INDUS
HOSPITAL
QUALITY CARE - FREE OF COST

THE INDUS HOSPITAL

BRIEF COVID -19 TREATMENT GUIDE

FOR ADULTS

CONTRIBUTIONS

Developed by Dr. Samreen Sarfaraz (Consultant Adult Infectious Diseases) at the Indus Hospital, Karachi with contributions from Professor Sohail Akhter (Pulmonologist) at the Indus Hospital, Karachi for reviewing and editing.

We are thankful to Sada Abbas, Assistant Manager, CRD for her help in designing the guidelines.

INDUS HOSPITAL
QUALITY CARE - FREE OF COST

CONTENTS

1. CATEGORIZATION

Patients can be categorized into asymptomatic, non-severe, severe, or critical COVID-19 based on their clinical presentation. As the disease progresses, the severity may change.

1.1 ASYMPTOMATIC

SARS CoV2 infection (PCR positive), but with no symptoms. Some asymptomatic patients may be pre-symptomatic if tested early (e.g. as part of contact tracing), hence they should monitor themselves for symptom development for a week.

1.2 NON-SEVERE

Oxygen saturation of 94% or greater and respiratory rate of less than 25 breaths/minute. These are further subdivided into:

1. **MILD**

   Patients with symptoms consistent with COVID-19 e.g. fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but without chest involvement i.e. dyspnea or abnormal chest findings.

2. **MODERATE**

   Patients who have dyspnea with/without clinical signs of lower respiratory tract infection (e.g. crepitation, bronchial breathing) or have radiographic evidence of pulmonary involvement (e.g. ground-glass opacities, infiltrates, consolidations).

1.3 SEVERE

Oxygen saturation <94% or respiratory rate of over 25 breaths/minute, which can be maintained by nasal cannulation or simple face-mask and there is no need for non-invasive ventilation (NIV), High Flow Nasal Cannula (HFNC), or mechanical ventilation (MV).

1.4 CRITICAL

Respiratory compromise severe enough to require NIV (including CPAP or BiPAP), HFNC or, MV, septic shock, and/or multiple organ dysfunction.

2. INVESTIGATIONS

2.1 ASYMPTOMATIC

No investigations required

2.2 NON-SEVERE DISEASE

No investigations are needed in mild disease. Investigations are only indicated in patients complaining of shortness of breath or having abnormal chest signs, persistent high-grade fever beyond 5-7 days, or those showing features suggestive of disease progression.

Only the following should be done as part of evaluation:

- Complete blood count (CBC)
- C-reactive protein (CRP)
- Lactate dehydrogenase (LDH)
- Chest X-ray (PA view)

2.3 SEVERE / CRITICAL DISEASE

FOR ALL PATIENTS

- CBC
- C-reactive protein
- Lactate dehydrogenase
- Liver function tests
- BUN Creatinine and electrolytes
- Arterial Blood Gases
- Serum lactate
- ECG
- Chest X-ray (PA view)

OPTIONAL INVESTIGATIONS (IN SELECTED CASES)

- Blood cultures: Only if bacterial co-infection is suspected
- Procalcitonin: Only if bacterial co-infection is suspected e.g. based on raised TLC, to decide if antibiotics are indicated.
- Troponin
- Echo
- Pro-BNP
- IL-6
- Ferritin
- D-Dimer
- CT scan chest

3. MANAGEMENT

3.1 ASYMPTOMATIC PATIENTS

They are infectious, and need home isolation for 10 days from the date of testing. If symptoms develop during this time, de-isolation can only be done once they have settled, for 3 days (see section on de-isolation).

There is currently no approved pre-emptive therapy which may prevent from developing symptoms. These include multivitamins.

3.2 NON-SEVERE DISEASE

1. **MILD**

- Should be managed at home isolation with symptomatic relief only e.g. Paracetamol for fever; anti-histamines, lozenges or gargles for sore throat or cough; ORS for diarrhea.
- Hydration and rest are important.
- There is no role of anti-infectives including Azithromycin, Hydroxychloroquine/ Chloroquine, Ivermectin, Doxycycline, Cefixime, Levofloxacin, or Moxifloxacin. Antibacterials have no benefit in viral infections, can result in side effects, and increase antimicrobial resistance. Routine outpatient use of aspirin or rivaroxaban is not recommended.
- Oxygen saturation is better monitored 2 to 3 times a day while awake (less frequently in young healthy people), especially post exertion.
  If it begins to reach 94% or less (even if transient for a few minutes, or post-exertion), the patient should be instructed to seek medical help.

