Guidelines

Clinical Management Guidelines for COVID-19 Infections
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Objectives

The objectives of this document are

- To provide public health and health care professionals guidelines regarding the clinical management of the COVID-19 infection
- To provide a protocol on the practical steps to deal with COVID-19 cases
- This guideline is not intended to override the clinical decisions that will be made by clinicians providing individualized patient care.
- This guideline will be updated as more information becomes available

Testing Criteria

Viral Lab testing for COVID-19

Testing should be performed using RT-PCR. Preferable samples are nasopharyngeal (NP) or lower respiratory samples. Other samples include oropharyngeal and nasal samples, though these may not be as sensitive and may require 2 or more samples to avoid a false negative test. Serology (IgM/IgG tests) are NOT recommended as primary means for diagnosis. Symptoms will appear 2-14 days after exposure to the virus, however contact history is not required to decide on testing. Individuals with the following symptoms may qualify for testing.

Respiratory symptoms alone
- Cough
- Shortness of breath or difficulty breathing

Or at least two of these symptoms
- Fever
- Chills
- Repeated shaking with chills
- Muscle pain
- Headache
- Sore throat
- New loss of taste or smell

Testing is based on symptoms and priority is given to certain individuals

High Priority
- Hospitalized patients with symptoms
- Healthcare workers and workers in congregate living settings with symptoms
- Residents in long-term care facilities or other congregate living settings, including prisons, shelters and hostels, with symptoms
- Patients with radiological features suggestive of COVID even if asymptomatic or without typical symptoms
Priority

- Outpatients with symptoms of potential COVID-19 infection
- Healthcare workers without symptoms, but with a history of exposure to a COVID positive patient
- Persons without symptoms, but with a history of close contact with a COVID positive patient

Clinical classification of suspected or confirmed COVID-19 patients

Patients can be classified into asymptomatic, mild, moderate, severe or critical based on their presentation.

Asymptomatic
SARS CoV2 infection but with no symptoms

Mild
Presence of symptoms consistent with COVID as above without any hemodynamic compromise, need for oxygen or chest x-ray findings.
Oxygen saturation ≥94%

Moderate
Hypoxia (Oxygen saturation <94% but >90%) or chest X-ray with infiltrates involving <50% of the lung fields
No complications and manifestations related to severe condition

Severe
In adults, clinical signs of pneumonia (fever/ cough) plus, any of the following:
- Respiratory rate > 30
- Severe respiratory distress;
- SpO2 ≤ 90% on room air.
- Chest X-ray involving >50% of lung fields

Critical
Any of the three manifestations

1. ARDS
   Onset: Within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms.
   Chest imaging: (X-ray or CT scan): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.
   Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/edema if no risk factor presents
   Oxygenation impairment in adults
   - Mild ARDS: PaO2/FiO2: >200 mmHg and ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O).
   - Moderate ARDS: PaO2/FiO2 ≤ 200 mmHg and >100 mmHg (with PEEP≥ 5 cmH2O).
   - Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O)

2. Multiorgan dysfunction
Acute life-threatening organ dysfunction caused by a dysregulated host response to suspect or proven viral or bacterial infection. Signs of organ dysfunction include:

- Altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.

3. **Septic shock**
   Persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L

### Criteria for admission of suspected or confirmed COVID-19 patients

**Asymptomatic and mild disease**
Asymptomatic and mild 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 for isolation

Patients with mild or asymptomatic 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 hospital admission for observation if resources allow:

- Immunosuppressed (on long term steroids or other immunosuppression)
- 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.

**Moderate, severe and critical disease**
Patients with the above categories should be admitted to a hospital for further management.

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

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

### Management

**Prophylaxis**

*There is no role of prophylactic chloroquine or hydroxychloroquine at this time.* Both these drugs are being studied for treatment of COVID. The results thus far are not robust enough that either drugs can be clearly labeled as effective in treatment of COVID. Moreover, given the side-effects associated with use of chloroquine or hydroxychloroquine (especially chronic use), the limited stocks (for moderately sick) and the lack of data showing use will prevent the infection, prophylactic use is strongly discouraged.
Management of 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 rhinorrhea. There is a theoretical risk with the use of NSAIDS or ACE-inhibitors in COVID-19. However, clinical data regarding this is lacking and at this point, a strong recommendation to avoid or to continue these medications cannot be made.

