Clinical management guidelines for suspected or confirmed COVID-19 infection in adults

How to cite the COVID-19 clinical management guidelines:

The taskforce regularly reviews and update the recommendations in these guidelines as new evidence emerge. Ensure that the most recent version of the guidelines is used. Smart phone users may access these guidelines using the QR code. Other resources related to COVID-19 are available at the ministry website: https://moh.nugmyanmar.org/coronavirus/
This document may be shared freely without any restrictions by health professionals in Myanmar.
# Contents

NEW EVIDENCE AND RECOMMENDATIONS ........................................................................................................ 4
QUICK REFERENCE GUIDE ...................................................................................................................................... 5
LIST OF ABBREVIATIONS .................................................................................................................................. 8
INTRODUCTION .................................................................................................................................................... 10
DEFINITIONS OF DISEASE SEVERITY .................................................................................................................. 10
INVESTIGATIONS .................................................................................................................................................... 12
GENERAL PRINCIPLES OF MANAGEMENT .......................................................................................................... 12
SYSTEMIC CORTICOSTEROIDS ............................................................................................................................ 14
PREVENTION OF VENOUS THROMBOEMBOLISM ............................................................................................... 16
MANAGEMENT OF VENOUS THROMBOEMBOLISM (VTE) ....................................................................................... 18
OXYGEN SUPPLEMENTATION ................................................................................................................................ 19
  NASAL PRONGS .................................................................................................................................................. 19
  SIMPLE FACE MASK ........................................................................................................................................... 20
  HIGH CONCENTRATION RESERVOIR MASK (NON-REBREATHTHING MASK) ...................................................... 21
  USING OXYGEN FROM TWO SOURCES .............................................................................................................. 21
  VENTURI OXYGEN MASK .................................................................................................................................... 21
AWAKE PRONE POSITIONING ................................................................................................................................ 24
ANTIVIRALS ............................................................................................................................................................ 26
  REMDESIVIR .......................................................................................................................................................... 26
  MOLNUPIRAVIR ..................................................................................................................................................... 29
IMMUNOMODULATORY AGENTS ........................................................................................................................... 30
  BARicitinib ............................................................................................................................................................ 30
  TOCILIZUMAB .................................................................................................................................................... 31
BREATHING/RESPIRATORY SUPPORT .................................................................................................................... 33
NON-INVASIVE VENTILATION ................................................................................................................................... 35
  CONTINuous POSITIVE AIRWAY PRESSure (CPAP) ............................................................................................. 35
  BI-LEVEL POSITIVE AIRWAY PRESSure (BIPAP) .................................................................................................. 38
  HIGH FLOW NASAL CANNULA (HFNC)  HIGH FLOW NASAL OXYGENATION (HFNO) ...................................... 39
ANTIBIOTICS ............................................................................................................................................................. 40
PALLIATIVE CARE ................................................................................................................................................... 41
REFERENCES .......................................................................................................................................................... 42
NEW EVIDENCE AND RECOMMENDATIONS

This is an updated living guidance based on rapidly emerging new evidence and information. The World Health Organisation’s living guideline on Therapeutics and COVID-19, published on 14 January 2022¹, the COVID-19 rapid guideline: Managing COVID-19 v20.1 of the National Institute for Health and Care Excellence, UK, published on 2 January 2022² and the Coronavirus 2019 (COVID-19) Treatment Guidelines of the National Institutes of Health of the US, updated on 1 February 2022³ are considered. The evolving trend of Omicron variant as the main COVID variant of concern throughout the world and the proportion of effective vaccination coverage in Myanmar are also considered. Logistical and cost constraints of the new medications are also weighed into the recommendations.

The following are new clinical evidence and recommendations for or against treatments edited to the previous versions of the NUG COVID-19 guideline.⁴,⁵

- The list of clinical conditions which put patients at high risk of progression to severe COVID-19 infection is extended (see page 11-12).

- In prevention of venous thromboembolism, prophylactic dose of low molecular weight heparin (LMWH) is recommended in most cases instead of intermediate and therapeutic doses. This change in recommendation is based on the emerging evidence of increased bleeding without a reduction in mortality in higher LMWH usage.⁶ Therapeutic dose of LMWH is still recommended in cases where venous thromboembolism is suspected. Conditional recommendation is made for therapeutic LMWH dosing in those who require low flow oxygen and have a D-dimer >4 times above the upper limit of normal without an increased bleeding risk (see page 16).

