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Ministry of National Health Services,
Regulations & Coordination

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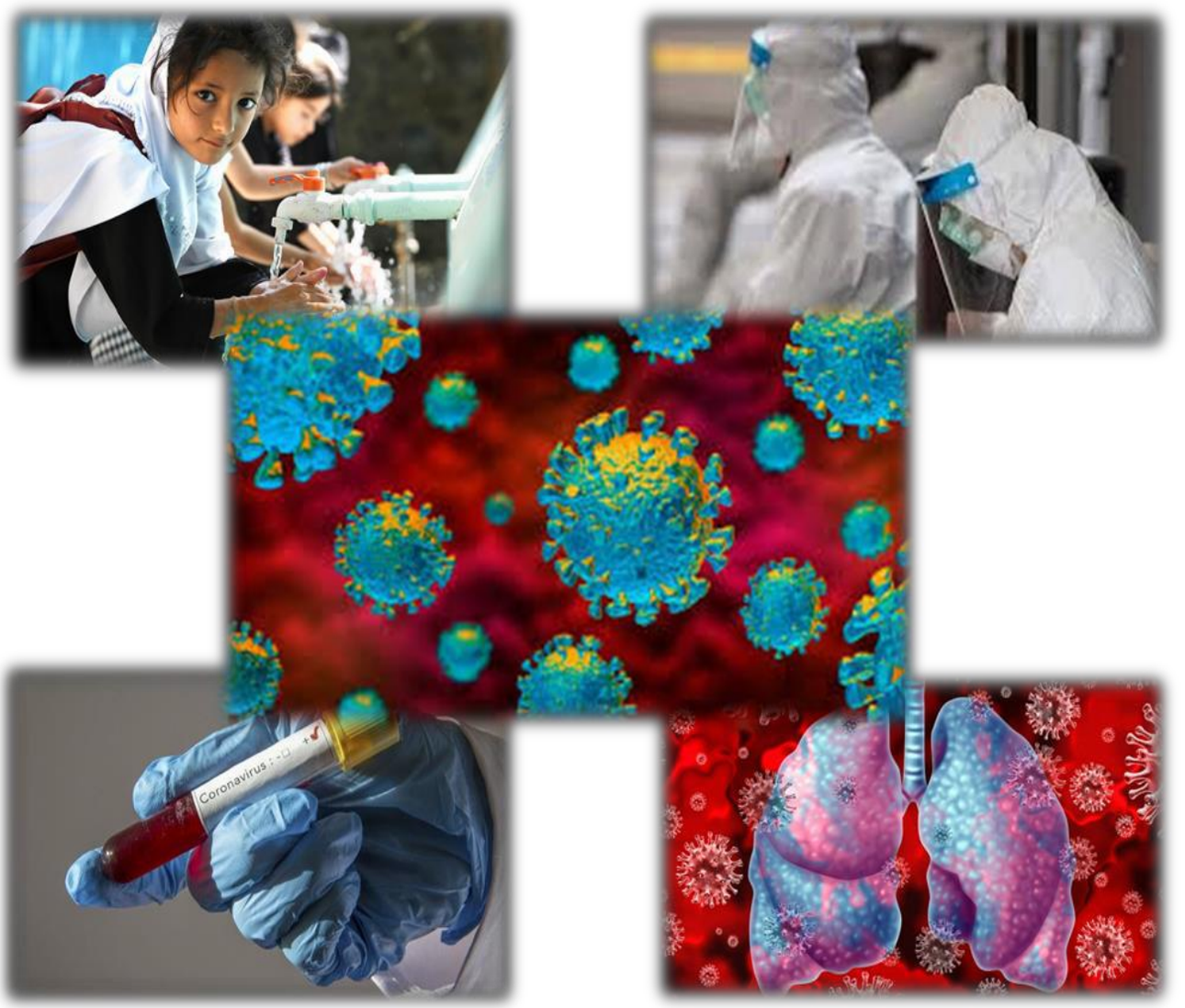
Guidelines

Clinical Management Guidelines for COVID-19 Infections



Testing

The test for SARS CoV-2 (COVID-19) should be offered to all with symptoms consistent with the disease. These include (but are not limited to):

