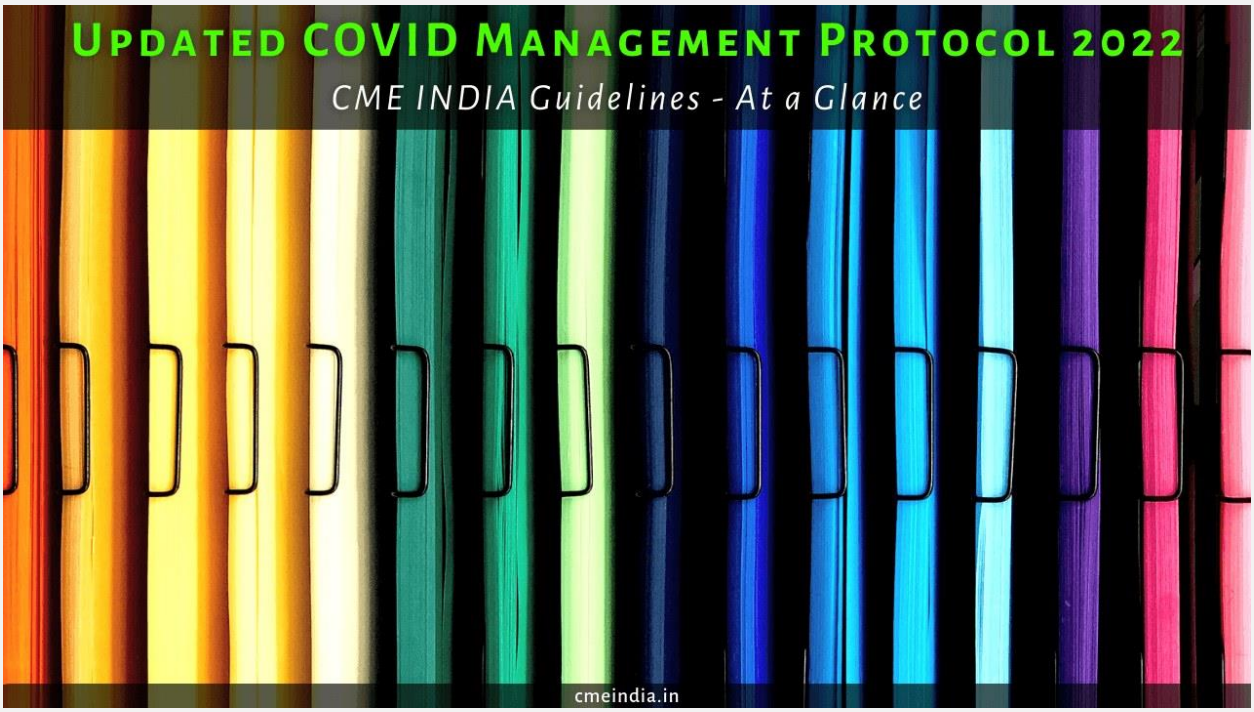
At a Glance - Updated CME INDIA COVID Management Protocol 2022



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Expert Consensus on COVID-19 Management, January 8, 2022

Although Community transmission of Omicron seems unavoidable, practicing 'COVID APPROPRIATE BEHAVIOUR' which includes the use of face mask, social distancing, etc. seems to help prevent/delay the transmission.

Third (Omicron) Wave

- **There is consistent evidence that Omicron has a substantial growth advantage over Delta**
- **It is spreading significantly faster than the Delta variant in India.**
- **Doubling time between 1.5 – 3 days.**

- Due to immune evasive properties of the omicron, population susceptible to omicron has remarkably increased.
- **Order of susceptibility could be:**
  Unvaccinated >> Double dose vaccinated> Three dose vaccinated >> Hybrid (Infected + Vaccinated)
- It's very likely that although **omicron may evade the first line of defense** (antibodies), however the second line of defense (T cells) are likely to protect against development of severe disease.

- Covid symptoms linked to the new omicron variant stated to be "extremely mild" by the South African experience and Indian experience so far.
- Feeling extremely tired for few days, body ache and headache - these are usual presenting complains.
- 1 to 2 days fever, sore throat and mild cough is being noticed as early Indian experience. It usually settles within 5 days.

Usual Experience of Possible Omicron Cases by Indian Physicians

1. Fever has been a common feature usually mild and goes away in next 2-3 days.
2. Scratchy throat or sore throat is common to all and most problematic.
3. Weakness generalised quite common for few days.
4. Headache is a predominant symptom sometimes very severe.
5. Body ache in almost half of the patients and stays for couple of days in most cases.
6. Few patients had severe back ache.

7. Most cases CRP and D-DIMER are within normal limits.
8. Oxygen saturation is hardly affected. Respiratory distress is rare.
9. Most are asymptomatic by 4-6 days.
10. Productive cough could be distinguishing feature from delta which presented with dry cough usually during 2nd wave.
11. Loss of smell and taste – Not being found so far.
12. Atypical symptoms like night sweats, diarrhoea also being reported.
13. Highly infectious as whole family or contacts is getting infected at least presenting with some symptoms.

- It is better to follow "Watch List for all Variants (CDC)/ Symptoms may appear 2-14 days after exposure."

• Fever with or without chills
• Cough
• Shortness of breath or difficulty breathing
• Fatigue
• Muscle or body aches
• Headache
• New loss of taste or smell
• Sore throat
• Congestion or runny nose
• Nausea or vomiting
• Diarrhea

Look for emergency warning signs

• Trouble breathing
• Persistent pain or pressure in the chest
• New confusion
• Inability to wake or stay awake
• Pale, gray, or blue-colored skin, lips, or nail beds, depending on skin tone

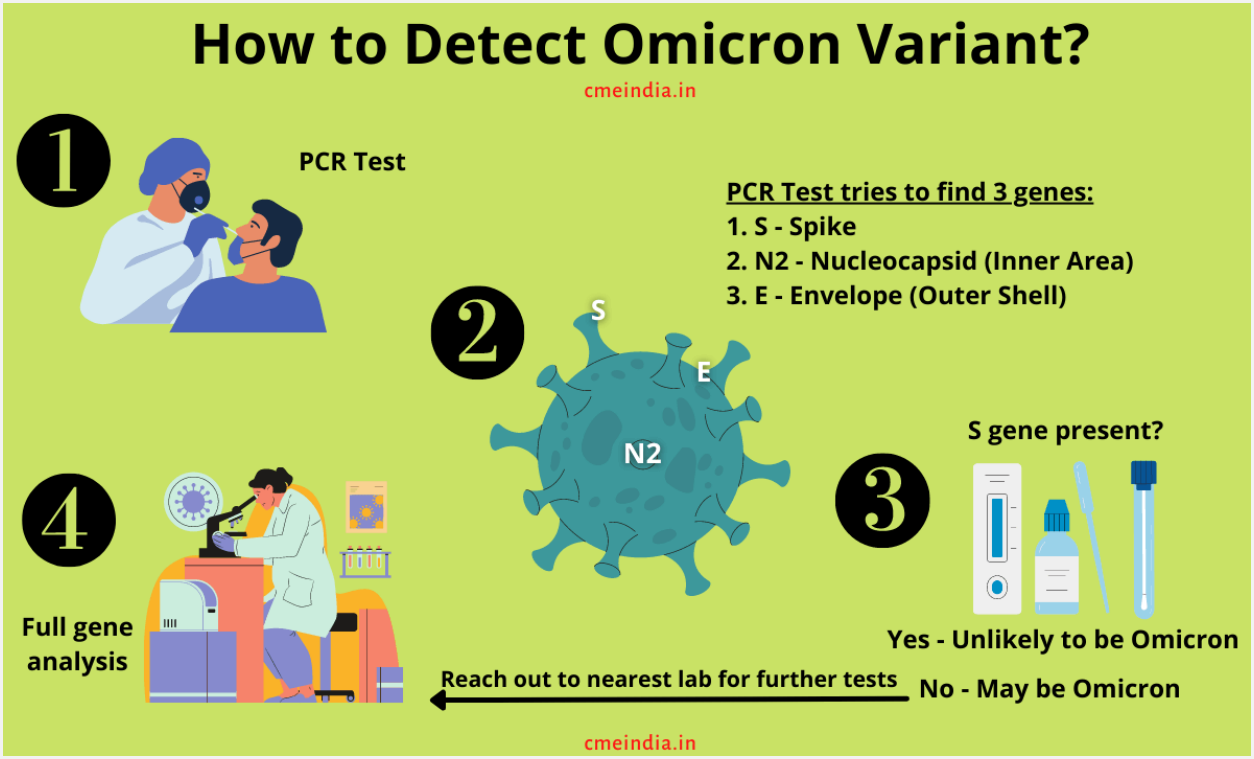
The trick of diagnosing Omicron illness is to go for usual tests at present.