- In high-risk patients with mild to moderate COVID infection, an additional recommendation is made to consider the use of antivirals, remdesivir or molnupiravir if remdesivir is not available, suitable or tolerated, to prevent disease progression (see page 27 - 29).

- In treatment for patients with severe COVID-infection who require high flow oxygen, NIV or mechanical ventilation, as an additional anti-inflammatory agent to corticosteroids, oral baricitinib can be considered as an alternative to tocilizumab (see page 30).
### Definition of disease severity

**Mild illness.** Symptomatic without features of viral pneumonia or hypoxaemia. Common symptoms: fever, cough, fatigue, anorexia, shortness of breath, myalgia. [WHO classification]

**Moderate illness.** Clinical symptoms and signs of pneumonia (fever, cough, dyspnoea) with no features of severe pneumonia. SpO₂ >93% on room air.

**Severe illness.** Clinical pneumonia and one of the following (respiratory rate >30/min, severe respiratory distress or SpO₂ ≤93% on room air)

**Critically illness.** Clinical symptoms and signs of any of the following: acute respiratory distress syndrome (ARDS), sepsis, septic shock, or multi-organ failure.

- People >65 and immunosuppressed individuals may present with atypical symptoms.
- ‘Silent hypoxia’ is common.

### Consider the following

- Tests for SARS-CoV-2 virus by antigen RDT or GeneXpert® and RT-PCR if available.
- Check for malaria parasites by RDT or blood film in endemic areas if indicated.
- Check for dengue if rash is seen.
- CP, U&E, creatinine, RBS, LFT
- If possible, CRP, ferritin, D-dimer, LDH and CXR
- Test troponin and do ECG if any chest pain
- Procalcitonin, if possible, to rule out bacterial infections especially before considering tocilizumab

### Assess risk factors for severe illness

- Age >65
- Obesity
- Smoking
- Diabetes
- Hypertension
- Chronic respiratory diseases, cardiac diseases, chronic kidney diseases, cerebrovascular disease
- Cancer
- Immunocompromised state
- Pregnancy or recent pregnancy
- Mental health disorders such as depression and schizophrenia

### Manage according to disease severity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe or critically ill</th>
</tr>
</thead>
</table>
| - Give advice on self-isolation and good infection control practices.  
  - Can offer paracetamol for symptomatic treatment for fever and pain.  
  - Give advice on adequate hydration and nutrition.  
  - Do not recommend routine or prophylactic antibiotics.  
  - Counsel on symptoms that should prompt seeking urgent care.  
  - Do not recommend thromboprophylaxis. | - Give advice on self-isolation and good infection control practices.  
  - Train patients on self-monitoring BP, temperature, oxygen level and heart rate.  
  - Counsel on symptoms that should prompt seeking urgent care.  
  - Monitor closely for disease progression.  
  - Can consider antibiotics if suspicious of coexisting bacterial infection. Consider stopping | Admit to hospital if possible.  
**Remember STOP**  
- $S$: start steroids – dexamethasone 6mg PO/IV od or alternatives for 7-10 days in those who require O2 (see details in corticosteroid section).  
- $T$: start thromboprophylaxis – LMWH or alternatives, in standard dose, for 14 days or till discharge (see details in the thromboprophylaxis section).  
|
antibiotics if procalcitonin is negative.
- Test O₂ desaturation with sitting and standing for 1 min or walking 40 steps. If desaturation of >3% on testing, manage as severe.
- Do not recommend thromboprophylaxis.

- In high-risk group, can consider antivirals (remdesivir or molnupiravir).\(^n\) (see details under antivirals in mild to moderate disease with high risk of progression)

**O**: offer oxygen therapy (target O₂ saturation >93% or 88-92% if there is risk of type 2 respiratory failure). Titrate oxygen using appropriate interfaces to achieve target saturation (see flow chart in the oxygen therapy section).

**P**: try prone positioning (see details in the awake prone positioning section).

- **Consider ABBA**

  **A**: consider antivirals such as remdesivir for 5 days if within 10 days of symptom onset and on oxygen (conditional recommendation). Not recommended in those needing mechanical ventilation (see details in remdesivir section).