- Respiratory symptoms, such as cough and shortness of breath
- Fever
- Muscle pain
- Headache
- Sore throat
- New loss of taste or smell
- Severe fatigue

Types of tests

There are 3 tests currently available which are not interchangeable. For a detailed description please see the individual guidelines available on the website. The table below provides a summary:

Test	Sample	Test site	Period of positivity	Purpose	Whom to test	Advantages	Disadvantages
PCR (Individual)	**Nasopharyngeal, nasal, oropharyngeal**	**Specialized laboratory**	**2 days before symptoms, 2 to 8 weeks after symptoms**	**Clinical diagnosis**	**Individuals suspected of COVID-19 or contact tracing**	**Highly sensitive. Very low false-positive rate**	**Expensive. Remains positive after recovery**
PCR (Pooled)				**Screening asymptomatic individuals (e.g., pre-op, contact tracing)**	**Asymptomatic individuals at risk of transmitting**	**Reduces costs of testing**	**Less useful if prevalence is high. Cannot be used in patients with symptoms**
Antibody	**Blood**	**Laboratory or point of care**	**7 to 14 days after symptoms. Duration of positivity unknown**	**Clinical diagnosis, surveillance**	**For diagnosis late in the illness. Seroprevalence studies.**	**Cheap and accessible**	**Variable sensitivity and specificity. Late positivity. Does not inform about immunity or recovery**
Antigen	**Nasal or nasopharyngeal**	**Point of care**	**2 days before symptoms till 5 days after symptoms**	**Very early diagnosis**	**Rapid diagnosis in early disease**	**Rapid and can be deployed in the field**	**Negative needs to be confirmed by PCR. Low sensitivity after the initial few days**

Clinical classification of suspected or confirmed COVID-19 patients

Patients can be classified into asymptomatic, non-severe, severe or critical based on their clinical condition. As the disease progresses, the severity may change.

Asymptomatic

SARS CoV-2 infection but with no symptoms. Some asymptomatic patients may be pre-symptomatic if tested early (e.g. as part of contact tracing).

Non-Severe

Oxygen saturation of 94% or greater and respiratory rate of less than 25 breaths/minute.

Severe

Oxygen saturation <94% or respiratory rate of over 25 breaths/minute.

Oxygen saturation is maintained by nasal cannulation or simple facemask and there is no need for non-invasive ventilation (NIV), High Flow Nasal Cannula (HFNC), or mechanical ventilation (MV).

Critical

Respiratory compromise severe enough to require NIV (including CPAP or BiPAP), HFNC or, MV.

Criteria for admission of suspected or confirmed COVID-19 patients

Asymptomatic and non-severe disease

Asymptomatic and non-severe cases can be managed at home with home isolation.

Criteria for home isolation include (must fulfill all the below):

- Those with a separate room to stay in, with a separate bathroom
- Those consenting to isolation

Patients with asymptomatic or non-severe disease who do not have adequate home arrangements or do not consent to stay at home, should be shifted to a dedicated isolation facility (as opposed to a hospital).

However, the following may be considered for observation in the hospital if resources allow

1. Immunosuppressed patients (on long term steroids or other immunosuppression)
2. Co-morbid conditions: Heart Failure, Decompensated Liver Disease, Structural Lung Disease, Uncontrolled Diabetes, Chronic Kidney Disease

If the patients cannot be admitted, then clear instructions must be given to call if any worsening occurs. The local public health authorities must be informed about all those patients who are going on home isolation.

Severe and critical disease

These patients should be admitted to a hospital for further management.

- Severe disease: Admit to a well-ventilated general ward
- Critical disease: Admit to high dependency unit or ICU with negative pressure room

In all of the above wards, it is mandatory that oxygen and pulse oximetry be available.

There is **no** role for prophylactic chloroquine, hydroxychloroquine, azithromycin, or multi-vitamins at this time. There is no proven therapy to prevent a COVID-19 infection after exposure.
COVID-19 vaccines may, however, prove effective in control of this pandemic. Currently many vaccines have shown promising results from phase 3 trial preliminary results.

