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Medical Guidelines

Diagnosis and Management of COVID 19 as We Do in Pakistan

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Introduction

COVID-19 is caused by SARS-CoV-2 virus newest in the family of Corona viruses. It is mainly a respiratory virus and spreads through respiratory droplets. This virus typically causes a biphasic illness. In the first phase, also called viremic phase, virus enters our cells and multiplies. This phase typically lasts for 5-10 days, often with symptoms. Beyond day 10, 'live' virus is almost never found in the body in mild to moderate cases. The second phase occurs only in the 15-20% who develop moderate to severe disease (typically after the first 5-10 days). The second phase is due to dysregulated and excessive immune response. The maximum viral load and shedding occur around the first day of symptoms - after an incubation period of ~5 days. Since shedding starts before onset of symptoms, it spreads to other people before we can isolate the infected person.

CASE DEFINITIONS

Suspected Case

1: A patient with acute febrile illness (<14 days) and with ANY of the following symptoms

- Sore throat
- Cough (new onset or worsening of existing)
- Shortness of breath (new onset or worsening of existing)
- Flu like illness
- Headache
- Tiredness, body aches, fatigue
- Loss of sense of taste or smell
- Diarrhea, nausea or vomiting

v Altered mental status

- History of close contact with a confirmed or probable case of COVID-19
- History of residence in an area or travel to a country reporting local or community transmission* during past 14 days prior to symptoms onset

2: An asymptomatic patient with positive Antigen Rapid Diagnostic Testing (Antigen-RDT) for SARS-CoV-2, (PCR testing is required for confirmation)

Probable Case

Probable case is a suspect for which testing for COVID-19 is inconclusive or could not be performed for any reason or if there is high degree of clinical suspicion, and radiological findings suggestive of COVID-19 despite negative PCR.

Any unexplained death with respiratory distress as a terminal event with history of contact with confirmed or probable case of COVID-19 or a resident in an area reporting transmission of COVID pneumonia should also be considered as a probable case of COVID-19

Confirmed Case

A person with laboratory confirmation of COVID-19 infection by SARS-CoV2 RT- PCR or Antigen Rapid Diagnostic testing , irrespective of clinical signs and symptoms.

CLINICAL CLASSIFICATION

Patients can be classified into asymptomatic, mild, moderate, severe or critical based on their clinical presentation. Elderly and immune compromised patients may present with Atypical symptoms. In pregnant patients, pregnancy related symptoms may over-lap with COVID clinical presentation.

Asymptomatic

SARS CoV2 infection with no symptoms

Mild

Mild patients have symptoms suggestive of COVID-19 with stable vital signs and oxygen saturation is ≥ 93% at room air. Chest radiography shows no or minimal findings. Patients in this category have either no co morbidity or co-morbid in well controlled state that does not require hospitalization.

Moderate

Symptomatic patients with Hypoxia (Oxygen saturation while breathing room air and at rest ranging between 90% and 93%) and chest X-ray with infiltrates involving <50% of the lung fields are considered to be suffering from moderate disease.

Severe

In adults, with clinical features suggestive of pneumonia with Respiratory rate >30/min and signs of Severe Respiratory distress (i.e. accessory muscle use, inability to complete full sentences; central cyanosis, or presence of any other general danger signs). With severe hypoxia ($SpO_2 \leq 90\%$ on room air) fall in severe category. These patients usually have infiltrates involving >50% of lung fields.

Critical

Patients with acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy are labeled as critical COVID-19.

CRITERIA FOR ADMISSION

Asymptomatic and mild cases can be managed at home or isolation facility.

Patients with moderate disease should be admitted to a well ventilated isolation ward with oxygen availability and monitoring facility. Severe cases require admission to a high dependency unit (HDU) while critical disease should be managed in intensive care unit.