  **B**: consider baricitinib if available within 48 hours of starting on high flow O₂, CPAP, BiPAP or mechanical ventilation, when CRP ≥ 75 mg/L and there is no coexisting bacterial or other viral infection.\(^n\) Tocilizumab can be considered as an alternative to baricitinib (see details in the immunomodulators section)

- **B**: offer breathing support in the form of CPAP, BiPAP, HFNC or mechanical ventilation as appropriate if available. Timely support if oxygen saturation target not reached or sustained with high flow O₂ (see details in respiratory support section).

- **A**: consider antibiotics if bacterial infection is suspected. Consider stopping antibiotics if markers for infection, eg procalcitonin, do not indicate bacterial infection (see details under antibiotics section).

**Monitor COVID**

- **C**: circulation – beware of hypovolaemic and septic shock. Treat promptly.

- **O & V**: monitor oxygen and other vital signs to detect rapidly progressing respiratory failure, hypovolaemic and septic shock.

- **I**: monitor intake and output. Aim neutral fluid balance, euvolemia and urine output ≥ 0.5 mL/kg/h

- **D**: monitor diabetes and aim for high caloric diet.
## Decide on escalation

- Discuss and decide proactively.
- Involve the patient and the family.
- Decide whether full respiratory support including intubation or palliative care is appropriate.

*N = new evidence or new guidance*
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>Arterial blood gas</td>
</tr>
<tr>
<td>ACTT-1 trial</td>
<td>Adaptive COVID-19 Treatment Trial</td>
</tr>
<tr>
<td>AGP</td>
<td>Aerosol generating procedure</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransaminase</td>
</tr>
<tr>
<td>Anti-IL6</td>
<td>Interleukin-6 receptor antagonist</td>
</tr>
<tr>
<td>APTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BD</td>
<td>Latin: <em>bis in die</em>, twice a day</td>
</tr>
<tr>
<td>BiPAP</td>
<td>Bilevel positive airway pressure</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Corona Virus Disease 2019</td>
</tr>
<tr>
<td>CP</td>
<td>Complete picture</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTPA</td>
<td>CT pulmonary angiogram</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>DKA</td>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>DOAC</td>
<td>Direct oral anticoagulant</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>EPAP</td>
<td>Expiratory positive airway pressure</td>
</tr>
<tr>
<td>FIO2</td>
<td>Fraction of inspired oxygen</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-intestinal</td>
</tr>
<tr>
<td>HFNC</td>
<td>High flow nasal cannula</td>
</tr>
<tr>
<td>HFN0</td>
<td>High flow nasal oxygen</td>
</tr>
<tr>
<td>HHS</td>
<td>Hyperosmolar hyperglycaemic syndrome</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Disease Society of America</td>
</tr>
<tr>
<td>INR</td>
<td>International normalised ratio</td>
</tr>
<tr>
<td>IPAP</td>
<td>Inspiratory positive airway pressure</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td>MR</td>
<td>Modified release</td>
</tr>
<tr>
<td>NaCl</td>
<td>Sodium chloride</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute of Health Research</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>OD</td>
<td>Latin: <em>Omne in die</em>, Once a day</td>
</tr>
<tr>
<td>PaCO2</td>
<td>Partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PaO2</td>
<td>Partial pressure of oxygen</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>RBS</td>
<td>Random blood sugar</td>
</tr>
<tr>
<td>RDT</td>
<td>Rapid diagnostic test</td>
</tr>
<tr>
<td>RECOVERY trial</td>
<td>Randomised Evaluation of COVid thERapY trial</td>
</tr>
<tr>
<td>RECOVERY-RS trial</td>
<td>RECOVERY – respiratory support trial</td>
</tr>
<tr>
<td>REMAP-CAP trial</td>
<td>Randomised, Embedded, Multi-factorial, Adaptive Platform</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory rate</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>SaO₂</td>
<td>Arterial haemoglobin oxygen saturation</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus 2</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Sodium glucose co-transporter 2 inhibitors</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Peripheral capillary oxygen saturation</td>
</tr>
<tr>
<td>U&amp;E</td>
<td>Urea and electrolytes</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated heparin</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>VT</td>
<td>Tidal volume</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
INTRODUCTION

One of the central tenets of the National Unity Government is to promote the safety and welfare of the people of Myanmar. These guidelines are intended for clinicians and healthcare workers who are treating patients with COVID-19 under very challenging circumstances. These guidelines are ‘living guidance’ based on current available clinical evidence with reference to recommendations from professional societies and international health organisations. Clinical evidence on COVID-19 and its management is rapidly evolving. We have considered the practicality and availability of resources in Myanmar. Given the current situation on the ground, we have deliberately tried not to be prescriptive or dogmatic in specifying care settings (e.g., who should be hospitalised or who should be admitted to intensive care). We have, however, attempted to make recommendations on care in all settings for adults. Our guidelines do not apply to management in children or pregnant women.