• The accuracy of existing molecular (PCR, NAAT) tests appears uncompromised by COVID-19 variant Omicron (B.1.1.529)

- Preliminary evidence suggests that this is also true for the accuracy of rapid antigen tests.
- Thus, current SARS-CoV-2 PCR diagnostics continue to detect this variant.
- Several labs have indicated that for one widely used PCR test, one of the three target genes is not detected (called S gene dropout or S gene target failure) and this test can therefore be used as marker for this variant, pending sequencing confirmation.
- Using this approach, this variant has been detected at faster rates than previous surges in infection, suggesting that this variant may have a growth advantage. (WHO)
- The ability of diagnostic tests to detect the Omicron variant is critical to tracking its spread and putting in place measures to halt transmission.
- RAT (Rapid Antigen Test):
    - The majority of these assays detect the nucleocapsid rather than spike protein and are therefore anticipated to be unaffected by the mutations specific to the Omicron variant
    - The clinical sensitivity of rapid antigen tests varies depending on when the test is performed in the illness course.
    - Tests performed too early may be falsely negative because the amount of virus at the time of sampling is below the limit of detection for the assay. Thus, if people infected with the Omicron variant are developing symptoms earlier due to pre-existing immunity, then sampling at the time when symptoms begin may result in a false negative result. Testing may be repeated within 24 to 48 hours per CDC suggestion. (CDC)
    - Most rapid antigen tests in current use are not validated - and are therefore not interpretable - for specimen types OTHER than the anterior nares (e.g., the throat).
- Do RT-PCR, Look for S gene dropout. But the usual RT PCR kits are based on two gene detection which does not include detection of S gene. Kit by Thermo-Fischer is based on three gene detection including S gene. Enquire from Lab if it uses a kit to detect S gene Drop out.
- In India, it is not possible to go for Genomic sequencing in all cases. S gene dropout gives you a SIGNAL to track the variant's spread without genomic sequencing, which is usually only performed for a subset of PCR-positive samples (where capacity is available).
- OMISURE KIT:
    - The Tata Medical and Diagnostics has developed a kit 'OmiSure' that can detect the Omicron variant of COVID-19. The kit will identify infection from Omicron variant and will be available by January 12. The kit is priced at Rs 250.
    - It can detect the Omicron variant of SARS-CoV2 in nasopharyngeal/ oropharyngeal specimens during the RT-PCR tests.
    - The test kit is compatible with all standard Real-Time PCR Machines. This kit can detect the Omicron variant as well as other variants of SARS-CoV2 reported so far. Currently, Omicron patients are detected only after genome

sequencing. But this test can help eliminate that step and detection can be done during the testing.

- The test run time of this kit is 85 minutes. The result turnaround time, including sample collection and RNA extraction, is 130 minutes.



This updated guideline is in tune to tackle new challenges.

Quick Look:

Asymptomatic

No Blood tests needed as such, physician discretion needed.

Isolation as per National Protocol/State Protocol.

Monitor SpO2 with Pulse oximeter TPR/BP/Blood sugar.

Features suggestive of Moderate illness

- SpO2 <94%.
- Respiratory rate >24/min even without co-morbidities.
- Red flag signs++.

ADMIT

Mild symptoms but NO COMORBITIES

- Fever <100 degree, Cough (Dry, may be productive if omicron), loss of smell and test is not being reported with Omicron, profuse sweating maybe.
- Normal SpO2.
- Vital signs – normal.
- Respiratory rate <24/min.

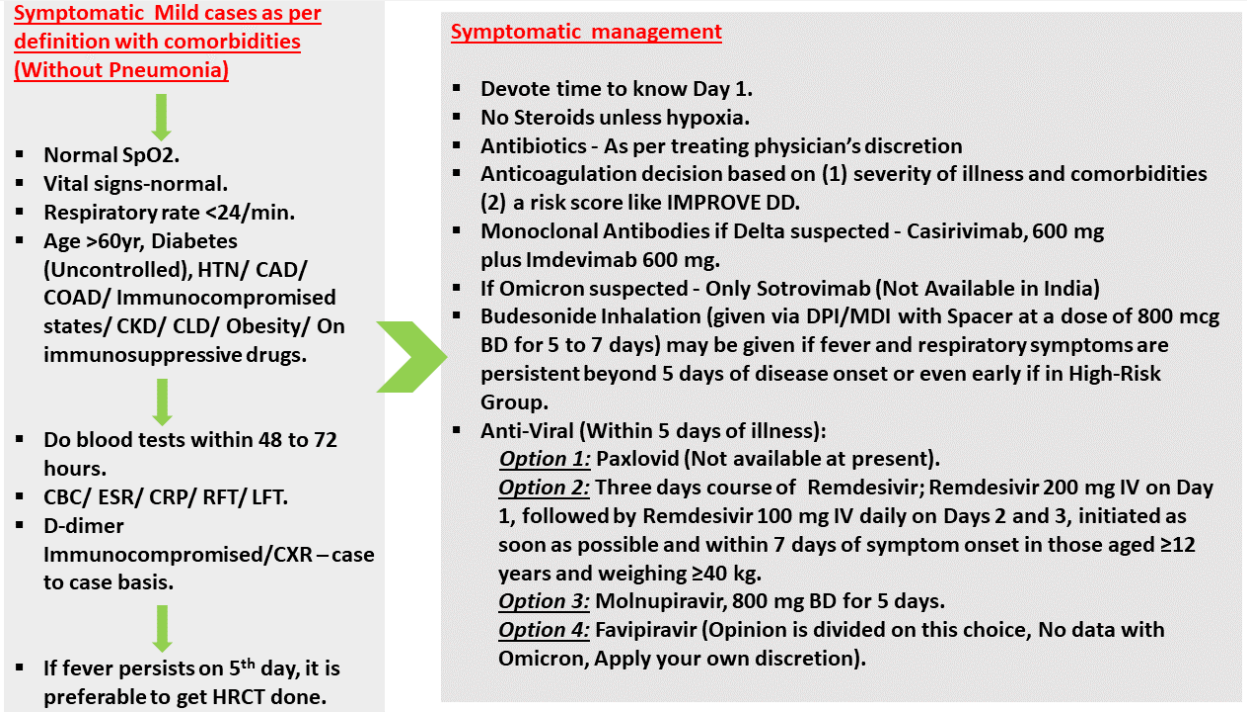
Do

- CBC.
- CRP.
- Blood sugar in all, Monitor blood sugar frequently
- Physician discretion if CXR/D-dimer/RFT/LFT/ECG needed.

- Home isolation under guidance of health care provider available.
- If Red flag signs develop – Admit.

- Manage Symptomatically.

- Most of Omicron Illness improves by 5th day.
- No Heroic measures needed.
- No Antibiotics needed unless secondary infection is suspected.



Mild Disease: Home Isolation

Identify

i. Symptomatic patients meeting the case definition for COVID-19

New Alert for considering delta variants mainly

- Extra-pulmonary symptoms such as vomiting and diarrhea.
- Conjunctivitis.
- Neurological symptoms.
- Loss of smell/taste.
- A fairly constant feature is disproportionate fatigue.

ii. No evidence of viral pneumonia or hypoxia/SpO2 > 94 % on Room Air (Many guidelines now consider mild disease if SpO2 >90%).

iii. Respiratory rate < 24/min.

iv. Do not routinely go in for a CT Scan; a CT scan is indicated only if:

- There is a strong clinical suspicion and the RT PCR is negative.
- Serious comorbidities exist or are suspected such as pneumothorax, or pulmonary mycosis.
- The usual CT Severity Score in mild disease is < 8/25 and < 25% (on a score of 25 or as % lung involvement).

v. Always identify a caregiver who must be the point of contact with the health care provider during the course of the illness.

Table: Day to day working protocol to identify severity

* **Mild Illness:** Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
* **Moderate Illness:** Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) <94% on room air at sea level.

Manage:

(Mild Illness)

i. Isolation and all COVID appropriate behavior

ii. Monitoring

- Check SpO2 three to four times, NIBP, HR, Temperature.
- The 6MWT will ascertain evidence of hypoxia identified by SpO2 less than 94% or an absolute drop in SpO2 by more than 3% from base line during or at end of the test. Patients over 60 years of age may have a shorter - 3-minute walk test (3MWT) if they are unable to perform a 6-minute test.

iii. What to inform patients?

Monitor following things:

1) Temperature with a clinical thermometer every 3 to 4 hours. Maintain a chart. Temperature more than 100°F for more than 5 days, in spite of tablet Paracetamol, should be informed to the doctor.

2) Look for Pulse rate, if possible, by putting fingers in the wrist below the thumb. Count the numbers for 1 minute. Check for every 3 to 4 hours. Maintain a chart. More than 100 per minute for more than 5 days, in spite of Tablet Paracetamol, should be informed to the doctor.

3) Look for Respiratory rate, if possible, by putting palm on abdomen while lying straight. Check for every 3 to 4 hours. Maintain chart. Keep your physician informed if the rate is persistently above 20 per minute.

4) Check oxygen saturation by Pulse oximeter, every 5 to 6 hours. Ensure that oximeter fluctuations have stabilized before you take the reading. Maintain chart. Less than 94% in the last three readings is an emergency.

5) Six Minute Walking Test (SMWT) is very important and you do it two times daily during regular oxygen saturation measurement. Check oxygen saturation and start walking for six minutes in a normal way, maybe inside the room, now check oxygen saturation again, If the oxygen saturation has dropped below 93% or if there is an absolute drop of more than 3% to 5%, patient is at risk and may need hospital care.

Other important advice:

• Patients may perform warm water gargles and take steam inhalation twice a day.
• Sequential change of position every 1- 2 hours; supine, prone, sitting up, right lateral and left lateral.
• Continue taking medicines that you were already on for any pre-existing comorbidity - diabetes, hypertension, asthma, cancer etc. and consult a health care provider.
• Support own mental wellbeing:

i. Do not watch negative news and social media posts excessively.
ii. Meditate and talk with family and friends.
iii. Read books.
iv. Do walking and light exercises within the room.
v. Have proper sleep.