No specific treatment (including chloroquine hydroxychloroquine, azithromycin, ivermectin or, famotidine) is recommended for asymptomatic or mild disease.

Management of moderate, severe, and critical disease
Patients with moderate disease should receive supportive therapy. All patients must be assessed for the Cytokine Release Syndrome (CRS). For this the following investigations are suggested

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

Additional investigations indicated include

- Liver function tests
- BUN Creatinine and electrolytes
- Blood cultures
- Blood glucose levels
- EKG
- Arterial Blood Gas (for severe and critical cases)
- Serum lactate (for severe and critical cases)
- Respiratory cultures (for severe and critical cases)

Optional investigations include

- Procalcitonin
- Troponin
- Echo
- Pro-BNP
- IL-6
- CT scan chest

NOTE:
Chest radiographs of patients with COVID-19 typically demonstrate bilateral air-space consolidation, though patients may have unremarkable chest radiographs 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, the diagnostic value of chest CT imaging for COVID-19 may be low and dependent upon radiographic interpretation. Patients who present early e.g. within two days of diagnosis may have a normal CT and there might be presence of CT abnormalities in patients prior to the detection of SARS-CoV-2 RNA. Given the variability in chest imaging findings, chest radiograph or CT alone is not recommended for the diagnosis of COVID-19. The American College of Radiology also does not recommend CT for screening or as a first-line test for diagnosis of COVID-19.
Specific therapy

Supportive care
The mainstay of management for COVID-19 is oxygen therapy via nasal cannula or face mask. If available high flow oxygen can also be used to maintain saturation. All patients with low saturations should be placed in the 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.

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 steroid) or procalcitonin. There is no role of prophylactic antibiotics to prevent a secondary infection.

Hydroxychloroquine and chloroquine
These are no longer recommended given recent studies showing potential harm and lack of clear benefit.

Anticoagulation
As patients with COVID-19 may be hypercoagulable, anticoagulation plays an important role in therapy. For all doses mentioned below, adjustment will be required in case of renal impairment or morbid obesity (BMI ≥ 40kg/m²)

If the patient was already on oral anticoagulation for another indication (such as atrial fibrillation):
- In moderate disease: Continue same
- In severe/critical: Consider switching to parenteral therapy

If the patient was not on anticoagulation at the time of admission
- In moderate disease: Start standard DVT prophylaxis (enoxaparin 40 mg once daily once daily)
- If Severe disease: Start aggressive prophylaxis (Enoxaparin 40mg every 12 hourly)

Indications for therapeutic anticoagulation (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
- D-Dimer over 3 times normal upper limits

Dose: Enoxaparin 1mg/kg every 12 hourly
Duration: 1 to 3 months (Switch to rivaroxaban on discharge if diagnosis was presumptive or based on D-dimer elevation)

Dose: Rivoxaban10 mg OD (once a day)
If documented VTE follow standard guidelines for duration

Dose adjustment

Acute Renal Failure
Prophylaxis:
**Remdesivir**
Indication: Moderate and severe COVID requiring oxygen therapy regardless of if CRS is present. This can also be given in critical COVID, however, with the available data, it is unlikely to be of benefit in this patient population
**Dose**: 200 mg IV on day 1 followed by then 100 mg IV daily on days 2-5

**Remdesivir**
Indication: Moderate and severe COVID requiring oxygen therapy regardless of if CRS is present. This can also be given in critical COVID, however, with the available data, it is unlikely to be of benefit in this patient population.