MANAGEMENT

Prophylaxis

There is no proven therapy to prevent a COVID-19 infection after exposure. There is no specific treatment for COVID-19 infection (including chloroquine, hydroxychloroquine, ivermectin, famotidine, montelukast, colchicine or any other drug or therapy).

Mild Disease

Mild cases should be treated with supportive care only. This includes acetaminophen for fever, oral hydration in case of diarrhea and antihistamines for cough sore throat and runny nose. Steam inhalation may also help sore throat and dry cough. Patients should be reassured that low-grade fever may persist for over a week. Fever may also be biphasic (that may recur after settling) and this does not require antibiotics.

Pulse oximetry should be checked every 4 to 6 hours and preferably after exertion as Oxygen Saturation may drop after activity prior to any changes at rest. Oxygen saturation may be monitored more frequently in the elderly and those with comorbidities. Nonspecific treatment (including steroids, chloroquine, hydroxychloroquine, azithromycin, antibiotics, ivermectin or, famotidine) is recommended for mild disease. Steroids may lead to worse outcomes with delaying of viral clearance if used in mild disease. In addition, increase mortality due to use of steroids in patients not requiring supplementary Oxygen has been reported.

Moderate, Severe, and Critical Disease

Patients with moderate disease should receive supportive therapy.

All patients must be assessed for the Cytokine Release Syndrome (CRS). Clinical features suggestive of CRF include:

- Persistent fever > 100 ºF
- Difficulty in breathing
- Progressive hypoxemia
- Increasing infiltrates on chest X-Ray

INVESTIGATIONS

Following investigations are suggested.

- Serum Ferritin
- C-reactive protein
- Lactate dehydrogenase
- D-Dimers
- Chest X-ray (P.A view)

Additional investigations indicated include.

- Liver Function Tests (LFTs)
- Serum Urea and Creatinine
- Serum electrolytes
- Blood cultures
- Respiratory Cultures
- Blood glucose levels
- ECG
- Arterial Blood Gas (for severe and critical cases)
- Serum lactate (for severe and critical cases)
- Procalcitonin
- Troponin
- Echocardiography
- Pro-BNP
- IL-6 levels
- HRCT scan chest

TREATMENT

1. Oxygen

1) Oxygen therapy delivered in escalating manner via nasal cannula, face mask and non-rebreather mask.
2) Preference should be given to HFNC (High Flow Nasal Cannula) if available.
3) Awake proning should be encouraged in cooperative patients.

2. Anticoagulation

Obtain at baseline and daily: CBC, INR, D-Dimers

Inclusion: All admitted patients with severe or critical COVID-19 **Exclusion:** High risk of bleeding as judged by treating physician	**Hold anticoagulation if:** Platelet count < 50,000 INR > 1.5 Current or recent bleeding

D-Dimers Value	Enoxaparin (LMWH)	Rivao-raxaban	Apixaban
<1000	40 mg S/C daily	15 mg once a day	2.5-mg twice a day
>1000	40 mg S/C twice a day	20 mg once a day	5 mg twice a day

If patient has documented thromboembolic disease (Ultrasound Doppler or CT for PE) give therapeutic dose of anticoagulation:

Enoxaprin 1 mg /kg 12 hourly for 1-3 months

For Renal compromised patients with cr. clearance <15 ml/min

Un-fractioned heparin is preferred. 80 units/kg IV bolus then continuous infusion of 18 units/kg/hr with 6 hourly monitoring of APTT

For morbid obesity with BMI > 40 kg/m2 increase prophylactic and therapeutic dose of anticoagulation by 30%

3. Steroids

Steroids have demonstrated a mortality reduction 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.