• Nutritional support—high protein diet

Red flag signs (If developed likely to deteriorate):

- High-grade fever/ severe cough.
- Shortness of breath (while walking, talking, sitting), tightness in chest.
- Feeling of disorientation.
- Slurred speech/seizures.
- Unable to wake up or stay awake.
- Respiratory rate ≥ 24/ min.
- Oxygen saturation < 94% on room air.
- A low threshold should be kept for patients with high-risk factor/co-morbidities.
- P/F ratio < 300.
- Focus on 3 Lab tests:
    1. Neutrophil Lymphocyte Ratio >3.2 or RDW above 14.5.
    2. Raised CRP.
    3. Raised D-Dimer.

Note: D-dimer has been shown to increase with age, which can cause a lower specificity (i.e., more false positive tests) in older patients. So, age adjusted D dimer may be useful which can be calculated by: The formula is: Age (years) x 10 ug/L for patients > 50 years of age. Example: Patient age 88 = age adjusted d-dimer of 880 ug/L would be normal for 88 years.

Raised CRP- 5 times of ULN limit, rising CRP from baseline 3 times and D dimer - 2 times above normal limit - Need to act fast.

iv. Treatment

(Treatment of Mild Cases)

Do Remember that Omicron Illness, as known till date, is usually MILD. No heroic measures needed. Just treat it symptomatically.

- Rehydration.
- Antipyretic (Paracetamol) Take paracetamol tablet 650 mg every 4-6 hours if you have fever - not more than four times in 24 hours. If fever is more than 101 degrees F, do tepid sponging using tap water (not cold water or ice) or take a shower. Mefenamic acid 500mg tablet can be added if fever not subsiding with paracetamol provided renal function is normal.
- Nutritional support.
- No role of Azithromycin/ Doxycycline (**Note:** However, most of centers/experts use these drugs on personal experiences and many found them useful.).
- Supportive: Anti-tussive SOS/ Vitamin C 500 mg BD or 2 weeks/ T. Zinc 50 mg OD for 2 weeks Vit D 2000 units once daily or 60000 IU once weekly for 4-8 weeks. (Used during second wave but these medications have no scientific basis to use in Omicron illness. These can be used only if physician suspects deficiency).
- Tab Melatonin or Clonazepam if needed to allay anxiety.
- Say No to HCQS.
- Say no to Ivermectin (Investigational drug) - has weak antiviral properties in high concentrations, difficult to achieve with therapeutic current doses in Pulmonary endothelium, still few state guidelines recommend. Tab Ivermectin (200 mcg/kg once a day for 3 to 5 days) may be considered in patients with high-risk features. (Avoid in pregnant/ lactating and very elderly beyond 80 years) Category: Optional.
- **Note on Anti-viral:**
    - *As there is persistently high morbidity and mortality attributable to covid-19, we agree that effective antivirals have an obvious appeal.*
    - *As there is reduced viral load, it would lessen the severity and duration of disease, as well as the risk of transmitting the virus.*

Multiple therapeutic agents are now available for non-hospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression.
Option 1: As per available data we favor the use of ritonavir-boosted nirmatrelvir (Paxlovid) in most high-risk, non-hospitalized patients with mild to moderate COVID-19.
Option 2: If ritonavir-boosted nirmatrelvir (Paxlovid) is not available or cannot be used because of drug interactions, then sotrovimab is the choice not the Casirivimab, plus Imdevimab as it is not effective against Omicron. Avoid in Omicron cases. Sotrovimab is indicated for omicron related infection. But casirivimab + imdevimab (antibody cocktail) is still relevant for Delta variant So local variant susceptibility should be considered in the choice of most appropriate neutralising antibody therapy.
Option 3: Sotrovimab is not available in India so clearly Remdesivir may be the option. Remdesivir is back after PINETREE trial and is supposed to be effective for Omicron.
Option 4: Molnupiravir should only be administered when the other 3 options are either not available or cannot be used.
Option 5: Favipiravir - No data with Omicron illness. Avoid it.

- **Molnupiravir:**

  - The Subject Expert Committee (SEC) on COVID-19 of the Central Drugs Standard Control Organisation (CDSCO) on Tuesday 28, Dec 21 recommended granting permission to manufacture and market anti-Covid pill Molnupiravir for restricted emergency use for the treatment of adult patients. Now it is available.
  - Molnupiravir is an orally administered form of ribonucleoside that prevents the replication of SARS-CoV-2, which causes Covid-19. It forces SARS-CoV-2 to try to replicate its genetic material. However, as the replication process begins, the pill inserts errors into the genetic code of replicating Virus.
  - Mechanism of drug is independent of spike protein mutation so it should work against Omicron. But true results will surface with test of times. Molnupiravir was shown reduce hospitalization or death by 30%. In MoVE-OUT study over which Molnupiravir got EUA has no patients with Omicron. An earlier trial (Move-In) of Molnupiravir in hospital inpatients was discontinued because of lack of efficacy.
  - **When to start?** Molnupiravir should be administered as soon as possible after a diagnosis of COVID-19, and within five days of symptom onset. It is stated to prevent progression of disease leading to hospitalization
  - **Whom should it be given?** "Treatment of mild-to-moderate COVID-19 in adults with a positive result of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options

authorized by FDA are not accessible or clinically appropriate" - As per Original EUA Authorized Date: 12/23/2021.

- **Summary of the evidence:**
  - Two RCTs reported on treatment of unvaccinated patients with COVID-19 with either 800 mg of molnupiravir or placebo for five days.
  - In one phase 3 trial (MOVe-OUT trial) reported on the outcomes of death, hospitalization and serious adverse events, patients with mild-to-moderate COVID-19 received either molnupiravir or placebo within 5 days after the onset of symptoms.
  - In the phase 2a trial reporting on the outcomes of death and serious adverse events in patients with symptom duration
  - **COVID-19-related mortality may be lower in patients receiving molnupiravir rather than placebo (RR: 0.11; 95% CI: 0.01, 0.86; low CoE).**
  - **COVID-19-related hospitalizations and the composite of all-cause hospitalization or death may trend towards a reduction among patients receiving molnupiravir rather than no molnupiravir (RR: 0.68; 95% CI: 0.48, 1.00; low CoE and HR: 0.69; 95% CI: 0.48, 1.01; low CoE, respectively).**
  - **Matter of Concern:**

▪ Patients treated with molnupiravir may not experience greater serious adverse events
▪ than those receiving placebo (RR: 0.43; 95% CI: 0.17, 1.11; low CoE). But these are based on findings from animal reproduction studies.
▪ Molnupiravir may cause fetal harm when administered to pregnant individuals.
▪ There is possibility of viral mutagenesis in persons with compromised immune systems who are unable to clear the virus.
▪ Females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for 4 days after the last dose.
▪ Men of reproductive potential who are sexually active with females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for at least three months after the last dose of molnupiravir.
▪ Molnupiravir does not require renal or hepatic dose adjustment
▪ It is also not recommended in children <18 years of age for the concern of bone growth.

We recommend use of Molnupiravir in:

1. Ambulatory patients (>/= 18 years) with mild to moderate COVID-19
2. Only with high risk for progression to severe disease (patients who have associated Comorbidities like Diabetes, CKD, COPD Heart Disease, COPD,

immunocompromised states, Obesity or elderly people more than 60 years of age)
3. Must be initiated within 5 days of symptom onset.
4. If Option 1(ritonavir-boosted nirmatrelvir (Paxlovid), Option 2 Sotrovimab, Option 3 Remdesivir not feasible due to availability and home-based option. Obviously, it is Option 4.
5. It is a conditional recommendation with low certainty of evidence.
All points 1 to 5 to be considered

- **Dose**: Overall, the course has 40 pills. 800 mg (four 200 mg capsules) taken orally every 12 hours for five days, with or without food. Completion of the full five-day treatment course is important to maximize viral clearance and minimize transmission of SARS-CoV-2. Once started the course should be completed.

Side effects - The most common adverse reactions for Molnupiravir:
• Diarrhea (2%)
• Nausea (1%)
• Headache
• Dizziness (1%)
Drug interactions:
• Nil

- **The drug is not authorized:**

1. For use in patients less than 18 years of age.
2. For use longer than five consecutive days.
3. For use in pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
4. For use pregnant women.
5. For initiation of treatment in patients hospitalized due to COVID-19.

- **Contraindications:**
    1. Molnupiravir is not recommended for use in patients who are pregnant. Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. No human data.
    2. Avoid Pregnancy for 4 days after the last dose
    3. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for four days after the last dose of molnupiravir.

4. Lactational mothers - No details known but based on the potential for adverse reactions in the infant from molnupiravir, breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir.

- **Paxlovid:**

  - Not available now in India, when available prefer Paxlovid over Molnupiravir.
  - FDA approved for EUA.
  - Paxlovid (combination of nirmatrelvir 150mg and ritonavir 100mg). The treatment disrupts the replication of SARS-CoV-2 in the body by binding to the 3CL-like protease, an enzyme crucial to the virus' function and reproduction.
  - **Antiviral with a difference (Reasons to prefer Paxlovid)**: This novel antiviral pill showed almost 90% efficacy in preventing hospitalizations and deaths in high-risk patients, and recent data from Pfizer suggests the drug retains its effectiveness against the fast-spreading Omicron variant of the coronavirus.
  - **How is it given?** - Paxlovid is administered as three tablets (two tablets of nirmatrelvir and one tablet of ritonavir) taken together orally twice daily for five days, for a total of 30 tablets. Paxlovid is not authorized for use for longer than five consecutive days.
  - **Possible side effects of Paxlovid**:

• Impaired sense of taste
• Diarrhea
• High blood pressure
• Muscle aches.
• Using Paxlovid at the same time as certain other drugs may result in potentially significant drug interactions
• Using Paxlovid in people with uncontrolled or undiagnosed HIV-1 infection may lead to HIV-1 drug resistance.
• Ritonavir may cause liver damage, so caution should be exercised when giving Paxlovid to patients with preexisting liver diseases, liver enzyme abnormalities or liver inflammation.