DEFINITIONS OF DISEASE SEVERITY

We use World Health Organization’s case definition and severity definitions of COVID-19 infection. We stipulate a higher oxygen saturation level to define severe disease (< 93% on room air), compared to < 90% as defined by the WHO. This is to allow time for preparation either to secure oxygen supplies or to arrange an admission to a health facility as delays are anticipated.

Mild disease
- Symptoms of COVID-19 infection without features of viral pneumonia or hypoxia.
- Symptoms can be fever, cough, fatigue, anorexia, shortness of breath or myalgia.
- Loss of smell, loss of taste and other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported.
- Older people and people who are immunosuppressed may present with atypical symptoms such as reduced alertness and confusion.

Moderate disease
- Clinical signs of pneumonia (fever, cough, dyspnoea, rapid breathing) but no signs of severe pneumonia as defined below. \( \text{SpO}_2 > 93\% \) on room air

Severe disease
- Clinical signs of pneumonia (fever, cough, dyspnoea, rapid breathing) and one of the following features:
  - Respiratory rate > 30/min,
  - Severe respiratory distress or \( \text{SpO}_2 \leq 93\% \) on room air

Critical disease
Features of acute respiratory distress syndrome (ARDS), sepsis or septic shock as defined as below.

| Acute respiratory distress syndrome (ARDS) | The original definition of ARDS is based on \( \text{PaO}_2/\text{FiO}_2 \) ratio derived from arterial blood gas (ABG) analysis. It is categorised into mild, moderate and severe ARDS. However, ABG is not widely available currently and \( \text{FiO}_2 \) cannot be accurately measured as venturi masks are not widely used. Pragmatically, it can be inferred that a patient is likely to be at least in the mild form of ARDS if:
  - Oxygen saturations are < 93% on oxygen supplementation of \( \geq 6\text{L/min} \) of oxygen \( \text{(SaO}_2/\text{FiO}_2 \leq 315) \) and
  - Onset of desaturation within 1 week of new or worsening of respiratory symptoms and |

Ministry of Health, National Unity Government
Myanmar National COVID-19 Evidence and Guideline Taskforce
VERSION: 3.0 Published: 11 February 2022
▪ respiratory failure not fully explained by cardiac failure or fluid overload
▪ (Chest x-ray showing bilateral peripheral pulmonary infiltrates not explained by volume overload or heart failure)

**Sepsis**

Adults with acute life-threatening organ failure(s) caused by dysregulated host response to infection.

Signs of organ failure include altered mental status, laboured or fast breathing, low oxygen saturation, oliguria, tachycardia, low volume pulse, hypotension, cold extremities, skin mottling or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinaemia.

**Septic shock**

Adults with persistent hypotension despite volume resuscitation requiring vasopressors to maintain systolic blood pressure >90 mmHg

**HIGH RISK CONDITIONS**

(NEW) The following co-morbidities are considered as high-risk conditions which could make people progress to have severe covid infection if infected.8-13,18

<table>
<thead>
<tr>
<th>High level evidence (evidence presented in at least one meta-analysis or systematic review)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Chronic lung diseases limited to:</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Chronic liver disease limited to:</td>
</tr>
<tr>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Heart conditions (such as heart failure, coronary artery disease or cardiomyopathies)</td>
</tr>
<tr>
<td>Mental health disorders limited to:</td>
</tr>
<tr>
<td>Mood disorders including depression</td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Obesity (BMI ≥30 kg/m²)</td>
</tr>
<tr>
<td>Pregnancy and recent pregnancy</td>
</tr>
<tr>
<td>Smoking (current and former)</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate level evidence (evidence presented in observational studies)</th>
</tr>
</thead>
</table>
INVESTIGATIONS

The tests that can be done in a timely fashion on the ground are limited. The following tests are suggested.

