with placebo (HR 0.52, 95% CI 0.33 – 0.80).

   Baricitinib 4 mg once daily for 14 days or until discharge from hospital, whichever is sooner, should be considered in patients with rapidly increasing oxygen requirement and systemic inflammation in spite of systemic corticosteroids.

Tocilizumab has also been recommended in the same setting as Baricitinib, and there is no clear evidence so far to recommend one in preference to the other. Clinicians should decide which of these drugs to use based on considerations such as availability, cost, route of administration, etc. We do not recommend using both Baricitinib and Tocilizumab. Tocilizumab is also recommended in some COVID-19 patients on mechanical ventilation, but there is little data to support use of Baricitinib for patients on mechanical ventilation.

The dose of Baricitinib should be reduced to 2 mg daily for adults with an eGFR between ≥30 to < 60 ml/min, and to 1 mg daily or 2 mg on alternate days if eGFR 15 – 29 ml/min. Baricitinib should be used in patients with severe hepatic impairment only if the potential benefit far outweighs the potential risk. Baricitinib is not recommended if eGFR <15 ml/min, or absolute neutrophil count $<0.5 \times 10^9$/L, or during active tuberculosis infection or during pregnancy.

If both Baricitinib and Tocilizumab are not available, tofacitinib may be considered as an alternative.

b. Tofacitinib: Tofacitinib 10 mg twice daily for up to 14 days or until hospital discharge was studied in a randomized controlled trial (STOP-COVID) among hospitalized patients most of whom (89.3%) were also on corticosteroid therapy. 63.2% of those in Tofacitinib arm were on low-flow oxygen therapy, and 13.2% were receiving oxygen through high flow devices. Patients were excluded if they were receiving invasive mechanical ventilation on day of randomization. Tofacitinib was reported to reduce the combined outcome of death and respiratory failure at 28 days compared with placebo (18.1 % vs 29.0 %, risk ratio 0.63, 95% CI 0.41 – 0.97), and however all-cause mortality difference was not statistically significant (2.8% vs 5.5% in the placebo arm; risk ratio 0.49, 95% CI 0.15-1.63). 14.1% of those in the Tofacitinib arm had serious adverse events compared to 12% in placebo group.
Based on this one RCT data, tofacitinib may have some clinical benefit however the evidence is not as strong as for Baricitinib or Tocilizumab.

Tofacitinib should be considered for patients with rapidly increasing oxygen requirement and systemic inflammation in spite of systemic corticosteroids (but not on mechanical ventilation) *only if* Baricitinib or Tocilizumab are not available.

Tofacitinib should be avoided in patients with known immunosuppression, cancer needing active treatment, or a history of thrombosis or current thrombosis. Dose should be reduced to 5 mg twice a day if eGFR <60ml/min.

c. Sarilumab: Sarilumab is a recombinant humanized anti-IL-6 monoclonal antibody. It was studied in two adaptive design randomized clinical trials of patients with severe or critical COVID-19 but failed to show statistically significant benefit. However, in the REMAP-CAP trial involving critically ill patients, it was shown to have similar efficacy to tocilizumab, with more median organ support free days (OR 1.50; 95% CrI, 1.13-2.0) and higher likelihood of hospital survival (OR 1.51; 95% CrI, 1.06, 2.20) compared to control. Patients were enrolled in the Sarilumab arm until 5 months after randomization had been closed in the standard care arm, limiting the strength of the evidence.

In clinical settings where Tocilizumab has been recommended and is not available or not feasible to use, Sarilumab may be considered as an alternative.
When Baricitinib is available, Baricitinib should be used in preference to Sarilumab in a patient not requiring mechanical ventilation.

Sarilumab is only used in addition to corticosteroid therapy, like Tocilizumab. Patients being started on Sarilumab should also be considered for treatment with Ivermectin as prophylaxis for disseminated strongyloidiasis.
Sarilumab and Tocilizumab should be used with caution in patients with the following:

- Active serious bacterial, fungal or viral infection other than SARS-CoV-2 infection
- Significant immunosuppression
- Absolute neutrophil count <500 cells/µL
- Thrombocytopenia <50,000 cells/ µL
- ALT >5 times the upper limit of normal
- Known hypersensitivity to Tocilizumab or sarilumab
- A high risk for bowel perforation

E. INFECTION CONTROL

Isolation for those who have been infected
Irrespective of vaccination status, all COVID-19 infected individuals should follow isolation guidelines as stated below:

Asymptomatic infection: Isolation can be stopped after 10 days from date of swab collection for positive test.
In case of an infected essential worker, when an earlier discontinuation of isolation is desired, isolation can be stopped **after 7 days**, with **a negative antigen or PCR test obtained within prior 48 hours**. A well-fitting mask must be put on around others until 10 days completed from positive test.

Mild to moderate illness (SpO2 ≥93): Isolation can be stopped after at least 10 days from the day of symptom onset (the first day of symptoms being day 0), provided that symptoms (except

mild cough, or changes to sense of smell or taste) have improved and at least 24 hours have passed since last fever without use of fever-lowering medication.
In case of an infected essential worker, when an earlier discontinuation of isolation is desired, isolation can be stopped **after 7 days**, provided that at least 24 hours have passed since last fever without use of fever-lowering medication, AND other symptoms have improved, AND a **negative antigen or PCR test was obtained within prior 48 hours**. A well-fitting mask must be put on around others until 10 days completed from symptom onset.