- **Contraindications:**

• With certain drugs that are highly dependent on those enzymes for metabolism and for which elevated concentrations of certain drugs are associated with serious and/or life-threatening reactions.
• With drugs that, conversely, strongly induce those same enzymes, leading to the faster breakdown of nirmatrelvir or ritonavir, as reduced concentrations of nirmatrelvir or ritonavir may be associated with potentially losing virologic response and developing viral resistance.
• Paxlovid cannot be started immediately after discontinuing such medications because the effects of those medications remain after discontinuation.
• Paxlovid is not recommended in patients with severe kidney or severe liver impairment. In patients with moderate renal impairment, a reduced Paxlovid dose is needed.

- **Remdesivir in mild cases:**
    - Remdesivir - 3 days course approved by CDC. Remdesivir 200 mg IV on Day 1, followed by Remdesivir 100 mg IV daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg.
    - PINETREE trial which showed that 3 consecutive days of IV Remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death compared to placebo.
- Steroids MUST NOT be used in patients with only mild disease. Concept of starting steroid on day 1 is detrimental and must be discouraged.
- **Budesonide Inhalation** (given via DPI/MDI with Spacer at a dose of 800 mcg BD for 5 to 7 days) may be given if fever and respiratory symptoms are persistent beyond 5 days of disease onset or even early if in High-Risk Group STOIC and (PRINCIPLE Trial).
- Controversies with Early Steroid - *It is totally unscientific to start steroids in viral replication phase. It has become a common practice in India that primary care physicians start on Day 1. This harms immensely the patient's immune system as viral replication is accelerated due to immune suppression. We recommend to completely avoid steroid within 7 days of illness. (Unless indicated for a specific condition).*
- **Prophylactic dose of LMWH** if risk factor for thrombotic disease - Enoxaparin dose is 1mg/ kg OD not 40mg od for all or Inj Fondaparinux 2.5mg s/c OD. For bed ridden

patients in Home-isolation, one may consider to use Apixaban 2.5 mg BD Alternatively: Tab Aspirin 75 mg (or clopidogrel 75/ mg) in high-risk groups.

- The decision to anti-coagulate or use an anti-platelet agent should be based on a validated risk score such as the IMPROVE DD, and not only on D-dimer which is often confounded by many factors.

- **Anti-SARS-CoV-2 Monoclonal Antibodies (Antibody Cocktail)**

• Tertiary Care Centers may continue to use Regeneron to deserving and affording high-risk patients (preferably for those who don't have detectable antibodies against SarsCoV-2), pending Proof of Omicron infection (which takes about 4 to 5 days after RT PCR report). **But the combo has not been found effective against Omicron variant.**
• Sotrovimab is new monoclonal antibody formulation by GSK shown to be effective against Omicron by pseudoviral assays. Drug is not yet FDA approved and unlikely to be available soon.
• **Casirivimab and imdevimab should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.**

- **Approved molecules as Emergency use authorization (EUA):**
    1. Casirivimab,600 mg plus Imdevimab 600 mg: Antibody cocktail- now available in India.
    2. Bamlanivimab 700 mg plus etesevimab 1,400 mg: Now not recommended as use of bamlanivimab plus etesevimab has been found to increase in the proportion of the variants of concern (VOC) Gamma (P.1) and Beta (B.1.351). These VOCs have reduced susceptibility to both bamlanivimab and etesevimab.
    3. Single monoclonal antibody (Sotrovimab). Efficacy for Omicron has been found in studies.

This therapy must be initiated in highly selective high-risk patients only as per following table:

FDA's EUA defines high-risk patients as meeting at least one of the following criteria:
• Have a body mass index ≥35;
• Have chronic kidney disease;
• Have diabetes;
• Have immunosuppressive disease;
• Are currently receiving immunosuppressive treatment;
• Are ≥65 years of age;
• Are ≥55 years of age AND have cardiovascular disease, OR hypertension OR chronic obstructive pulmonary disease/other chronic respiratory disease;
• Are 12–17 years of age and have BMI ≥85th percentile for their age and gender based on CDC growth charts, OR sickle cell disease, OR congenital or acquired heart disease, OR neurodevelopmental disorders, for example, cerebral palsy, OR a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), OR asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

- **When to start?** Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or a nucleic acid amplification test and within 10 days of symptom onset.

- **How to give?**

    - The intravenous administration takes about 20 to 30 minutes, preferably give in 1 hour.
    - **The authorized dosage is 600 mg of casirivimab and 600 mg of imdevimab + 100ml NS administered together as a single intravenous infusion over 1 hr.**
    - **(Add 10 mL of co-formulated casirivimab (5ml) and imdevimab (5ml) into a prefilled 0.9% Sodium Chloride 100ml).**
    - For the subcutaneous route, four syringes of 2.5 ml (2 each of Casirivimab & Imdevimab) need to be administered concurrently at four different sites on the abdomen or thigh. Patients should be monitored during the infusion and observed at least one hour after the completion of the infusion and 15--30 minutes after the subcutaneous injection.

- **How supplied?** Each pack of Antibody Cocktail (Casirivimab and Imdevimab) contains one vial of Casirivimab and one vial of Imdevimab totaling 2400 mg of the antibody cocktail (one vial of Casirivimab (1200 mg) and one vial of Imdevimab (1200 mg)). Each pack can treat two patients as the dosage per patient is a combined dose of 1200 mg (600 mg of Casirivimab and 600 mg of Imdevimab) administered by intravenous infusion or subcutaneous route. The vials need to be stored at 2°C to 8°C. If opened for the first patients' dose, a vial can be used for the second patients' dose within 48 hours if stored at 2°C to 8°C.

- **How much priced?** The price for each patient dose [a combined dose of 1200 mg (600 mg of Casirivimab and 600 mg of Imdevimab)] will be INR 59,750 inclusive of all taxes. The maximum retail price for the multidose pack (each pack can treat two patients) is INR 119,500 inclusive of all taxes.

- **Alert**: Receipt of a COVID-19 vaccine should be deferred for at least 90 days in those who have received anti-SARS-CoV-2 monoclonal antibodies.

Note: As per revised Home-isolation guidelines, HOME ISOLATION ENDS at 7 days for those COVID PATIENTS who are fully vaccinated and remained asymptomatic (no fever) for last 3 days.

Repeat RT PCR TESTING is also not required

MoH dated 5/1/2022 guideline on home isolation is available at - https://www.mohfw.gov.in/pdf/RevisedHomeIsolationGuidelines05012022.pdf

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Moderate Disease

Identify

i. Respiratory rate > 24 /min.

ii. SpO2 90-94% on room air (Many guidelines now consider SpO2 84-90%).

iii. CT Severity Score (on a score of 25 or % lung involvement) 8-15/25 or 25-50%.

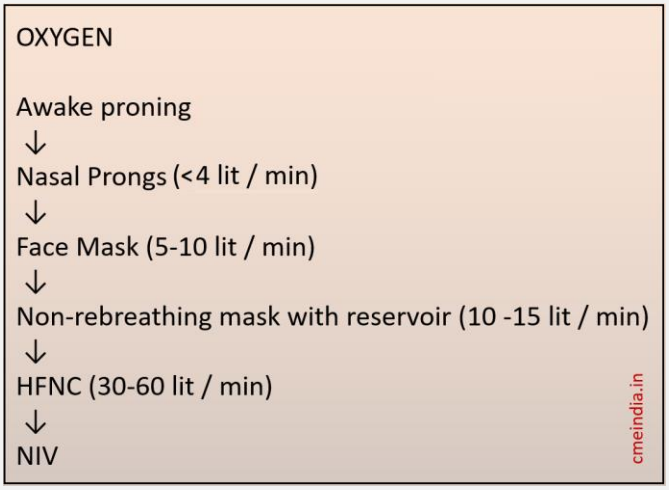
Manage:

(Moderate Illness)

i. Admit in ward

ii. Oxygen Support:

- Target SpO2: 92%+ (88-92% in patients with COPD and Type 2 respiratory failure).
- Preferred devices for oxygenation: O2 face mask in most as it can deliver around 40 to 60 % oxygen at 6 to 10L/min.
- Awake proning may be used in those with persistent hypoxia despite use of high flow oxygen (sequential position changes every 1-2 hours); in fact intermittent awake proning can be recommended in all patients, to allow them to get used to the position.



iii. Laboratory and Clinical Monitoring to Guide Treatment

- Clinical Monitoring: Work of breathing, Hemodynamic instability, Change in oxygen requirement.
- Serial CXR, HRCT Chest (if worsening).

- Lab monitoring:
    - CRP.
    - D-dimer & Ferritin 48-72 hrly.
    - CBC, LFT, KFT 24-48 hrly.
    - IL-6 levels to be done if deteriorating (subject to availability).

(Note: Close monitoring of SpO2 either by themselves or in a hospital/Isolation center is needed for starting Steroids rather than CRP/D-dimer/NLR monitoring.)

iv. Drugs

A. Antiviral therapy

- Remdesivir (Most of the guidelines do not recommend it).
- Dose: Inj Remdesivir 200 mg IV on day 1.
- Then, 100 mg IV daily for 4 days (can be extended up to 10 days in case of progressive disease).