▪ Test for SARS-CoV-2 virus by antigen RDT or GeneXpert® and RT-PCR if available.
▪ Check complete picture (CP), urea & electrolytes (U&E), creatinine, random blood sugar (RBS), liver function tests (LFT) as baseline tests.
▪ Test C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase (LDH) and chest-x ray (CXR), if possible, to determine disease severity.
▪ Check for malaria parasites by RDT or blood film in endemic areas if indicated.
▪ Check for dengue if rash is seen.
▪ Test troponin and do ECG if there is any chest pain.
▪ Test procalcitonin, if possible, to inform decision on antibiotics or to rule out bacterial infections especially before giving tocilizumab.

D-dimer is not useful to rule in or out thromboembolism in COVID-19 infection as it will be high as part of the inflammatory response to the viral infection.

GENERAL PRINCIPLES OF MANAGEMENT

Mild disease
Majority of the patients with mild COVID infection will recover without significant symptoms or consequences. The following set of advice can be considered.

▪ Give advice on self-isolation and good infection control practices.
▪ Can offer paracetamol for symptomatic treatment for fever and pain.
▪ Give advice on adequate hydration and nutrition.
▪ Do not recommend routine or prophylactic antibiotics.
▪ Counsel on symptoms that should prompt seeking urgent care.
▪ Do not recommend thromboprophylaxis.
▪ Consider antivirals (remdesivir within 7 days of symptom onset or molnupiravir within 5 days of symptom onset) in the high-risk group (see the list of high-risk conditions). (NEW)

Moderate disease
Majority of the patients with moderate COVID infection will still recover without significant consequences. However, close monitoring of oxygen saturation and vital signs are essential as the course of the disease can change swiftly and patients can deteriorate rapidly. The following steps are recommended.

▪ Give advice on self-isolation and good infection control practices.
▪ Train patients on self-monitoring BP, temperature, oxygen level and heart rate.
▪ Counsel on symptoms that should prompt seeking urgent care.
▪ Monitor closely for disease progression.
Consider antibiotics if suspicious of coexisting bacterial infection. Consider stopping antibiotics if procalcitonin is negative.

Test O₂ desaturation with sitting and standing for 1 min or walking 40 steps. If desaturation of > 3% on testing, manage as severe.

Do not recommend thromboprophylaxis.

Consider antivirals (remdesivir within 7 days of symptom onset or molnupiravir within 5 days of symptom onset) in the high-risk group (see the list of high-risk conditions). (NEW)

‘Silent hypoxia’ or ‘happy hypoxia’
It is a common phenomenon in COVID-19 pneumonitis that patients can tolerate and look well with very low oxygen level till they deteriorate rapidly at the end with multiorgan failure. Regular checking of the oxygen saturation and acting upon it promptly and appropriately can save lives.

**Exertional desaturation**
In those with SpO₂ ≥93% on air, the presence of exertional desaturation should be tested with a 1-minute sit-to-stand test (by asking the patient to sit and stand in a comfortable but fast pace for 1 minute) or a 40-steps walking test. If there is an absolute fall of SpO₂ by 3% (from 95% to 92%), there is an element of viral pneumonitis; oxygen supplementation is likely to be needed soon.

Preparations should be made for an oxygen supplementation to be ready for use in case it is needed. Exertion should be limited with close monitoring of the oxygen saturation. Restrict exertion to the bare minimum even for basic daily activities. For example, use urinals or a commode instead of walking to the toilet.

**Severe and critical disease**
When possible, patients with severe and critical illness should be managed in hospital setting. Therapeutics that should be used and those that could be considered are described in detail in the following section.
SYSTEMIC CORTICOSTEROIDS

Rationale
The RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial in the UK in 2020 showed that dexamethasone reduced deaths by one third in ventilated patients and by one fifth in patients receiving oxygen only. It was concluded that 1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone. There was no benefit among those patients who did not require respiratory support.19

The REMAP-CAP (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia) trial20 used hydrocortisone. Although the hydrocortisone trial arm was stopped early due to the release of the positive outcome result of dexamethasone by the RECOVERY trial team, the preliminary result showed significant reduction in organ support free days and in-hospital mortality. There were other smaller studies that showed similar positive outcomes with corticosteroids.21-23 International health organisations, therefore, have recommended the use of steroids in severe COVID-19 infection.24,25

Indications
Offer corticosteroids in people with severe COVID-19 infection whose oxygen saturation is ≤93% on room air.