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

**Therapy in Cytokine Release Syndrome (CRS)**
Cytokine Release Syndrome is defined as ANY of the following in the presence of moderate, severe or critical disease:
1. Ferritin >1000 mcg/L and rising in last 24 hours
2. Ferritin >2000 mcg/L in patient requiring high flow oxygen or ventilation
3. Lymphopenia <800 cells/ml, or lymphocyte percentage <20% or Neutrophil to lymphocyte ratio of >5

and two of the following:
- Ferritin >700 mcg/mL and rising in the last 24 hours
- LDH > 300 IU and rising in the last 24 hours
- D-Dimer >1000ng/mL (or >1mcg/ml) and rising in the last 24 hours
- CRP >70 mg/L (or >10 hsCRP) and rising in the last 24 hours, in absence of bacterial infection
- If any 3 presents on admission no need to document rise

**Steroids**
In early CRS steroids are preferred.
**Dose**: 0.5 to 1 mg/kg/d of methyl prednisone or equivalent for 5 days
**Avoid** if no evidence of CRS

**Tocilizumab**
Reserved for patients in whom worsening occurs despite steroids or those who present as severe/critical disease in CRS. As tocilizumab greatly increases the risk of secondary infection, only use in cases of confirmed CRS
**Dose**: 4 to 8 mg/kg iv. Not over 800mg (maximum).
Can repeat in 12 hours once only
**Weight-based tocilizumab dose**
Standard dosing for 80mg vial

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50kg</td>
<td>320</td>
</tr>
<tr>
<td>51-70kg</td>
<td>480</td>
</tr>
<tr>
<td>71-90kg</td>
<td>640</td>
</tr>
<tr>
<td>&gt;90kg</td>
<td>800</td>
</tr>
</tbody>
</table>

Standard dose for prefilled syringes (IV use) 162mg/0.9 ml

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50kg</td>
<td>2 syringes (324mg)</td>
</tr>
<tr>
<td>51-70kg</td>
<td>3 syringes (486 mg)</td>
</tr>
<tr>
<td>71-90kg</td>
<td>4 syringes (648 mg)</td>
</tr>
<tr>
<td>&gt;90kg</td>
<td>5 syringes (810mg)</td>
</tr>
</tbody>
</table>

Contraindications:
- Active TB
- Zoster
- Sepsis and positive blood culture
- Suspected GI perforation
- Multiple Sclerosis
- Allergy to Tocilizumab
- ALT > 5 times or Bilirubin > 2
- ANC <2000 or Thrombocytopenia <50
- Pregnancy (relative contraindication)

Investigational therapy

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

Discontinuation of Isolation

There are no data regarding re-infection with SARS-CoV-2 after recovery from COVID-19. Viral RNA shedding declines with 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:

In those who are symptomatic, the following symptom-based strategy is recommended:
- At least 10 days from the start of symptoms AND at least 3 days after resolution of symptoms (fever and respiratory symptoms)

In those who are asymptomatic, the following time-based strategy is recommended:
- Ten days from the date of the test

Note: A test to document cure is not required in the above-mentioned patients.

However, for the following two consecutive negative PCR tests a minimum of one day apart are required to discontinue isolation:
1. Immunocompromised patients
2. Those living in congregations such as jails, dorms or madrasas (if going back to the congregation
3. Healthcare workers dealing with immunocompromised patients

Test-based isolation discontinuation may also be done on the discretion of the treating physician

Disclaimer:

1. This document is a guideline and NOT a substitute for good clinical practice and judgment of clinician for individual cases
2. Literature is rapidly evolving & this document may not necessarily reflect all the updated day to day information.

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.

The Ministry acknowledges the contribution Dr Syed Faisal Mahmood, Dr Nousheen Nasir, Dr Samreen Sarfaraz, Dr Shelha Baqi, Dr Fyezah Jehan, Dr Farah Qamar, Dr Farheen Ali, Dr Ejaz Ahmed Khan, Dr Muneeba Ahsan, Dr Salma Abbas, Dr Faisal Sultan, Dr Sunil Dodani, Dr Amjad Mahboob, Dr Naseem Akhtar, Dr Asma Adil, Dr Javed Bhutta, Dr Urooj Aqeel and HSA/ HPSIU/ NIH team to compile these guidelines.