(Use based on limited available evidence and case to case basis only)

- **Explain** - Only reduces days of hospitalization without significant improvement in mortality rates.
- **Start Early** - Using this agent after 10 days of symptom onset has no benefits.
- **Reserve -** Best reserved for moderate disease (respiratory rate > 24 < 30 and Fever & oxygen saturation below 92) within first 5 to 7 days of symptom onset.
- **Safety -** One should remember that drug is not a safe drug especially in presence of moderate to severe liver or renal disease.
- **Hospitalize** - Strictly not to be given at HOME.

B. Convalescent plasma (CP)

- It may be considered in carefully selected patients but all standard guidelines do not recommend it.

C. Anti-inflammatory or immunomodulatory therapy

- Inj. Dexamethasone 6 mg IV OD or Oral dexamethasone 6 mg OD for 5-10 days or inj. Methyl Prednisolone 0.5 -1 mg/kg ≈ 60mg OD x 5 -10 Days Stop or taper if significantly better.
- **Dexamethasone 1.5 mg = Methylprednisolone 8mg = Prednisolone 10 mg. So, taking 12 mg Dexamethasone daily is equal to 64 mg methylprednisolone.**
- Good to keep this in mind when prescribing steroids.
- Anticoagulation: Low dose prophylactic UFH or LMWH (weight based e.g., enoxaparin 0.5mg/kg per day SC). Enoxaparin dose is 1mg/ kg OD not 40 mg OD for all or Inj Fondaparinux 2.5mg s/c OD in High-Risk Group. In ESRD, Unfractionated Heparin – 5000U SC BD.

D. Stay ALERT for Cytokine Storm (on Day 7/8 of disease)

During Moderate illness keep watch for:

- Unremitting fever.
- Cytopenia, Hyperferritinemia.
- If the patient in the second week having SOB (even with previous normal CT), rising CRP above 50, CT worsening, fever onset in the second week, etc. points towards impending cytokine storm.
- Daily CRP monitoring and steroid dose adjustments are crucial here.

E. Consider Antibody Cocktail (Casirivimab and Imdevimab) (Details given above)

Severe Disease

Identify

Any one of:

i. Respiratory rate > 30 /min.

ii. SpO2 < 90% on room air.

(Many guidelines follow <85% now)

Manage:

(Severe Illness)

Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.

Treatment options:

Tab Baricitinib 4mg 1 OD upto 14 days/till hospital discharge

+

Inj Remdesivir 200 mg IV once, then Remdesivir 100 mg IV once daily for 4 days

+

Inj Dexamethasone 6 mg IV or PO once daily for up to 10 days or until hospital discharge.

VTE prophylaxis

* Baricitinib dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge.

* eGFR ≥60 mL/min/1.73 m2: Baricitinib 4 mg PO once daily.

* eGFR 30 to <60 mL/min/1.73 m2: Baricitinib 2 mg PO once daily.

* eGFR 15 to <30 mL/min/1.73 m2: Baricitinib 1 mg PO once daily.

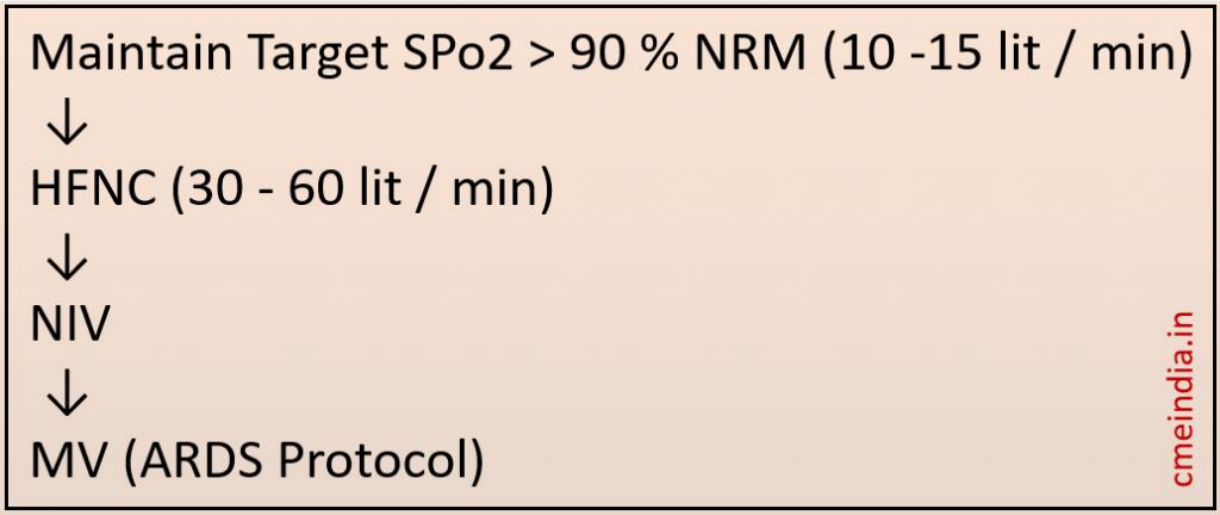
* eGFR <15 mL/min/1.73 m2: Baricitinib is not recommended.

Critical Disease:

- Needing MV/septic Shock
- MDT
- Consider - Inj Dexamethasone 6mg + iv Tocilizumab

VTE Prophylaxis:

i. Respiratory support Oxygen delivery by nasal cannula, face mask, Venturi mask, or mask with reservoir bag ± NIV*



ii. Consider broad spectrum empirical antibiotic treatment for possible superadded bacterial pneumonia/infection (↑S.PCT/Significant Leukocytosis/Leukopenia).

iii. Inj Dexamethasone 6mg iv OD or Inj Methylprednisolone 1 to 2mg/kg in 2 divided doses for 5 to 10 days. In appropriate indication [Clinical worsening, Age<60, no diabetes, dexamethasone dose could be- 0.2 – 0.4 mg/kg/day (12 – 24 mg /day)].

iv. Anticoagulation

- Unless contraindicated, FULL anticoagulation (on admission to the ICU) with enoxaparin, i.e., 1 mg kg s/c q 12 hourly (dose adjust with Cr Cl < 30mls/min) in those patients with a D-dimer > 3-5 X ULN and those with a rising D-dimer. Heparin is suggested with CrCl < 15 ml/min.
- In all other ICU patients medium dose anticoagulation; enoxaparin 0.5 mg/kg q 12 hourly.

v. Inj Remdesivir 200mg iv Day 1 Followed by 100mg IV OD (Day 2-5)

(Antivirals may be considered if duration of illness < 10-14 days)

vi. Tocilizumab may be considered on a case-to-case basis preferably within 24 to 48 hours of progression to severe disease Tocilizumab (Off-label) may be considered when all of the below criteria are met:

- Severe disease.
- Significantly raised inflammatory markers (CRP &/or IL-6).
- Not improving despite use of steroids.
- No active bacterial/ fungal infections.
- The recommended dose is 4 to 8mg/kg (with a maximum dose of 800 mg at one time) in 100 ml NS over 1 hour (dose can be repeated once after 12 to 24 hours depending on clinical response).
- IDSA conditionally suggests the use of tocilizumab among hospitalized patients with progressive severe or critical covid-19 and with elevated inflammatory markers. NIH recommends it in combination of dexamethasone if patient is experiencing a rapid respiratory decline with following criteria:

1. [1] Hospitalized within the last 3 days, admitted to an intensive care unit in the last 24 hours, and require either invasive mechanical ventilation, non-invasive ventilation, or high flow nasal cannula OR
2. [2] Hospitalized within the last 3 days, not admitted to the intensive care unit, have rapidly increasing oxygen requirements requiring either noninvasive ventilation or high flow nasal cannula, and who have increased markers of systemic inflammation.

If not available

Itolizumab

Very small study - By Biocon company - 30 patient study. Dose - 1.6 mg/kg in 250 ML NS over 6 hours. (- 25 mg in the first hour and the remaining dose over 5 hours)

If well tolerated and improvement in patient observed, clinician has the discretion to repeat a dose (after 1 week for itolizumab or after 12 hours for tocilizumab only after expert opinion) Informed consent is mandatory.

Bevacizumab and Sarlijumab are other options.

vii. JAK Inhibitors: Among hospitalized adults with severe COVID-19 having elevated inflammatory markers but not on invasive mechanical ventilation, the IDSA panel suggests baricitinib rather than no baricitinib. (Conditional recommendation, Moderate certainty of evidence). Baricitinib appears to demonstrate the most benefit in those with severe COVID-19 on high-flow oxygen/ non-invasive ventilation at baseline.

Among hospitalized patients with severe COVID-19 who cannot receive a corticosteroid (which is standard of care) because of a contraindication, the IDSA guideline panel suggests use of baricitinib with remdesivir rather than remdesivir alone (Conditional recommendation, Low certainty of evidence).

Tab Baricitinib 4 mg once daily for 10 days (*Renal modification - 2mg once daily if GFR is between 30 to 60ml/ml/min, avoid if GFR < 30 ml/min) Cost: 4mg tab, 30Rs /tab.

We do recommend it.

viii. Supportive measures

- Maintain euvolemia.