Patients must meet the minimal criteria listed in each column [for either Row A or Row B]		
Any ONE of these criteria	**PLUS any ONE of these signs at time of assessment**	**PLUS Any TWO of the following Lab Criteria**
A. Low physiologic reserve due to: **• Age ⩾60 years** **• Cardiomyopathy** **coronary artery disease** **• Lung disease** **• Organ transplant recipient** **• End stage renal disease (ESRD)**	• Fever ⩾39° C • Progressive hypoxemia requiring ≥10 liters of oxygen to maintain saturation of > 93% • Respiratory rate >30 breaths/min	**D-dimers** >1000 ng/mL (or >1mcg/ml) and rising in the last 24 hours **CRP level** >70 mg/L and rising in the last 24 hours **Serum Ferritin**>700 ng/mL and rising in the last 24 hours **LDH>**300 IU and rising in the last 24 hours
B. <60 years	• Fever >39^0 without antipyretics) • Progressive hypoxemia requiring ≥10 liters of oxygen to maintain saturation of > 93% • Respiratory rate >30 breaths/min	**D-dimer** >1000ng/mL (or >1mcg/ml) and rising in the last 24 hours **CRP level** >70 mg/L and rising in the last 24 hours **Serum Ferritin** >700 ng/mL and rising in the last 24 hours **LDH** >300 IU and rising in the last 24 hours

Dosing:

Tocilizumab: 4-8 mg/kg once intravenously (IV) over 60 minutes.

If no *clinical improvement* in CRS occurs after the first dose, an additional dose may be administered at an interval of at least 08 hours after the first dose

Maximum dose should not exceed 800 mg per infusion

Contraindications: Active TB, Herpes Zoster, Sepsis, GI Perforation, Multiple Sclerosis, Allergy to Tocilizumab, ALT levels>5 times, Platelets < 50,000, Severe Neutropenia and Pregnancy

Indications

1. All patients with severe and critical COVID-19 (i.e any patient requiring supplemental oxygen to maintain oxygen saturation of >93%)
2. CRP levels >70 mg/L and rising in the last 24 hours, in the absence of bacterial infection

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

7 to 10 days

Longer treatment (with tapering dose) may be given in prolonged hypoxia and those with new onset fibrosis on CT

4. Tocilizumab

Tocilizumab, an IL-6 inhibitor - has a narrow spectrum of action, which means that this agent will only help patients that fit certain criteria as mentioned below.

Complications; Patient who received Tocilizumab, in addition to steroids were more susceptible to bacterial and fungal Infections.

Unpublished data showed improvement in some selected inviduals, however in a recent double blind, Randomized controlled trial,Tocilizumab was not effective in preventing mechanical ventilation or death among moderately ill patients hospitalized due to COVID-19. (Stone et al NEJM 2020)

5. Antibiotics

Routine use of antibiotics is not recommended.

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 of prophylactic antibiotics to prevent a secondary infection.

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 leukocyte count, with neutrophilia 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.

6. Antifungals

Fungal Co-infections with Aspergillosis and invasive candidiasis being reported with increasing frequency among COVID patients, and it can be associated with progression of disease and worse outcome.

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 may be helpful in diagnosis.

The drug of choice for CAPA is voriconazole.

Amphotericin B to be used in patients of suspected Mucormycosis in the background of COVID diseases.

7. Remdesivir

Remdesivir is an antiviral agent and may be of benefit early in the disease i.e., during the viral phase of the illness (within 10 days). It may reduce the duration of symptoms from 15 days to 10 days.

WHO has issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients.

• 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.

Dose: 200 mg IV on day 1 followed by then 100 mg IV daily on days 2-5

8. Convalescent Plasma

Plasma therapy is still in investigation stage and should be used cautiously as part of clinical trial

Most of the trials have showed little or no benefit of convalescent plasma in improving outcome of the patient.

Vaccination in COVID-19

Vaccination

Vaccination remains the most effective tool for prevention of COVID -19. Though different vaccines have different efficacy rates ,but all vaacines provide protection from severe dengue and death. Vaccines currently available in Pakistan are Sinopharm and Sinovac (inactivated virus vaccine), Cansino Sputnik V and Astra Zeneca (viral vector vaccines) and Pfizer (m-RNA) vaccines.