References:


For more information, please contact:

HSA/ HPSIU/ NIH, PM National Health Complex, Islamabad

http://covid.gov.pk/

Annexure

Summary algorithm of COVID management

Patient fulfilling testing criteria

PCR Negative

Send home
Quarantine 14 days
Retest if symptoms worsen

No hemodynamic
compromise, need for
oxygen or chest x-ray
findings.
AND
Oxygen saturation ≥94%

Mild or asymptomatic

Home or isolation facility

Supportive care
Call if any worsening

PCR Positive

Assess severity of
patient

Hypoxia (Oxygen saturation <94% but >90%)
OR
Chest X-ray with infiltrates involving <50% of the lung fields
AND
No complications and manifestations related to severe condition

Moderate

Hospital ward

Oxygen via nasal cannula/face mask
Prone positioning
Anticoagulation
Watch for CRS

Evidence of CRS

Steroids
Tocilizumab (if severe or failure of steroids)

At least 10 days since start of symptoms
AND
At least 3 days since complete resolution of fever and respiratory symptoms
AND
Not immunocompromised/HCW/Lives in a congregation

Move out of isolation

Signs of pneumonia plus
any of the following:
Respiratory rate > 30
Severe respiratory distress; SpO2 ≤ 90% on room air,
Chest X-ray involving >50% of lung fields
ARDS
OR
Multiorgan failure/shock

Severe or Critical

Hospital HDU/ICU

Oxygen via NIV or intubation
Prone positioning
Anticoagulation
Watch for CRS
Clinical Management Guidelines for COVID-19

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Criteria</th>
<th>Where to manage?</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>SARS CoV-2 infection with no symptoms</td>
<td>Home</td>
<td>Follow home management guidelines</td>
</tr>
<tr>
<td>Mild disease</td>
<td>Presence of symptoms consistent with COVID without any hemodynamic compromise, need for oxygen and no chest X-ray findings</td>
<td>Home</td>
<td>For those who don’t have home arrangements for isolation can be shifted to isolation facility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Follow home management guidelines</td>
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<tr>
<td></td>
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<td></td>
<td>All supportive care with paracetamol for fever, ORS for diarrhoea and antihistamines for rhinitis,</td>
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<td></td>
<td>NO specific treatment</td>
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<td></td>
<td>For any warning signs call 1700/1122 for assistance and guidance or consult health care facility</td>
</tr>
<tr>
<td>Moderate disease</td>
<td>Hypoxia (SpO2 &lt;94% but &gt;80% or Chest X-ray infiltrates involving &lt;50% of the lung fields)</td>
<td>Isolation unit inside hospital.</td>
<td>Supportive care, investigations</td>
</tr>
<tr>
<td></td>
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<td>Oxygen through a face mask, nasal cannula</td>
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<td>Voluntary prone positioning</td>
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<td></td>
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<td></td>
<td>If already on antiocoagulation continue the same if not start on standard DVT prophylaxis (enoxaparin 40mg OD)</td>
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<td></td>
<td></td>
<td>Remdesivir is moderate and severe COVID requiring oxygen therapy regardless of if CRS is present. Use in critical patients as per available data is unlikely to be of benefit.</td>
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<tr>
<td></td>
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<td></td>
<td>In case of Cytokine release storm:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>a) Steroids 0.5-1 mg/kg/d of methylprednisolone for 5 days. Avoid if no evidence of CRS</td>
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<tr>
<td></td>
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<td></td>
<td>b) Todtizumab is reserved for patients in whom worsening occurs despite steroids or those who present as severe/critical disease in CRS</td>
</tr>
</tbody>
</table>

| 1: Symptoms: |
| Cough |
| Shortness of breath |
| Fever |
| Asthenia/lethargy |
| Chills |
| Muscles pain |
| Headache |
| Sore throat |
| New loss of taste or smell |

| Warning Signs: |
| Fever > 7 days or new fever after initial defervescence |
| SOB exertion or RR>20 |
| SpO2 of <94% on room air |
| Persistent palpitations |
| Pleuritic/Chest pain |
| Haemoptysis |
| New confusion/lethargy |
| Severe diarrhoea and dehydration |
| Excessive vomiting |

| Investigations required. |
| All patient with moderate or above category need to be assessed for cytokine storm |
| CBC |
| Ferritin |
| C-Reactive Protein |
| Lactate Dehydrogenase |
| D-Dimer |
| Chest X-ray [PA view] |

| Additional investigations |
| Liver Function tests |
| BUN, creatinine and electrolytes |
| Blood cultures |
| Blood glucose levels |
| EKG |
| ABB (for severe and critical) |
| Serum lactate (for severe and critical) |
| Respiratory cultures (for severe and critical) |

| Optional investigations include |
| Procalcitonin |
| Troponin |
| Echo |
| Pro-BNP |
| IL-6 |
| CT scan Chest |
### Severe Disease