- If sepsis/septic shock: manage as per existing protocol and local antibiogram.
- **EMCO:** (Extracorporeal Membrane Oxygenation) At present There are insufficient data to recommend either for or against the use of extracorporeal membrane oxygenation in patients with COVID-19 and refractory hypoxemia.

ix. Monitoring

- Serial CXR, HRCT Chest (if worsening).
- Lab monitoring: CRP, D-dimer & Ferritin 24-48 hrly; CBC, LFT, KFT daily; IL-6 levels to be done if deteriorating (subject to availability).
- Clue for cytokine storm:
    - Yes. We can predict. If the patient in the second week having SOB (even with previous normal CT), rising CRP above 50, CT worsening, fever onset in the second week, etc. points towards impending cytokine storm. Daily CRP monitoring and steroid dose adjustments are crucial here.

x. Critical Illness recommendations by NIH (UK)

- Hospitalized and requires oxygen delivery through High-flow Device of NIV. Use one of the following:
    1. Dexamethasone.
    2. Dexamethasone plus Remdesivir.
- For patients having rapidly increasing oxygen needs and systemic inflammation: Add either Baricitinib or Tocilizumab to one of the two above options.
- Hospitalized and requires IMV or EMCO.
    1. For most patients - Dexamethasone.
    2. For patients who are within 24 hours of admission - Dexamethasone plus Tocilizumab.

xi. Lung Transplantation

When to consider lung transplantation for COVID-19 patients?

1. Candidates should be younger than 65 years of age. Existing experience from ECMO bridge to lung transplantation shows poor outcomes in older patients.

2. Candidates eligible for transplantation should have only single organ dysfunction.

3. Sufficient time should be allowed for lung recovery. It is in the best interest of the patient to be able to survive without a transplant given the suboptimal long-term survival rates of lung transplantation (about 60% at 5 years).

4. There should be radiological evidence of irreversible lung disease, such as severe bullous destruction or evidence of established fibrosis.

5. The patient should be awake **and, in a position,** to discuss and consent to his transplantation.

6. Patients should be able to participate in physical rehabilitation while on the transplantation waiting list.

7. Patients should fulfil the remaining typical criteria for transplantation. For example, **adequate body**-mass index and absence of other notable comorbidities, such as severe coronary artery disease etc.

8. The patient should have a recent negative SARS-CoV-2 PCR test result, or infectivity assays using deep respiratory tract samples showing the absence of viable virus.

9. The transplantation centre should have substantial experience with cases involving high-risk transplantation.

10. The centre should have access to a broad donor pool and low waiting-list mortality.

As such, lung transplantation should be considered only in a selected group of patients with COVID-19-related ARDS as the ultimate effect and results of offering this life-saving therapy in this population remain unknown.

Consideration for following drugs - Colchicine, piroxicam, itolizumab, bevacizumab are also relevant as tocilizumab has scarce availability

- **Piroxicam use:** Some physicians have used in those cases where oxygen was needed but beds were not available in moderate cases in dose of 20mg SL dispersible tablet and observed improvement in oxygen saturation. We do not recommend it in absence of any case-controlled study.
- **Colchicine use: Except few studies, most of studies did not find any significant improvement. It is now being used in mild, moderate and severe cases despite any recommendations by standard guidelines.** • It is considered if fever persists despite paracetamol• Loading dose: 1.5 mg followed by 0.5 mg of colchicine 60 minutes later if no adverse gastrointestinal effects • Maintenance dosage: 0.5 mg BD until discharge or a maximum of 21 days (reduce to OD if body weight <60 kg) Contraindicated if eGFR<30mL/min/1.73m^2. **We do not recommend either for or against the use of colchicine for the treatment of nonhospitalized patients.** Do not use it in hospitalized patients.
- **Tofacitinib/ baricitinab: If used, consider the following:**
    - Two drugs are available, but we recommend to use Baricitinib only as there are no clinical data on the use of tofacitinib to treat COVID-19.
    - For the Initial Viral Replicative Phase of Illness (First 5 days of illness) we recommend AGAINST the use of steroids or any other immunomodulatory medicines during this period.
    - For the Inflammatory Phase of Illness (From Day 6 of onset of symptoms) Immunomodulatory Treatment is recommended for the covid-19 positive patients with any of the following signs of deterioration (after exclusion of alternative causes like secondary infections etc.):
        - SpO2 below 94% at rest on room air.
        - SpO2 falling by > 4% from baseline after 6-minute walk at normal pace.
        - CRP > 30 mg/l; or Doubling of CRP from baseline in second week of illness (if baseline values available).
        - HRCT Severity score >9 score.

- It has been recommended to start anticoagulation treatment for all patients on JAK inhibitors who have intermediate or high-risk factors for thrombosis. Drug and duration should be decided on Individual basis, based on age, risk factors and D-Dimer levels. (Risk Factors: reduced mobility, active cancer, prior history of DVT, prior h/o anti-phospholipid antibody syndrome, elevated D-dimer levels (>2 times the upper limit of normal).

- **Methylene Blue:**
  - As there are only anecdotal reports, it is not indicated.
- **Bevacizumab - (Avastin 400mg single dose vial):**
  - It is an anti VEGF recombinant humanized monoclonal antibody.
  - **It is being tried** with severe COVID-19, with respiratory rate ≥30 times/min, oxygen saturation ≤93% with ambient air, or partial arterial oxygen pressure to fraction of inspiration O_2 ratio (PaO_2/FiO_2) >100 mmHg and ≤300 mmHg, and diffuse pneumonia confirmed by chest imaging.
  - It is priced between Rs37,500 to Rs39,000.
  - Bevacizumab 7.5mg/kg body weight + 0.9% NaCl 100ml, intravenous drip.
- **2-Deoxy-D-Glucose by DRDO**
  - A total of 110 patients were part of the Phase-II clinical trials of DRDO's 2-DG drug. The results showed that in terms of improvement of vital signs of COVID-19 symptomatic patients there was a difference of 2.5 days compared to Standard of Care (SoC). (INDE-GENIUS study)
  - The 2 DG drug, like glucose, spreads through the body, reaches the virus-infected cells and prevents virus growth by stopping viral synthesis and destroys the protein's energy production. The drug also works on virus infection spread into lungs which help us to decrease patient’s dependability on oxygen."
  - The anti-COVID drug 2-DG has been developed in powder form and is ingested orally by dissolving it in water.
  - Phase III trial on (40 patients) report led to DCGI approval - 8th May 2021
  - Dose and Regimen: 2-DG: 45 mg/kg body weight AM + 45 mg/kg body weight PM, twice daily for not more than 10 days. Instructions for preparation of one dose (morning or evening) of 2-DG (Dose level - 90 mg/kg body weight/day, administered in two equally divided doses approximately 12 hours apart) DO NOT USE the reconstituted dose solution for further dosing of the patient. Each dose of 2-DG should be prepared using a fresh 5.85 g sachet.

- **At present, we do not recommend for or against its use.**

- **Virafin**
  - On April 23, 2021, Virafin had received restricted, emergency use approval from the Drug Controller General of India (DCGI).
  - 'Virafin' is pegylated interferon alpha-2b. Interferons are signalling proteins that help the body's immune system defend against viral infections. Pegylated interferon alpha 2b have been used to help treat Hepatitis C.
  - Its phase 2 trial results were published in the *International Journal of Infectious Diseases*, in its April 2021 issue.
  - It was conducted with 40 patients who had moderate COVID-19 – 20 of them were assigned to the control arm and 20 to the treatment arm.
  - It was used in RT-PCR confirmed SARS-CoV-2 infection, pneumonia with no signs of severe disease, respiratory rate 15-30 breaths/min, oxygen saturation 90%–94%.
  - Each dose of Virafin costs Rs 9,000 per injection.
  - **Due the many flaws in the study, we do not recommend its use at present**.

- **Fluvoxamine:** It is a selective serotonin reuptake inhibitor (SSRI). It is not FDA-approved for the treatment of any infection. There is insufficient evidence either for or against the use of fluvoxamine for the treatment of COVID-19.
- **Drugs not to be used:**
  1. Baricitinib with tocilizumab.
  2. Interferons (alfa or beta) for the treatment of severely or critically ill patients with COVID-19.
  3. Kinase inhibitors:
     a. Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib).
     b. Janus kinase inhibitors other than baricitinib (e.g., ruxolitinib, tofacitinib).
  4. Non-SARS-CoV-2-specific intravenous immunoglobulin (IVIG). But it should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
  5. Sarilumab for patients who do not require ICU-level care or who are admitted to the ICU for >24 hours but do not require invasive mechanical ventilation, non-invasive ventilation, or high-flow oxygen.
  6. The anti-IL-6 monoclonal antibody siltuximab.

Guideline for tackling Mucormycosis Prevention and treatment

ALERT

- ***Rhino-Orbito-Cerebral** Mucormycosis **(ROCM)** being a rapidly progressive disease, even a slight delay in the diagnosis or appropriate management can have devastating implications.*
- *Outcome can be optimized by early diagnosis prompted by awareness of warning signs and symptoms and high index of clinical suspicion, confirmation of diagnosis by appropriate modalities, and initiation of aggressive medical and surgical treatment by a multidisciplinary team.*

(Adapted from Mucormycosis Study Group Sir Ganga Ram Hospital, New Delhi and IJO-2021)

Suspected OR confirmed Mucormycosis

Look for

- Covid history.
- History of steroid therapy, other medication, hospital stay.
- Known medical history: DM, renal failure, immunocompromised pt, malignancy.
- Findings: Facial Swelling, Periorbital Swelling, Severe Headache, Nasal Blockage, Intraoral Pus Discharge, Gingival Abscess, Teeth Mobility.

Do Investigation

- Blood investigation: CBC, CRP, HbA1c, Renal profile.
- Radiological: CT PNS or 3D CT Face, MRI Findings - · Early stage: sinusitis · Intermediate stage: Bony erosion in maxilla · Aggressive stage: involvement of orbit and brain
- Diagnostic Nasal Endoscopy (DNE) + Otoscopy + Palatal Examination.
- Deep Nasal Swab for KOH smear & Fungal Culture.