Severe to critical Illness: Isolation can be stopped after at least 10-20 days from the day of symptom onset, provided that symptoms have improved, and at least 24 hours have passed since last fever without use of fever-lowering medications. The test-based strategy recommended below for severely immunocompromised individuals may be considered to inform decision-making.

Asymptomatic or symptomatic with a severe immunocompromising condition*: Isolation can be stopped after at least 10-20 days from the day of symptom onset, provided that symptoms have improved and at least 24 hours have passed since last fever without use of fever-lowering medications AND result of at least 2 consecutive respiratory specimen collected ≥ 24 hours apart (antigen test or PCR) are negative.

(*See appendix 2)

Quarantine for those who have been exposed
All vaccinated, unvaccinated and previously infected individuals who have a significant exposure to COVID-19 patients should stay in quarantine for 10 days total (last day of exposure being day 0) **OR** 7-days if a PCR test obtained within the prior 48 hours is negative.
If quarantine is discontinued after 7 days, a well-fitting mask must be put on around others until 10 days are completed from the day of exposure.

E. IMMUNIZATION

Vaccines

- Recent studies have demonstrated that unvaccinated individuals are at a much higher risk than individuals who have received 2-doses of COVID-19 vaccine, and furthermore, individuals who have received a booster dose of COVID-19 vaccine are at the lowest risk for symptomatic infection, hospitalization, and death from Delta as well Omicron variants of SARS CoV-2.
- **Since the individuals who have received a booster dose have the highest rate of protection, a 3rd dose of vaccine (2nd dose in case of J&J vaccine) is recommended for all individuals with the highest priority for high-risk patients including patients over 50-years old, chronic conditions, and immunocompromised as well as frontline workers.**
- **The COVID-19 vaccines are considered safe during pregnancy and lactation, and should be prioritized for this population.**

G. REFERENCES

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APPENDIX 1: Treatment recommendations summary according to the stage of COVID illness
(Updates on ***italics***)

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 ***Do not use monoclonal antibodies Bamlanivimab + Etesevimab, Casirivimab + Imdevimab or Regdanvimab.*** ***Consider Remdesivir 200 mg on day 1, then 100 mg daily on days 2 and 3, if moderate COVID, or if mild COVID and age ≥75, severe immunocompromising condition or multiple risk factors for progression to severe illness***
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, ***OR Baricitinib 4 mg daily for 14 days or until discharge from hospital***, 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. ***Tofacitinib may be considered as alternative to Baricitinib, or Sarilumab may be considered as alternative to Tocilizumab, if neither Tocilizumab nor Baricitinib are available.*** 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 Empiric coverage with antibacterials or antifungals NOT recommended. Convalescent plasma therapy NOT recommended. Pharmacologic DVT prophylaxis recommended if no contraindications. **<u>If requiring oxygen supplementation through a high flow device or NIV:</u>** Consider Tocilizumab in single dose 8 mg/kg if rapidly increasing O2 need and systemic inflammation in spite of systemic corticosteroids. ***Baricitinib may be considered instead of Tocilizumab if mechanical ventilation has not been initiated.*** Also consider prophylactic treatment with Ivermectin (200 micrograms/kg/day for 2 days) for such patients. ***Tofacitinib may be considered as alternative to Baricitinib, or Sarilumab may be considered as alternative to Tocilizumab, if neither Tocilizumab nor Baricitinib are available.*** Remdesivir may be considered. **<u>If requiring mechanical ventilation or ECMO:</u>** Consider Tocilizumab. If Tocilizumab not available or not feasible to use, Sarilumab may be considered for use.

APPENDIX 2

High risk factors for progression to severe disease

Age ≥65 years
Primary series vaccination incomplete
Obesity (BMI ≥ 30 kg/m^2)
Smoking
Pregnancy and recent pregnancy
Cardiovascular disease, excluding hypertension as the sole cardiovascular diagnosis
Cerebrovascular disease
Diabetes mellitus
Chronic pulmonary diseases(e.g., COPD, moderate to asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
Advanced chronic kidney disease
Chronic liver disease
Sickle cell disease
Cancer
Neurodevelopmental disorders (e.g., cerebral palsy)
Recipients of solid organ transplant or hematopoietic cell transplant
Treatment with agents for immunosuppression
HIV infection, with CD4 cell count <350 copies/mm3
Other conditions that confer medical complexity (e.g., genetic or metabolic syndromes, severe congenital anomalies)
Medical related technological dependence (e.g., tracheostomy, gastrostomy, or on mechanical ventilation)

Severe immunocompromising conditions

Solid organ transplant recipient or hematopoietic cell transplant recipients on immunosuppressive medications
Hematologic malignancy
Malignancy on active chemotherapy
Ongoing treatment with immunosuppressive medications including high dose steroids (prednisolone ≥20 mg)
Severe immunodeficiency syndromes
Human immunodeficiency virus infection with CD4 count <200 cells/mm3
Within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)