<table>
<thead>
<tr>
<th>Severe disease</th>
<th>High Dependency Unit</th>
<th>Critical Care</th>
<th>Cytokine Release Storm (CRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In adults, clinical signs of pneumonia (fever/cough) plus any of the following:</td>
<td></td>
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<tr>
<td>* Respiratory Rate &gt;30</td>
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<tr>
<td>* Severe respiratory distress</td>
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<tr>
<td>* SpO2&lt;90 on room air</td>
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<tr>
<td>* Chest X-ray involving &gt;50% of lung fields</td>
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<tr>
<td>HDU need to be well ventilated with positive pressure and equipped as an ICU where the oxygen is supplied from a central source and the delivery systems are:</td>
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<tr>
<td>* High flow nasal cannula, CPAP, BIPAP, NIV.</td>
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<tr>
<td>* Monitor and bed, along with other supplies are similar to ICU</td>
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<tr>
<td><strong>Supportive care</strong></td>
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<tr>
<td>* Oxygen through High Flow Nasal Cannula, CPAP (NIV)</td>
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<tr>
<td>* Prone positioning for 12-15 hours</td>
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<td>* Anticoagulation: Switch to parenteral anticoagulation as aggressive prophylaxis dose as enoxaparin 40 mg q12h, if D-Dimers &gt;3 times normal give therapeutic dose enoxaparin 1mg/kg/q12h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Antibiotics only on specific indication, send cultures</td>
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<tr>
<td><strong>Remedies</strong></td>
<td></td>
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<td></td>
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<td>* Moderate and severe COVID requiring oxygen therapy regardless of if CRS is present. Use in critical patients as per available data is unlikely to be of benefit.</td>
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<td>In case of Cytokine release storm:\n 1. Steroids 3:0.5-1 mg/kg/d of methylprednisolone for 3 days. Avoid if no evidence of CRS.</td>
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<tr>
<td>2. Tocilizumab Is reserved for patients in whom worsening occurs despite steroids or those who present as severe/critical disease in CRS</td>
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</tbody>
</table>

### Critical Disease

<table>
<thead>
<tr>
<th>Critical disease</th>
<th>Any of the three manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>* ARDS (Adult Respiratory Distress Syndrome)</td>
<td></td>
</tr>
<tr>
<td>* Multifactor dysfunction</td>
<td></td>
</tr>
<tr>
<td>* Septic shock</td>
<td></td>
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<tr>
<td>Intensive Care Unit</td>
<td></td>
</tr>
<tr>
<td>An ICU need to be well ventilated and equipped with an ICU bed, a ventilator, a cardiac monitor, infusion pumps, and other items as per basic needs.</td>
<td></td>
</tr>
<tr>
<td><strong>Supportive care</strong></td>
<td></td>
</tr>
<tr>
<td>* Oxygen through mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>* Prone positioning for 12-15 hours</td>
<td></td>
</tr>
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<td></td>
</tr>
</tbody>
</table>

### Additional Notes

- Investigational therapies: Treatment modalities including (but not limited to) convalescent plasma, remdesivir or favipiravir should be used only in the setting of an approved research protocol by NIMS and includes consent and safety oversight.
- Routine use of hydroxychloroquine/chloroquine and Azithromycin is discouraged and not supported by evidence.
- De-escalation: The detection of RNA during convalescence does not indicate the presence of viable infectious virus. NOTE: A test to document Cure is not required in the below mentioned patients with the exception of immunocompromised patients. In those who are symptomatic symptom-based strategy is recommended. At least 10 days from the start of symptoms AND at least 3 days after resolution of symptoms (fever and respiratory symptoms). In those who are asymptomatic time-based strategy is recommended i.e. Ten days from the date of the test.

**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.