- Biopsy (in Sterile Saline for Mycology & Formol Saline for Histopathology)
- [At any point, in very high clinical suspicion - Day 1 till whenever and start liposomal amphotericin B (in very high clinical suspicion) without waiting for the Microbiology Reports]

Treatment

Antifungal medication

- Inj Amphotericin B (1.0-1.5 mg/kg/day).
- Inj Liposomal Amphotericin B (5-10 mg/kg/day).
- For 14 to 21 days.
- Note: Liposomal Amphotericin is preferred as it has relatively lesser nephrotoxic. The duration of therapy is highly individualized and should encompass the resolution of associated symptoms and findings normalization of radiologic findings, negative cultures from affected site, and resolution of immunosuppression.
- Tab Posaconazole GR 100 mg (step down or adjutant therapy) First day - 300 mg BD Other days - 300 mg OD for 45 days.

Alternate day perform · S. Creatinine · S. Electrolyte To avoid Nephrotoxicity and hypokalemia.

Regular follow-up (CT PNS every 15 days to 1 month).

Amphotericin B administration protocol.

Pre-hydration

- 500ml Normal saline 2 hr. before infusion Amphotericin B
- To reduces the risk of renal toxicity and hypokalemia: - 500ml Normal Saline + 1 Amp (20mmol) KCL

Hydration

- Dilution: 1mg in 10 ml.
- Always use 5% or 10% dextrose.

- Avoid Normal saline.
- 500 mL NS IV given pre-infusion.
- If fluid overloaded, use 250 mL pre/post or skip post-hydration.
- If hyperchloremic, may use normosol instead of NS.
- Protect from light during administration Drugs Recommended Dose Duration Amphotericin B 1.0-1.5 mg/kg/day 14 to 21 days depending on severity.

Surgical

Early stage (only sinus is involved no bony change):

- Excisional biopsy (deep bone) + sinus lining.
- FESS (Functional Endoscopic Sinus Surgery).

Confirmed or late stage (bony erosion):

- Debridement and curettage till healthy bone.
- Orbital exenteration if indicated after ophthalmologist opinion.
- FESS.

Test sampling.

- Bacterial or fungal cultural and sensitivity
- Histopathological investigation.

New Mantra in COVID cases

1. Baseline HbA1c on Admission.

2. The strict control of blood sugar levels (110-180 mg/dl).

3. Proper management of Diabetic Ketoacidosis (DKA).

4. Rational use of steroids in the high-risk group.

5. Adequate humidification with distilled water used in the humidifiers of the Conventional / Low Flow / High Flow Oxygen delivery systems.

6. Isotonic-Saline Nasal Douche / Spray x 2 Times a day.

7. Maintain the Hygiene of Oxygen Delivery Systems.

8. Complete ENT Evaluation.

New Sutra to Educate patients about the early signs and symptoms of Mucormycosis

1. Nasal Blockage.

2. Blood-tinged nasal discharge.

3. Headache.

4. Pain in the Eye.

5. One sided Facial Pain & Swelling or Numbness.

6. Toothache, Loosening teeth, discomfort during chewing.

7. Swelling of the Eye & Adnexa.

8. Double Vision.

Warning signs and symptoms of Rhino-Orbito-Cerebral Mucormycosis (ROCM)

- Nasal stuffiness
- Foul smell
- Epistaxis
- Nasal discharge - mucoid, purulent, blood-tinged or black
- Nasal mucosal erythema, inflammation, purple or blue discoloration, white ulcer, ischemia, or eschar
- Eyelid, periocular or facial edema
- Eyelid, periocular, facial discoloration
- Regional pain – orbit, paranasal sinus or dental pain
- Facial pain
- Worsening headache
- Proptosis
- Sudden loss of vision
- Facial paresthesia, anesthesia
- Sudden ptosis
- Ocular motility restriction, diplopia
- Facial palsy
- Fever, altered sensorium, paralysis, focal seizures

Prevention of Rhino-Orbito-Cerebral Mucormycosis in the setting of COVID-19 (IJO-2021)

- Judicious and supervised use of systemic steroids in compliance with the current preferred practice guidelines
- Judicious and supervised use of tocilizumab in compliance with the current preferred practice guidelines
- Aggressive monitoring and control of diabetes mellitus
- Strict aseptic precautions while administering oxygen (sterile water for the humidifier, daily change of the sterilized humidifier and the tubes)
- Personal and environmental hygiene
- Betadine mouth gargle twice a day (not nasal drops)
- Barrier mask covering the nose and mouth
- Consider prophylactic oral Posaconazole in high-risk patients (>3 weeks of mechanical ventilation, >3 weeks of supplemental oxygen, >3 weeks of systemic steroids, uncontrolled diabetes mellitus with or without ketoacidosis, co-morbidities with immunosuppression)

Post Discharge

i. Anti-coagulation

- We do not recommend anticoagulants and antiplatelet therapy for non-hospitalized patients with COVID-19. It should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy.
- All admitted patients should, if there are no contraindications, receive anticoagulants in a prophylactic dose. Some guidelines do not recommend it but others do. So, aspirin and statin are not recommended for everyone on discharge.
- The decision on use of anticoagulants needs to take into account the risk of thrombosis and of bleeding on anticoagulants.
- The National Institutes of Health (NIH) does not recommend routine post discharge VTE prophylaxis for patients with COVID-19.
- The signal for increased thrombotic risk is sufficient to recommend pharmacologic venous thromboembolism (VTE) prophylaxis in all hospitalized COVID-19 patients as long as there is no contraindication.
- Extended post-hospital VTE prophylaxis should be considered in patients with COVID-19 (up to 45 days- MAGELLAN, APEX and MARINER studies).
- It is reasonable to employ individualized risk stratification of thrombotic and bleeding risk, to consider patients with elevated risk of VTE [e.g., Reduced mobility, active cancer, prior DVT, elevated D-dimer (>2 ULN)]. VTE options include Apixaban 2.5 bid, rivaroxaban 10 mg daily or Enoxaparin SQ daily (prevention dose adjusted for weight).
- When the risk of thrombosis is high, (as assessed by the ISTH SIC score) and a high bleeding risk has been ruled out (using the HAS-BLED score), we would recommend therapeutic anticoagulation.
- A high HAS-BLED score (≥3) is indicative of the need for regular clinical review and follow-up, but should not be used per se as a reason for stopping oral anticoagulation. All scores are available through **online calculators.**
- At hospital discharge, patients must be educated on the signs and symptoms of VTE and advised to seek urgent medical attention should these develop.

- Post discharge VTE prophylaxis decisions should be individualized, taking into consideration the patient's risk factors, including reduced mobility, bleeding risks, and feasibility.
- **Pregnancy Issues:** If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, continue it. If hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended. After hospital discharge is not recommended for pregnant patients. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge needs individualization, access concomitant VTE risk factors. Anticoagulation therapy use during labor and should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy.
- Lactation Issues: Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn. These can be used by breastfeeding individuals with or without COVID-19 who require VTE prophylaxis or treatment.

  Note: Use of direct-acting oral anticoagulants during pregnancy is not routinely recommended due to lack of safety data.

ii. Corticosteroid therapy

- Based on data from the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, NIH guidelines recommend using dexamethasone 6 mg per day for up to 10 days for the treatment of COVID-19 in patients who are mechanically ventilated (level of evidence: AI—strong, based on ≥1 randomized trial) and in patients who require supplemental oxygen but who are not mechanically ventilated (level of evidence: BI—moderate, based on ≥1 randomized trial).
- It is advised to continue a course of dexamethasone for 10 days even after discharge in recovered COVID-19 patients who required oxygen during hospital admission.
- NIH guidelines recommend against the use of dexamethasone for COVID-19 cases not requiring supplemental oxygen due to lack of survival benefits and potential harmful effects (AI).

iii. Oxygen therapy

- Although there is no evidence about the beneficial use of oxygen therapy at home in discharged COVID-19 patients, short-term home oxygen therapy may be considered in

hypoxemic patients at rest (oxygen saturation <88% on room air). Risks and benefits should be weighed before discharging patients on home oxygen.

iv. Adjuvant therapies

- Some vitamins and minerals such as vitamin C, vitamin D, and zinc have been proposed for use in COVID-19 due to their beneficial antioxidant immunomodulatory effect, but NIH recommends against using them due to lack of safety and efficacy.
- We opine to use these on case-to-case basis.

Treatment of Post-Covid Symptoms

Investigate it

Not all patients will need all

- CBC: Anemia, Lymphopenia.
- CRP persistent inflammation or super aided infection.
- LFT, KFT, Blood Sugar.
- ECG - Bradycardia Cardiac involvement.
- Ferritin (inflammation and continuing prothrombotic state).
- D-dimer (thromboembolic disease).
- Troponin and D-dimer tests may be falsely positive, but a negative result can reduce clinical uncertainty.
- Troponin (acute coronary syndrome or myocarditis).
- Chest x-ray for all patients continued respiratory symptoms >12 weeks. Lung Fibrosis, Residual Pneumonitis, associated Fungal infections.

Issues and Management

Fever

- After recovery from Covid it is not uncommon to see resurgence of episodes of fever lasting few hours to days, especially after heavy physical activity. Such patients usually don't land up into serious complications.
- Rest, paracetamol and short 3-to-5-day course of Non-steroidal anti-inflammatory drugs like Mefenamic acid and Naproxen may be helpful.
- Some patients may require low dose of Non-steroidal Anti-inflammatory drugs for long duration. However, it may be important to monitor Kidney function in such cases.