⚠︎ Systemic steroid therapy should not be used for either prevention or treatment of mild to moderate COVID-19 (in those who do not need oxygen supplementation).19

Formulations and dosages
- Offer corticosteroids in the morning. This is to emulate the natural diurnal rhythm.
- Consider short term low dose proton pump inhibitors (omeprazole, lansoprazole, pantoprazole) along with corticosteroids.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>6 mg orally once a day or 6 mg intravenously once a day</td>
</tr>
<tr>
<td></td>
<td>▪ Oral use is adequate.</td>
</tr>
<tr>
<td></td>
<td>▪ Only use intravenous administration if the patient cannot swallow or tablets are inappropriate or unavailable</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>40 mg orally once a day</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>50 mg intravenously three times a day</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>16 mg orally twice a day (NEW)</td>
</tr>
</tbody>
</table>

Duration
7 - 10 days

Glycaemic management
Corticosteroids can cause hyperglycaemia even in patients who are not known to have diabetes. Blood glucose level should be monitored and acted upon, as necessary, to prevent hyperglycaemic emergencies.

Monitoring
- When steroids are administered in the morning, blood glucose can start rising from late morning to midday onwards until later afternoon and evening.
- In patients with diabetes, consider checking blood glucose level before breakfast, lunch and dinner time and before going to bed.
- In those without pre-existing diabetes, consider checking the level before lunch and dinner time.
Treating hyperglycaemia

- Ideally, aim for a random blood sugar (RBS) in the range of 110 – 180 mg/dL (6.0 – 10.0 mmol/L).26
- An RBS level up to 210 mg/dL (12 mmol/L) may be acceptable.26
- Hypoglycaemia is more dangerous than hyperglycaemia. For those who may be at risk of hypoglycaemia (e.g. with known chronic kidney disease or poor oral intake), a level up to 260 mg/dL (16 mmol/L) may be safer. Glycaemic targets should be individualised.
- If the RBS is consistently above the intended individualised target, then there may be a need to start or increase diabetes medications.
  - If the RBS is frequently < 100 mg/dL (< 6 mmol/L), then reduce or stop diabetes medications.

Types of treatment

- Stop SGLT2 drugs (eg empagliflozin, dapagliflozin, canagliflozin). SGLT2 drugs may increase the risk of ketoacidosis in acute illness.
- Stop metformin if hypotensive or renal failure. Metformin may cause lactic acidosis (uncommon).
- Continue using the usual oral hypoglycaemic agents but adjust the dose as necessary in mild and moderate COVID infection.
- Use gliclazide and insulin mainly for glycaemic control when needed in severe COVID infection.
  - **Gliclazide:** If not used before, start with 40 mg OD and titrate up to maximal dose of 160 mg BD with morning and mid-day dosing. Modified release preparations should be generally avoided as they may increase the risk of hypoglycaemia in acutely ill individuals. If gliclazide MR is used at all, titrate cautiously from 30 mg OD to 120 mg OD.
  - If glycaemic control is not achieved despite increasing gliclazide doses, consider adding in insulin with the decision from a responsible clinician.
  - **Insulin:** In steroid-induced hyperglycaemia, as adjunct to gliclazide, consider giving:
    - short-acting insulin (such as Actrapid and NovoRapid) in the morning and mid-day or
    - biphasic insulin (such as Mixtard 30 and NovoMix 30) in the morning or
    - insulin glargine (such as Lantus) once a day.
    - The estimated total daily dose is 0.3 mg/kg/day.
  - In insulin-treated patients taking corticosteroids, consider increasing the usual dose of insulin by 10-15% (e.g. if taking 30 units, increase to 34-36 units), then titrate according to blood glucose levels.
  - Insulin resistance will begin to fall when the dexamethasone has been stopped but may take a few days. Continue to monitor glucose 6 hourly and down titrate.