2. **MODERATE**

- These patients, while being managed at home, need monitoring for deterioration with frequent saturation checks including post exertion.
- Those who are immunocompromised or with severe co-morbids, should ideally be admitted to a hospital for observation (if bed space allows).
- Risk stratification using the CALL score (Comorbids, Age, Lymphocytes, LDH) may help decide on how closely patients should be monitored. This score is calculated on initial labs and not on serial lab values.
- 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)
- A 6-minute walk test (or pulse oximetry post-exertion) can be done to identify; drop in saturation to 4% below initial reading, or below 90%, increase in dyspnea or tachycardia (pulse >110/min) points to increasing severity.
- Patients with moderate disease do not require steroids, antibiotics, or anti-coagulants.
- Steroids can potentially increase viral shedding and have not been shown to benefit patients with normal oxygen saturation and respiratory rate.
- The decision regarding anticoagulation and steroids should not be based on inflammatory markers or D-Dimers alone
- Those moderate cases with CALL score ranging from 9-13 and clinically deemed at high risk for progression, may be considered for **Remdesivir therapy**, provided duration of illness is 10 days or less in an attempt to halt disease progression. (see details below)

CALL-Score	Comorbidity*	Age	Lymphocyte	LDH
	• None: 1 point • Present: 4 points	•≤60 years: 1 point •>60 years: 3 points	•>1.0 × 109/L: 1 point •≤1.0 × 109/L: 3 points	•≤250 U/L: 1 point •250–500 U/L: 2 points •>500 U/L: 3 points
	*Comorbidities include HTN, DM, cardiovascular disease, chronic kidney disease, chronic liver disease , chronic lung disease and HI V			

3.3 SEVERE DISEASE

1. These patients should ideally be admitted to a COVID-19 unit (shortage of beds as is observed, may however mean that many such patients have to be managed at home).

2. Mainstay of management for severe disease is oxygen therapy via nasal cannula or face mask. to maintain saturation above 94%.
Patients should be placed in a prone position for as long as they can manage.

3. **Steroids** have demonstrated a mortality reduction in several RCTs in severe coronavirus patients. The benefits demonstrated are a class effect rather than due to any particular drug. However, dexamethasone is preferred as it is cheap, long-acting with potent glucocorticoid activity. Methyl-prednisolone may be superior in patients with shock due to its mineralocorticoid activity.

   INDICATION:
   Any COVID-19 patient requiring oxygen

   DOSE:
   Dexamethasone: 6-8 mg per day. (IV preferred)
   Hydrocortisone: 50 mg every 8 hourly
   Methylprednisolone: 20 mg every 12 hourly
   Prednisone: 40 mg per day

   NOTE:
   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.

4. **Remdesivir**, an antiviral agent, found to be beneficial during the viral phase i.e. first 10 days of illness. If a patient is already improving on steroids and oxygen therapy, he may not require Remdesivir.

   INDICATION:
   Only in severe COVID-19 with symptoms for 10 days or less. (see also in moderate disease above)

   CONTRA-INDICATION:
   AST/ALT 5 times upper limit of normal. Use with caution if Creatinine clearance is less than 30ml/min.

   DOSE:
   200 mg IV on day 1, followed by 100 mg IV daily on days 2 to 5. No dose adjustment in renal failure.

5. **Anticoagulation**: Patients with severe COVID-19 are hypercoagulable and prophylactic anticoagulation is recommended in all patients provided they don't have venous thromboembolism (VTE). While it has been tried, there is limited data at this point to suggest the benefit of enhanced anticoagulation and empiric therapeutic anticoagulation. An isolated rise in D-dimer should not be an indication to start therapeutic anticoagulation but should prompt assessment for a VTE.