Management of non-severe disease

- Non-severe cases should be treated with supportive care only. This includes acetaminophen or NSAIDs for fever, oral hydration in case of diarrhea, and antihistamines for rhinorrhea. Patients should be reassured that low-grade fever may persist for over a week. Fever may also be biphasic (that is may recur after settling) and this does not require antibiotics.
- Pulse oximetry should be checked every 4 to 6 hours and post-exertion if possible. The frequency of checking saturation may be made more frequent in the elderly and those with comorbidities, and less frequent in those younger than 20 years.
- No specific treatment (including steroids, chloroquine, hydroxychloroquine, azithromycin, ivermectin or, famotidine) is recommended for asymptomatic or mild disease. Steroids may lead to worse outcomes if used in non-severe disease.
- No blood tests are required in non-severe disease unless there is a concern of disease progression. The decision regarding anticoagulation and steroids should not be based on lab results alone.

Correct use of pulse oximetry device

As the use of these devices are now common outside the hospital, the following instructions must be explained to the user to ensure an accurate reading.

- The saturation should only be recorded when
- The device has been on the finger for 15 to 20 seconds
- The reading is steady and not fluctuating
- The probe is not too tight (which would constrict the circulation) or too loose (may fall off)
- The finger must be kept still while taking a reading
- There must be no bright lights pointing towards the probe
- There should be no nail-polish or mehndi on the fingernail
- The probe must be kept clean, using an alcohol wipe
- The readout of the monitor should be on the same side as the nail
- Pulse oximetry should be performed every 4 to 6 hours, during waking hours
- The blood pressure is recordable and preferably there is no running IV line on that arm

Risk stratification

Patients with non-severe disease may still have severe symptoms such as high-grade fever and myalgias. Also, elderly patients and those with multiple comorbid conditions may be at an increased risk of severe disease.
In such patients, the CALL score (co-morbid, Age, Lymphocytes, LDH) may be applied to help decide on how closely patients should be monitored.
The CALL-score can be interpreted as follows:

- Between 4–6 points: Low risk (≤10% probability of progression)
- Between 7–9 points: Intermediate risk (10–40% probability of progression)
- Between 10–13 points: High risk (> 50% probability of progression)

Patients with a high CALL score, do not require additional therapy but should be observed more closely for the progression of the disease.
The CALL score should be applied to the first values obtained and not serially.

CALL-Score	
Comorbidity*	
• None:	1 point
• Present:	4 points
Age	
•≤60 years:	1 point
•>60 years:	3 points
Absolute Lymphocyte count	
•>1000 cells/cumm:	1 point
•≤1000 cells/cumm:	3 points
LDH	
•≤250 U/L:	1 point
•250–500 U/L:	2 points
•>500 U/L:	3 points

*Comorbidities include HTN, DM, cardiovascular disease, chronic lung disease and HIV

Management of severe and critical disease

Annexure 2 summarizes the different treatment modalities used in COVID-19

Investigations

The initial lab investigations should be dictated by the patient's clinical condition. However, the following labs are recommended if available.

- CBC
- C-reactive protein
- Lactate dehydrogenase
- Liver function tests
- BUN, Creatinine and electrolytes
- Arterial Blood Gas
- Serum lactate
- Respiratory cultures
- ECG
- Chest X-ray (P.A view)

Optional investigations include:

- Blood cultures
- Procalcitonin
- Troponin
- Echocardiogram
- Pro-BNP
- IL-6
- Ferritin
- D-Dimer
- CT scan chest

NOTE:
Chest radiographs of patients with COVID-19 typically demonstrate bilateral air-space consolidation, though may be normal early in the disease. Chest CT images from patients with COVID-19 typically demonstrate bilateral, peripheral ground glass opacities.

Because this chest CT imaging pattern is non-specific and overlaps with other infections, a CT-scan alone should not be used to diagnose COVID-19. Moreover, routine CT scan chest should not be performed in patients with non-severe COVID-19.

Supportive care

The mainstay of management for severe and critical COVID-19 is oxygen therapy via nasal cannula or face mask. If available, high flow oxygen can also be used to maintain saturations above 94%. All patients with

low saturations should be placed in a prone position. For those not intubated, voluntary awake prone positioning should be encouraged for as long as the patient can manage. For patients on the ventilator, 12 to 15 hours of prone positioning should be attempted. Early intubation is not recommended, and patients should be intubated only when they fail non-invasive ventilation.