Hyperglycaemic emergencies

- If blood glucose level is > 350 – 400 mg/dL (20-22 mmol/L), be vigilant of signs and symptoms of diabetes emergencies.
- Diabetic ketoacidosis (DKA) may present with ketone breath, hunger breathing, confusion and dehydration.
- Hyperosmolar hyperglycaemic syndrome (HHS) develops more slowly, and symptoms are non-specific, e.g. being unwell or confused. All patients with HHS are grossly dehydrated.
- Consider urgent blood tests (U&E, creatinine, bicarbonate, ketone) and immediate senior physician consultation.
PREVENTION OF VENOUS THROMBOEMBOLISM

Rationale
Patients with severe and critical COVID-19 infection have increased risk of thrombosis. COVID-19 is also associated with in situ immune-thrombosis in smaller pulmonary arteries and capillaries, which has been postulated to be related to a distinct COVID-19 pulmonary intravascular coagulopathy. Studies confirmed that thromboprophylaxis is associated with improved mortality in patients admitted with COVID-19.

Indications
- Consider in COVID-19 infection of severe and critical severity.
- Consider in those with additional risk factors (e.g. age >65 years, male, obesity, active cancer, previous thromboembolism, pregnancy, immobility and multiple comorbidities)
- Routine thromboprophylaxis is not recommended in mild and moderate cases.

D-dimers are likely to be elevated in severe COVID-19 due to inflammatory response.

⚠︎ Current data do not support the routine use of high D-dimer levels in isolation to guide decisions regarding investigation and anticoagulation.

Forms of thromboprophylaxis
Low molecular weight heparin (LMWH) is the treatment of choice but unfractionated heparin (UFH), fondaparinux or direct oral anticoagulants (DOACs) can be used as alternatives if LMWH is not available.

Doses for thromboprophylaxis

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Critical</th>
</tr>
</thead>
<tbody>
<tr>
<td>No routine thromboprophylaxis</td>
<td>No routine thromboprophylaxis</td>
<td>Consider standard prophylactic dose</td>
<td>Consider standard prophylactic dose*</td>
</tr>
<tr>
<td>Absence of signs of severe or critical disease</td>
<td>Clinical signs of pneumonia, but no signs of severe pneumonia, SPO2 &gt;93% room air</td>
<td>SPO2 &lt; 93% on room air, Respiratory rate &gt;30/min, Signs of severe respiratory distress</td>
<td>Requires life sustaining treatment, Acute respiratory distress syndrome, Sepsis, Septic shock</td>
</tr>
</tbody>
</table>

* Treatment dose may improve the outcome (less requirement for organ support) in severe cases (not in critical cases) but can also increase bleeding risk and using treatment dose for thromboprophylaxis is not suggested in this guidance for treatment in community.

Recommendation against the use of therapeutic LMWH in severe and critically ill patients who need high flow oxygen treatment (NEW)
- Several randomised controlled trials, the largest being REMAP-CAP trial showed that therapeutic heparin did not reduce mortality in severe and critically ill patients who need high flow oxygen or respiratory support but may have a higher risk of bleeding events. Therefore, therapeutic LMWH is now recommended against in this cohort of patients.

Conditional recommendation for the use of therapeutic LMWH in severely ill patients who need low flow oxygen treatment (NEW)
- In severely ill patients who need low flow oxygen, there was no difference in mortality or duration of illness between those receiving therapeutic LMWH or prophylactic LMWH in the larger REMAP-CAP trial but a reduction in mortality at Day 28-30 was observed in the therapeutic dose arm With high D-dimer >4 times of the upper limit when compared to that of prophylactic dose arm in smaller HEP-COVID and RAPID trials. NIH therefore conditionally recommends the use of therapeutic LMWH in those requiring low dose oxygen with high D-dimer of >4 times of the upper limit.
Therapeutic LMWH dosing used for this purpose is the same as that for management of venous thromboembolism in the next section.

### Thromboprophylaxis

<table>
<thead>
<tr>
<th>Drug and dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin 40 mg SC OD or</td>
</tr>
<tr>
<td>Fondaparinux 2.5 mg SC OD or</td>
</tr>
<tr>
<td>Unfractionated heparin 5000 units SC BD or</td>
</tr>
<tr>
<td>Rivaroxaban 10 mg PO OD or</td>
</tr>
<tr>
<td>Apixaban 2.5 mg PO BD</td>
</tr>
</tbody>
</table>

### Adjust dose in renal failure

<table>
<thead>
<tr>
<th>Agent</th>
<th>Creatinine Clearance</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>&lt; 30 mL/min</td>
<td>30 mg SC daily for prophylaxis</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>&lt; 30 mL/min</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>DOACs</td>
<td>&lt; 15 mL/min</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