   - Prophylaxis Doses

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

     Unfractionated Heparin
     - Normal renal function: 5000 units S/C BD
     - CrCl<30: Same dose

   DURATION
   Till discharge. Patients discharged on home oxygen will require prophylactic anticoagulation at home until they are off oxygen and mobile again. At discharge, a switch to oral rivaroxaban 10mg OD can be done for such patients.

- Therapeutic anticoagulation

  Indicated if there is documented presence of VTE (e.g. CT evidence of PE), OR strong suspicion for thromboembolic disease when investigation cannot be done

  Therapeutic Doses:

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

  Unfractionated Heparin
  - o Treatment: 80 units/kg iv bolus then continuous infusion of 18 units/kg/hour with 6 hourly monitoring of APTT
  - o CrCl < 30ml/min: Same dose
  - o Duration: If documented VTE follows standard guidelines. For presumed VTE, continue anticoagulation for 1-3 months

6. **Antibiotics** should only be used in cases where a bacterial infection is clinically suspected. There is no role of prophylactic antibiotics to prevent secondary infections.

3.4 CRITICAL COVID-19 CASES

1. **Oxygenation:** Maintain saturation around 94% with high flow oxygen, NIV, or MV. Early intubation and MV has not shown to be beneficial and should be reserved for those who fail on NIV.
   Proning for 14-16 hours is helpful.

2. **Inotropic support** is indicated for refractory shock.

3. **Steroids:** Are indicated. The dose may be higher and duration more prolonged than in severe cases depending on the severity of ARDS.

4. **Anticoagulation:** Prophylactic anticoagulation is indicated for all patients. Therapeutic anticoagulation to be given only if VTE is suspected or proven.

5. **Trial Drugs:**

   REMDISIVIR
   No mortality benefit has been documented in any study for critical COVID-19 patients.

   TOCILIZUMAB OR IVIG
   There is no benefit of these drugs in the management of ventilated critical cases as per international and TIH data.

6. **Antibiotics:** Empiric antibiotics should not be given as routine, including in patients on NIV or MV. Antibiotics should only be given when there is a suspicion of bacterial infection. A thorough search for the focus of infection should be done and appropriate microbiological cultures sent to guide empirical antibiotic therapy. A daily review for the need and duration of antibiotics should be done if therapy is commenced. Despite all supportive measures, patients with critical COVID-19 may worsen without improvement or after initial improvement.

CAUSES OF REFRACTORY/ PERSISTENT HYPOXIA

Hypoxia in severe/critical cases 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 due to COVID-19 may present with continued worsening of oxygen requirements despite giving steroids for over 24 to 48 hours. There are no proven options for this; increasing steroids and/or tocilizumab (TCZ) have been tried as Salvage therapy. The data on tocilizumab is evolving, with few studies showing benefit while the majority do not. The Indus Hospital's data showed a high risk of infection; the drug must be used with caution. Tocilizumab is also not useful in patients with static respiratory status and isolated worsening of inflammatory markers.

DOSE OF TCZ:
400 mg for patients up to 80 kg weight. Weight-based dosing at 4 to 8 mg/kg (with a maximum dose of 800 mg) should be used at extremes of weight. A second dose is not recommended due to the increased risk of infection.

CONTRAINDICATIONS:
Active TB, Zoster, sepsis, and positive blood culture, suspected GI perforation, multiple sclerosis, allergy to TCZ, ALT > 5 times normal or Total Bilirubin > 2, ANC <2000, thrombocytopenia <50, or pregnancy.

SECONDARY BACTERIAL INFECTIONS

Typically occur after the second week of illness. Patients who develop increasing, unexplained hypoxia coupled with new infiltrates on the chest x-ray, recurrence of fever, and/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/ tracheal culture. Empiric options, till cultures return, include vancomycin with either piperacillin-tazobactam (in antipseudomonal doses) or meropenem. Prompt de-escalation should be done in light of cultures. Antibiotics should be given for a finite duration and a daily review of need, duration, and side effects is required.