Steroids

Steroids have demonstrated a mortality reduction of 8.7% and 6.7% in severe and critical patients with COVID-19. However, use in non-severe patients may lead to an increase in mortality and should be avoided. The choice of steroid used is at the discretion of the clinician. However, dexamethasone is cheaper, easier to use in the outpatient setting, and has more potent glucocorticoid (anti-inflammatory) activity. On the other hand, methylprednisolone may be superior in patients in shock due to its mineralocorticoid activity. In patients with severe and critical disease, intravenous steroids are preferred. Also, doses of steroids required may be higher than mentioned in ARDS and shock.

Indication:
All patients with severe and critical COVID-19 (i.e., any patient requiring oxygen)
Dose:

Dexamethasone	6mg per day of dexamethasone (oral or intravenous)
Hydrocortisone	50mg every 8 hourly
Methylprednisolone	20mg every 12 hourly
Prednisone	40mg per day

(For extremes of weight use weight-based dosing of steroids)
Duration:
For 7 to 10 days
Longer treatment (with tapering dose) may be given in prolonged hypoxia and those with new onset fibrosis on CT

Anticoagulation

Patients with COVID-19 may be hypercoagulable, however, excessive anticoagulation may lead to a higher risk of bleeding. There is limited data at this point regarding enhanced anticoagulation and empiric therapeutic anticoagulation. Therefore, while empiric therapeutic anticoagulation is **not** recommended, a high index of suspicion must be kept for a Venous Thrombotic Event (VTE). While an elevated D-dimer may indicate a VTE, an isolated rise in D-dimer should not be an indication to start therapeutic anticoagulation but should prompt assessment for a VTE. Routine outpatient use of rivaroxaban is not recommended.

Prophylactic anticoagulation

Indication:

All admitted patients

Duration:

While admitted

Therapeutic anticoagulation

Indication (any of the following):

Documented presence of thromboembolic disease (such as ultrasound doppler or CT for PE)

Strong suspicion for thromboembolic disease when investigation cannot be done

Duration:

1 to 3 months (Switch to rivaroxaban on discharge if the diagnosis was presumptive)

If documented VTE follow standard guidelines for the duration

Prophylaxis Doses

Low Molecular Weight Heparin (LMWH)
Normal renal functions: 40 mg SC OD
CrCl < 30ml/min: 30mg SC OD

Unfractionated Heparin
Normal renal function: 5000 units SC 12hrly CrCl<30: Same dose

Therapeutic Doses

Low Molecular Weight Heparin (LMWH)
Normal renal functions: 1 mg/kg SC BD
CrCl < 30ml/min: 1mg/kg SC OD

Unfractionated Heparin
Treatment: 80 units/kg iv bolus then continuous infusion of 18 units/kg/hr with 6 hourly monitoring of APTT
CrCl < 30ml/min: Same dose

Remdesivir

Remdesivir is an antiviral agent and may be of benefit early in the disease i.e., during the viral phase of the illness. The utility of this drug late in the infection is limited and in one randomized controlled trial, no benefit was found beyond 10 days of illness. Moreover, the slight benefit of Remdesivir needs to be balanced against the cost of the drug. Also, while there is a more rapid improvement in patients on Remdesivir, there is **no** mortality benefit.

Indication:

Use only in severe COVID and in those with symptoms for 10 days or less.

- There is no benefit in using in patients with critical COVID or those with symptoms for over 10 days.
- Do not use if AST/ALT are 5 times upper limit of normal and use with caution if creatinine clearance is less than 30ml/min.
- Patients who are responding to supportive care and steroids may not always require Remdesivir.

Dose:

200 mg IV on day 1 followed by 100 mg IV daily on days 2 to 5

No dose adjustment in renal failure

Duration:

5 days.

Antibiotics

Antibiotics should only be used in cases where a bacterial infection is suspected, for example in cases with an elevated white cell count (in the absence of steroids). There is no role for prophylactic antibiotics to prevent secondary infections.

Investigational therapy

Other treatment modalities including (but not limited to) convalescent plasma, IVIG, plasmapheresis, ivermectin, or famotidine should be used only in the setting of a research protocol which includes consent and safety oversight.

Management of patients with refractory hypoxia or worsening symptoms

Patients with COVID-19 may worsen despite therapy or may worsen after initial improvement. However, the hypoxia in COVID-19 may be prolonged and if static, no additional therapy beyond supportive care is required. The following reasons may be looked for in such patients with refractory or worsening symptoms.