Cough

- Rule out super-infection.
- Rule out other complications as pleuritis (painful).
- Graded physical activity in case cough/fever/fatigue/breathlessness is precipitated by walking or talking.
- Medication where indicated:
    - Antihistaminic.
    - Nebulization with Budesonide, Bronchodilators.
    - Proton pump inhibitors (if reflux is suspected).
    - Cough Lozenges.
- Respiratory Exercises: Helpful in Chronic cough aimed at normalizing breathing patterns and increasing the efficiency of the respiratory muscles (including the diaphragm).

Technique

- The patient should sit in a supported position and breathe in and out slowly, preferably in through the nose and out through the mouth, while relaxing the chest and shoulders and allowing the tummy to rise.
- They should aim for an inspiration to expiration ratio of 1:2. This technique can be used frequently throughout the day, in 5–10-minute bursts (or longer if helpful). Other breathing techniques—such as diaphragmatic breathing, slow deep breathing, pursed lip breathing, yoga techniques (Pranayama) are immensely helpful.

Breathlessness

- Some breathlessness is common after covid-19. It tends to improve with breathing exercises.
- Treatment remains the same as for cough.
- But it is important to monitor oxygen by pulse oximeter. Oxygen level of 96% or above and the absence of desaturation on exertional tests like six-minute walk test is reassuring.
- Oxygen therapy should not be delayed at a level of 92% or below. Amount of supplemental oxygen should be titrated to target a range 94-98%.
- Survivors of covid-19 ARDS are at risk of long-term impairment of lung function and may require long-term home-based oxygen therapy.

Lung Fibrosis

- Pirfenidone 801 mg TDS is being tried but most of the pulmonologist do not advocate.
- It appears that majority of post Covid patients recover with time with insignificant/zero lung fibrosis over 3 to 4 months.
- The key is oxygenation, preventing secondary complications & nursing care.
- Nintedenib 150mg OD/BD is also being used as anti-fibrotic drugs. It needs to be used with LFT monitoring and only if HRCT shows Fibrosis.
- We recommend to start these drugs only after consultation of a Pulmonologist. Use of antifibrotic in COVID 19 trials are ongoing. No evidence in favor or against at present.

Silver Lining

- Serious interstitial lung disease is rare in patients who are not hypoxic.
- Lung changes are largely reversible in most of the patients despite high CT severity score.

Multisystem Inflammatory Syndrome in Adults

Diagnosis Clues

1. Evidence of acute or recent SARS-CoV-2 infection (documented by a nucleic acid amplification test [NAAT] or antigen or antibody testing) with minimal respiratory symptoms.
2. With laboratory markers of severe inflammation (e.g., elevated C-reactive protein [CRP], ferritin, D-dimer, cardiac enzymes, liver enzymes, and creatinine).
3. With various other symptoms, including fever and shock; and signs of cardiovascular, gastrointestinal, dermatologic, and neurologic disease.

Most adults in whom MIS-A has been described have survived.

MIS-A is defined by the following criteria:
▪ A severe illness requiring hospitalization in an individual aged ≥21 years;
▪ Current or past infection with SARS-CoV-2;
▪ Severe dysfunction in one or more extrapulmonary organ systems;
▪ Laboratory evidence of elevated inflammatory markers (e.g., CRP, ferritin, D-dimer, interleukin [IL]-6);
▪ Absence of severe respiratory illness; and
▪ Absence of an alternative unifying diagnosis.

Management

There are currently no controlled clinical trial data in patients with MIS-A to guide treatment of the syndrome.

Most of the cases have been managed by use of intravenous immunoglobulin, corticosteroids, or anti-IL-6 therapy.

NOTE: This is a consensus document based on best scientific evidence available. For management, please consider national and state guidelines preferably.

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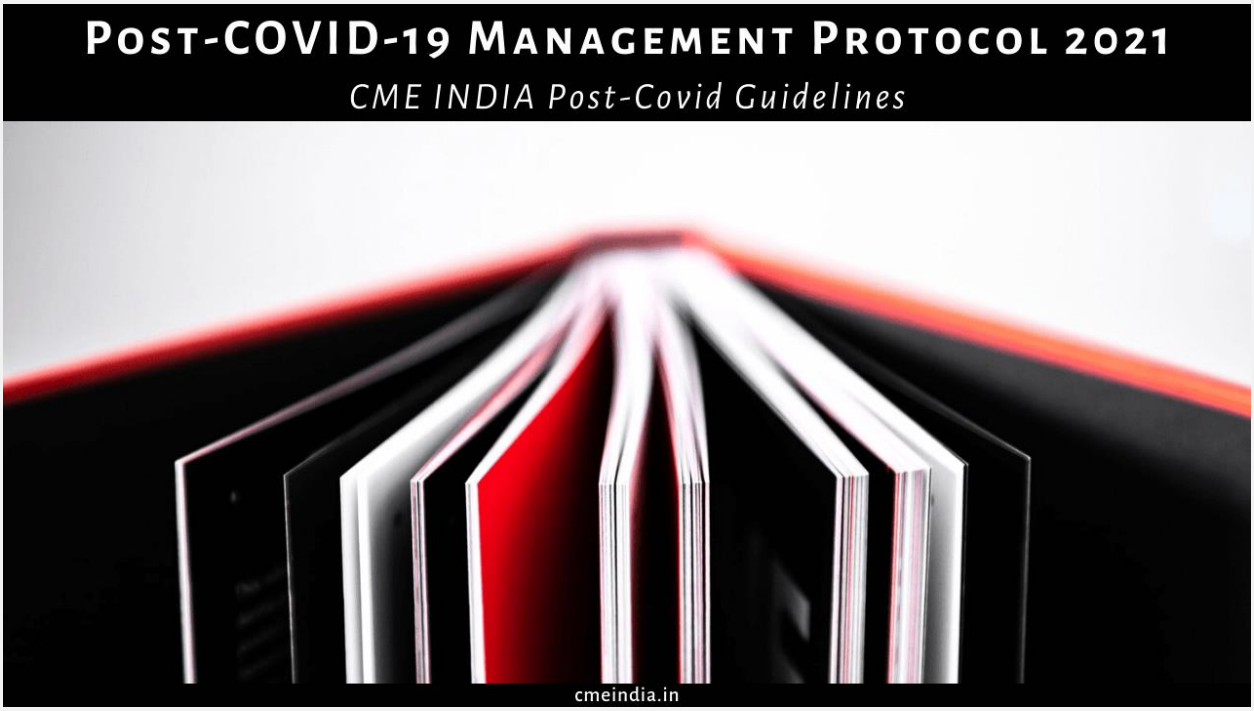

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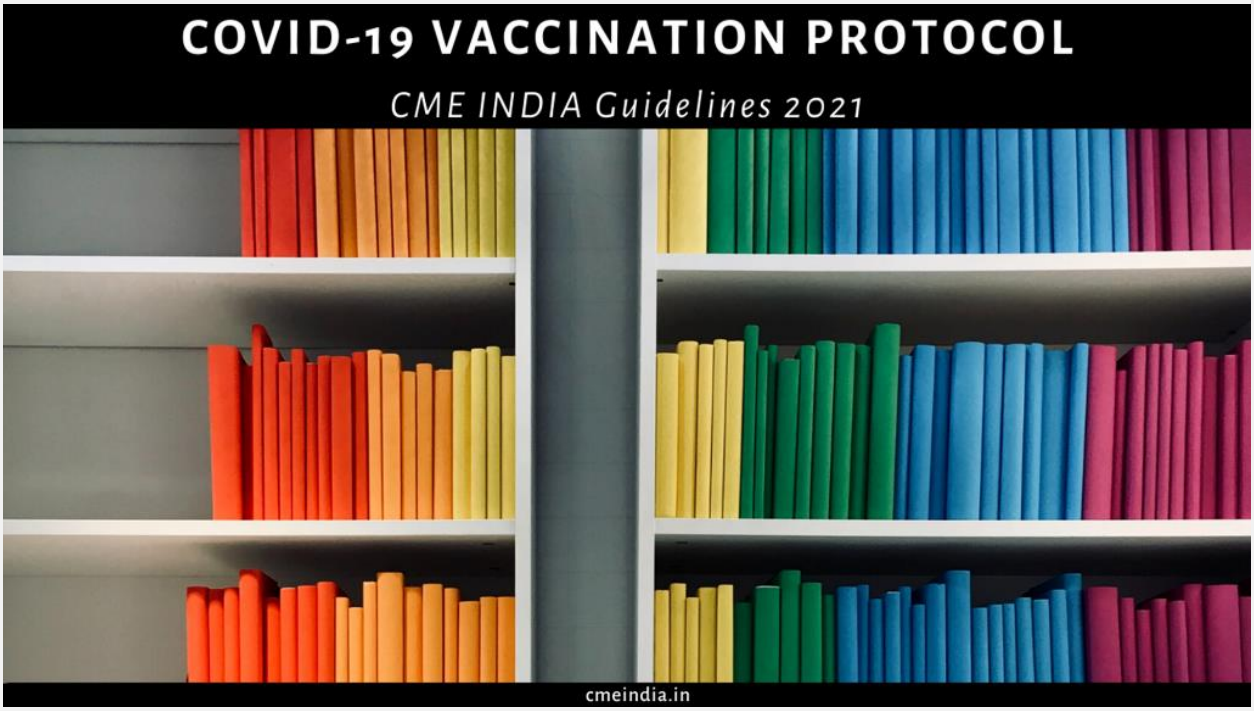

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