COVID-19 ASSOCIATED PULMONARY ASPERGILLOSIS (CAPA)

A recently described entity which should be considered in patients with a new infiltrate, hypoxia, and fever without leucocytosis or bacterial growth in sputum/ tracheal culture. 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 (VTE)

VTE should be suspected in patients with a sudden worsening in oxygenation without worsening in the chest X-Ray and white blood cell counts. A normal D-Dimer helps in exclusion of VTE but if elevated, is alone not sufficient to make a diagnosis and further investigations are warranted e.g CT-pulmonary angiogram and ultra-sound doppler. If these cannot be performed, therapeutic anticoagulation can be considered if there are no risks for bleeding in patients with strong clinical suspicion.

PULMONARY EDEMA

Is an important differential in patients who fail to improve oxygenation despite supportive care. Cases of direct myocardial injury, myocarditis, and myocardial infarction have been reported with COVID-19 and most patients suffering from severe/critical disease have underlying co-morbids which make them vulnerable to cardiac complications. When suspected it should be investigated and managed appropriately.

LONG COVID-19 SYNDROME

In some patients, the symptoms of COVID-19 may persist for a prolonged period (many weeks) and may be severe enough to affect the quality of life. No diagnostic criteria has been established as yet and no therapy proven in trials. Symptoms are variable and include low-grade fever, fatigue, difficulty in breathing, chest pain, joint pains, cognitive defects, and mood changes. Certain symptoms such as fever, joint pains, and fatigue may improve with a course of NSAIDs. For fatigue, graded, gradual increase in activity may help.

REINFECTION

Reinfection with SARS CoV2 has been documented though very few proven cases. It cannot be predicted if the second infection is more or less severe than the first. Based on current knowledge, reinfection is defined as a new onset of symptoms suggestive of COVID-19 with a positive PCR, 3 months or more after complete recovery. Presence or absence of antibodies after the first infection may not predict if the second infection will occur. Management of reinfection is the same as in the first infection.

DISCONTINUATION OF ISOLATION

The detection of RNA during convalescence does not indicate the presence of a viable infectious virus. Isolation precautions should therefore be discontinued on a symptom-based de-isolation strategy, which applies equally to the general public and all health care workers (including those dealing with immunocompromised patients). The following is recommended:

1. Asymptomatic individuals: Ten days from the date of the positive test.

2. Non-Severe COVID-19 in immunocompetent individuals: At least 3 days symptom-free AND at least 10 days from the start of symptoms. Fever is the symptom to consider in this context, as cough, fatigue, and anorexia may take longer to subside.