Ongoing hyper-inflammation

Patients with ongoing hyper-inflammation may present with continued worsening of oxygen requirements despite giving steroids. Unlike secondary infections and VTE, the patient will continue to worsen, without improvement over the 24 to 48 hours after steroids are initiated. There are no proven options for this, however, increasing steroids and/or adding tocilizumab have been tried.

Tocilizumab is reserved only in patients who have failed steroids and continue to worsen despite this. The data on tocilizumab is evolving, with few studies showing benefit while others do not. However, based on local data, the risk of infection is extremely high, and the drug must be used with caution. Tocilizumab must also not be used in patients with static respiratory status and isolated worsening of inflammatory markers. The dose is 400mg for patients weighing up to 80 kg.

Weight-based dosing at 4 to 8 mg/kg (with a maximum dose of 800 mg) should be used at extremes of age. A second dose is not recommended due to the increased risk of infection.

Contraindications include active TB, herpes zoster, sepsis, and positive blood cultures, suspected GI perforation, multiple sclerosis, allergy to Tocilizumab, ALT > 5 times or Bilirubin > 2mg/dl, ANC <2000, thrombocytopenia <50, or pregnancy.

Secondary infections

Secondary infections typically occur after the second week of illness. Early secondary infections are not common and therefore empiric antibiotics on presentations are not recommended. However, in patients who develop new hypoxia, especially with new infiltrates on the chest x-ray, new onset fever or rising total leucocyte count should be evaluated for secondary bacterial pneumonia. The choice of antibiotics will depend on the local antibiogram and should be dictated by the sputum culture. Empiric options, till cultures return, include vancomycin with either piperacillin-tazobactam (in antipseudomonal doses) or meropenem.

A newly identified entity, COVID Associated Pulmonary Aspergillosis (CAPA) has also been described. CAPA should be considered in patients with a new infiltrate and hypoxia and fever, without leukocytosis or bacterial growth in the sputum culture. Tests like Galactomannan and beta-D Glucan do not appear to be helpful in diagnosis and are often negative. The drug of choice for CAPA is voriconazole.

Venous Thrombotic Event

Pulmonary embolism and Deep Vein Thrombosis may occur more frequently in patients with COVID-19. VTE should be suspected in patients with a sudden worsening in oxygenation without worsening in the chest x-ray and white blood cell counts. D-dimer may be helpful if this is normal as this essentially rules out a VTE. However, if the D-dimer is elevated, further investigations may be warranted (ultrasound doppler or CT scan for PE). If these cannot be performed, therapeutic anticoagulation can be offered if there are no risks for bleeding.

Pulmonary edema

As severe COVID-19 is more common in individuals with existing comorbid conditions and SARS CoV-2 may also cause myocarditis; pulmonary edema should also be considered as a possible cause of failure to improve oxygenation. Patients with ARDS should be kept in a negative balance and in case of new infiltrates without evidence of infection a trial of diuresis may be considered.

Other causes

In patients with critical COVID and new fever, other causes of infection should be evaluated including central line infection and urinary tract infections. Bowl ischemia may occur and may be the cause of unexplained acidosis.

Guidelines for discharge from inpatient facilities

When deciding to discharge a patient, the team should take into consideration the time since onset of initial symptoms, as patients within 8 to 12 days of symptom onset are at the highest risk for complications. In addition to meeting the main criteria listed below, patients who received biologics (e.g. tocilizumab) during the current hospitalization should be monitored in the hospital for at least 48 hours after treatment initiation.

Clinical criteria for discharge to home include:

1. Overall improvement in the fever curve without antipyretics.
   If possible, the patient should have no fever spikes ≥ 101 F for ≥ 48 hours
2. Improved or stable respiratory symptoms (e.g. improved shortness of breath or cough)
3. Less than 3% decline in saturations on activity, and a decreasing oxygen requirement.

For patients who have not completed the recommended period for isolation, ensure that home isolation facility is available. Clearly write and inform the calculated day and date when the patient can come safely out of isolation.

Ongoing management

Post discharge, VTE prophylaxis is not routinely recommended. The decision to prescribe it should be individualized, taking into consideration the patient's risk factors, including reduced mobility, bleeding risks, and feasibility.

Those patients who were on steroids for greater than 10 days will require a tapering dose of oral steroids together with a proton pump inhibitor or an H2 blocker.
Home oxygen therapy may be considered in those patients that are hypoxemic at rest with oxygen saturation <90% on room air. Counsel these patients to increase their activities as tolerated and in small increments. Advise patients to sleep in a prone or in a left lateral position to improve oxygenation.

Discharge counseling

Patients will want to know if there are any dietary restrictions. Counsel them that there are no dietary restrictions, and the patient should continue with their normal diet. It is important to keep hydrated.
Some vitamins and minerals such as vitamin C, vitamin D, and zinc have been proposed for use in COVID-19, but there is no safety and efficacy data. Certainly, patients must avoid large doses of vitamins.
Take the time to counsel patients regarding any misgivings about the disease and try to dispel the stigma and anxiety around the disease.

Discontinuation of Isolation

Viral RNA shedding declines with the resolution of symptoms and may continue for days to weeks. However, the detection of RNA during convalescence **does not** indicate the presence of viable infectious virus.
Isolation precautions can therefore be discontinued in the following conditions
Asymptomatic individuals:
Ten days from the date of the test
Non-Severe COVID in immunocompetent individuals:
At least 3 days symptom-free AND at least 10 days from the start of symptoms
Severe or Critical COVID or immunocompromised*:
At least 3 days symptom-free AND at least 20 days from the start of symptoms
*Immunocompromised is defined as on chemotherapy for cancer, received a hematopoietic stem cell or solid organ transplant within one-year, untreated HIV infection with CD4 T lymphocyte count < 200, combined primary immunodeficiency disorder, and receipt of prednisone >20mg/day for more than 14 days
Note: For those with symptoms beyond 20 days or those on prolonged NIV or ventilator, 2 consecutive negative PCR, a minimum of one day apart may be done to discontinue isolation.

Long COVID

In some patients, the symptoms of COVID-19 may persist for a prolonged period. The exact terminology (“Long COVID”, “Post-COVID syndrome”, “Long Haul COVID”) is under consideration. Similarly, no diagnostic criteria have been established as yet. Symptoms are variable and include low-grade fever, fatigue, difficulty in breathing, joint pains, and chest pain and may be severe enough to affect the quality of life. Management of Long Term COVID is difficult. Certain symptoms such as fever, joint pains, and fatigue may improve with a course of NSAIDs. Anxiety and difficulty breathing may respond to benzodiazepines. For fatigue, graded, gradual increase in activity may help.

Reinfection

Reinfection with SARS CoV-2 has now been documented with unknown frequency. Moreover, it is unknown whether the second infection is more or less severe than the first. Exact definitions for reinfection are being developed. However, based on current knowledge, reinfection should be considered in patients who have a new onset of symptoms with a positive PCR 3 months after complete recovery. The presence or absence of antibodies after the first infection may not predict if the second infection will occur. It is therefore important to stress the importance of preventative measures in all patients who have recovered. Management of reinfection is the same as in the first infection.

Note: The above recommendations are being regularly reviewed by the Ministry of National Health Services, Regulations & Coordination and will be updated based on the international & national recommendations and best practices.