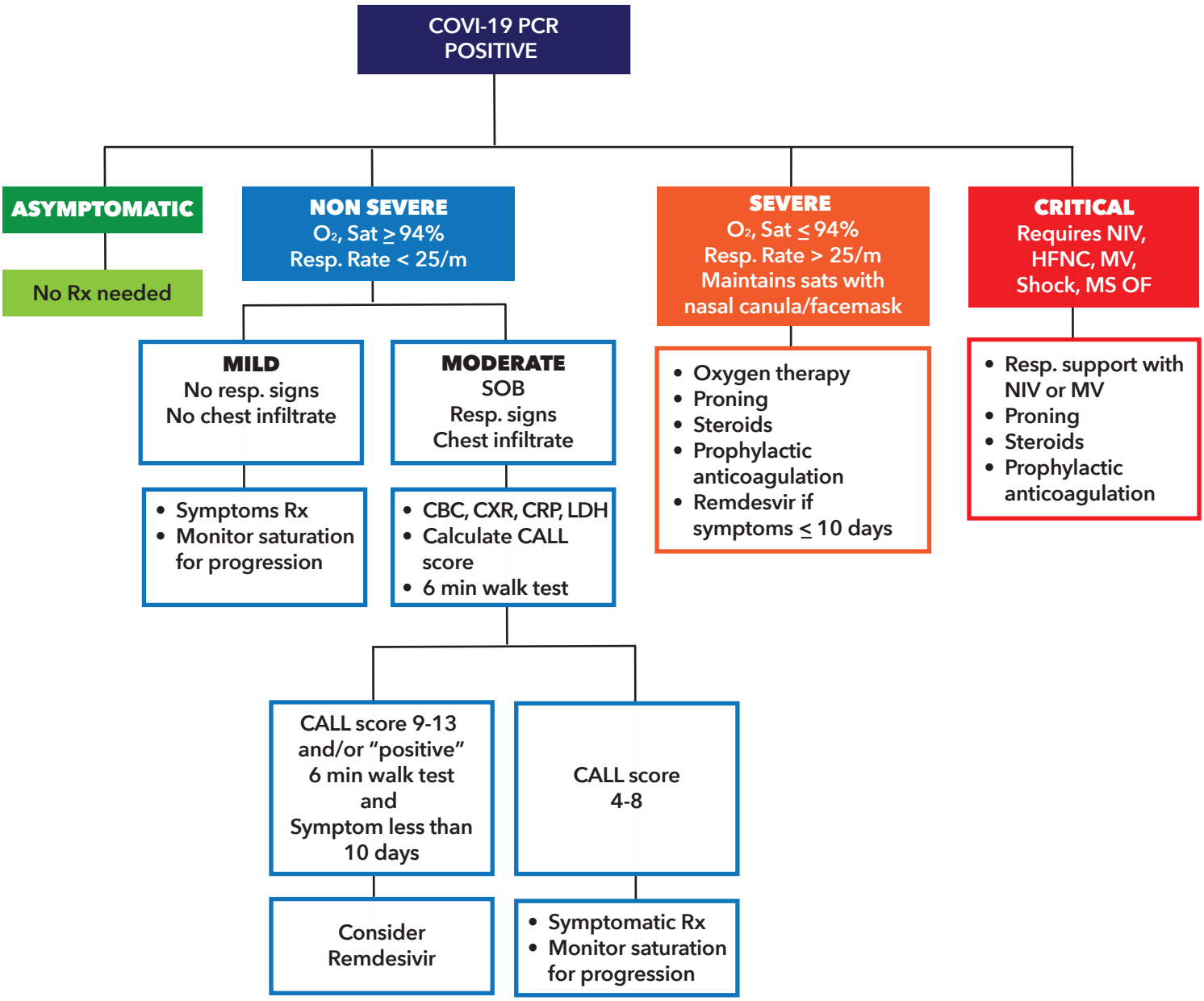
3. Severe or Critical COVID-19 and immunocompromised*: At least 3 days symptom-free AND at least 20 days from the start of symptoms.
   *(*Immunocompromised subject is defined as: on chemotherapy for cancer; recipient of hematopoietic stem cell or solid organ transplant within one year; untreated HIV infection with CD4 count < 200; combined primary immunodeficiency disorder; and on prednisone >20mg/day for more than 14 days.)*

Role of test-based de-isolation
In the following 2 cases only, there is a need for 2 consecutive negative PCR, minimum of one day apart.

1. Long COVID syndrome

2. Those on prolonged NIV or ventilator for shifting out of isolation to normal ICU/HDU

ANNEXURE


COVI-19 PCR POSITIVE
ASYMPTOMATIC
No Rx needed
NON SEVERE
O2, Sat ≥ 94%
Resp. Rate < 25/m
SEVERE
O2, Sat ≤ 94%
Resp. Rate > 25/m
Maintains sats with nasal canula/facemask
CRITICAL
Requires NIV, HFNC, MV, Shock, MS OF
MILD
No resp. signs
No chest infiltrate
MODERATE
SOB
Resp. signs
Chest infiltrate
• Symptoms Rx
• Monitor saturation for progression
• CBC, CXR, CRP, LDH
• Calculate CALL score
• 6 min walk test
• Oxygen therapy
• Proning
• Steroids
• Prophylactic anticoagulation
• Remdesvir if symptoms ≤ 10 days
• Resp. support with NIV or MV
• Proning
• Steroids
• Prophylactic anticoagulation
CALL score 9-13 and/or "positive" 6 min walk test and Symptom less than 10 days
CALL score 4-8
Consider Remdesivir
• Symptomatic Rx
• Monitor saturation for progression

REFERENCES

1. Adapted from National Clinical Management Guidelines for COVID-19 infection.

2. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19.
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

3. A living WHO guideline on drugs for COVID-19.
https://www.bmj.com/content/370/bmj.m3379

4. Criteria for releasing COVID-19 patients from isolation.
https://www.who.int/news-room/commentaries/detail/criteria-for-releasing-covid-19-patients-from-isolation

5. Duration of Isolation and Precautions for Adults with COVID-19.
https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html