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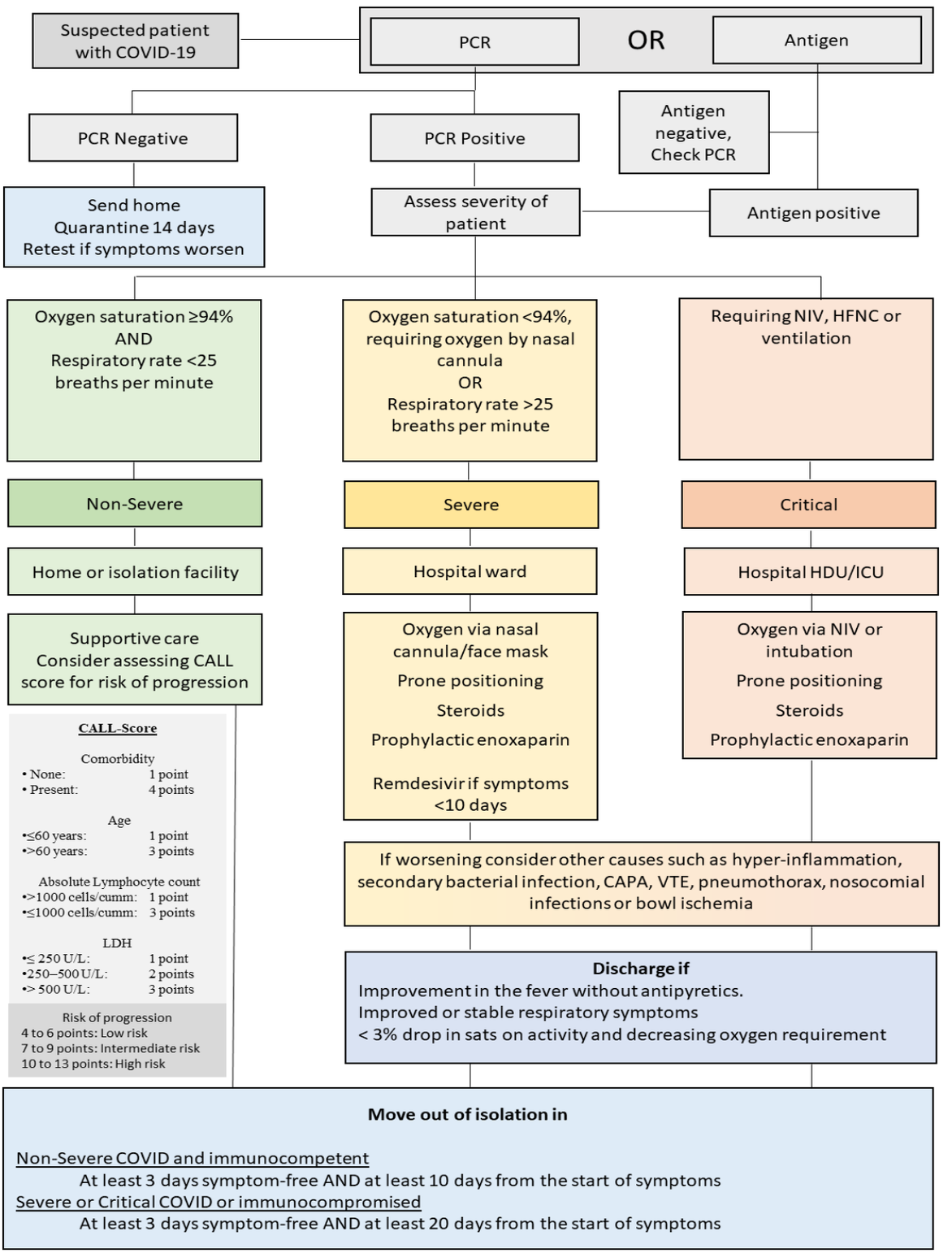
Annexure 1

Summary algorithm of COVID management



Annexure 2

Therapeutic agent	When to use	When not to use
Steroids	Severe or critical patients	Non-Severe or asymptomatic patients
Prophylactic anticoagulation	All hospitalized patients	Non-Severe or asymptomatic patients
Therapeutic anticoagulation	Proven or high suspicion of VTE	Patients with isolated elevated D-dimers or no evidence of VTE
Rivaroxaban	As continuation therapy when therapeutic anticoagulation was given	Non-Severe or asymptomatic patients
Remdesivir	Severe patients with less than 10 days of symptoms	Non-Severe, asymptomatic or, critical patients or in whom symptoms are longer than 10 days
sAntibiotics	Proven or strong suspicion of secondary infection	For "prevention" of secondary infections or in patients with no clear evidence of bacterial infection
Tocilizumab	Patients who have worsened despite the initial 24 to 48 hours of steroids	Patients who have not received a trial of steroids or with elevated markers only
Multivitamins	In patients who may be nutritionally depleted or have poor intake	As part of routine care in COVID-19
IVIG	As part of a clinical trial	Outside a clinical trial
Plasmapheresis	As part of a clinical trial	Outside a clinical trial
Chloroquine/HCQ	As part of a clinical trial	Outside a clinical trial
Ivermectin	As part of a clinical trial	Outside a clinical trial