### Cautions and contra-indications

- Do not give thromboprophylaxis if patient has active bleeding, recent bleeding, or platelet count < 30 x 10⁹/L
- Do not add thromboprophylaxis if the patient is already on anticoagulation
- Do not use DOACs in pregnancy
- Do not use DOACs if creatinine clearance (CrCl) < 15 mL/min

### Monitoring

- Signs of bleeding in all cases especially in those who are also taking antiplatelets.
- If unfractionated heparin (UFH) is used, check renal function and platelet count at day 5-7, to detect heparin-induced thrombocytopenia (presenting with a fall in platelet count and new thrombosis).
- Monitoring by D-dimer is not useful as it is already high with inflammation in COVID-19 infection.

### Duration of thromboprophylaxis

- A total of 14 days in severe and critically ill cases or until hospital discharge, whichever comes first (NEW).
MANAGEMENT OF VENOUS THROMBOEMBOLISM (VTE)

If patient has clinical signs of venous thrombosis, and investigations are available, consider ultrasound of the limbs for deep vein thrombosis (DVT) or CT pulmonary angiogram (CTPA) for pulmonary embolism (PE) to confirm the diagnosis. Positive D-dimer in isolation should not be used as a diagnostic test as D-dimer may be raised in severe COVID-19 cases, bacterial infection, myocardial infarction and coagulopathy, etc. Negative D-dimer is helpful to rule out VTE in clinically suspected cases.

Suspect possible thrombosis in the following situations:
- Unilateral limb swelling
- Sudden deterioration of oxygenation/respiratory distress
- Hypoxia out of keeping with CXR findings
- Reduced blood pressure
- New onset tachycardia

Treatment of DVT or PE

**LMWH** is the treatment of choice as less drug-interaction with other medications (such as antiviral, immunomodulatory therapies). Injectable anticoagulant can be changed to DOAC upon discharge/when stable condition.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic dose</th>
<th>Dose adjustment in renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>1.5mg/kg in one dose or in split doses per day</td>
<td>1 mg/kg/24h if CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>Fonadparinux</td>
<td>Weight &lt; 50 kg: 5 mg in one dose or in split doses per day 50-100 kg: 7.5 mg in one dose or in split doses per day &gt; 100 kg: 10 mg in one dose of in split doses per day</td>
<td>Do not use if CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Loading dose 5000 units followed by continuous iv infusion of 18 units/kg/hour (needs monitoring regularly with APTT).</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>15 mg BD x 21 days, then 20 mg OD</td>
<td>Avoid if CrCl &lt; 15 mL/min</td>
</tr>
<tr>
<td>Apixaban</td>
<td>10 mg BD x 7 days, then 5 mg BD</td>
<td>Avoid if CrCl &lt; 15 mL/min</td>
</tr>
</tbody>
</table>

**Duration of treatment**
3 months

**Considerations in resource limited situations**
- Rely on clinical assessment. If severe COVID-19, consider intermediate dose LMWH provided no history of renal disease or bleeding if blood tests cannot be done. Step down to standard dose when severity changes.
- DOACs may be used (off-label or unlicensed) if injectable thromboprophylaxis drugs are not available but risk of GI bleeding may be higher compared to LMWH, especially when patients are taking steroids, NSAIDs or anti-platelets, or previous history of GI bleeding.
- If high clinical suspicion of DVT or PE, consider starting treatment dose, and plan for imaging (US or CT) as earliest as practicable to confirm the diagnosis.
OXYGEN SUPPLEMENTATION

Rationale
Low or lack of oxygenation to the body as a consequence of pneumonitis is one of the major causes of mortality in COVID-19 infection. Oxygen supplementation is to correct alveolar and tissue hypoxia.

Target oxygen saturation
Aim for SpO$_2$ > 93% in all patients$^{39,40}$ except in those with high risk of CO$_2$ retention (e.g. in known or suspected underlying chronic obstructive pulmonary disease (COPD), life-long smoker and in morbidly obese patients) in which case, aim for SpO$_2$ between 88 to 92%.$^{15,41}$

NASAL PRONGS

- Nasal prongs are easy and comfortable for the patient.
- Oxygen flow rate can be from 1 L/min up to 6 L/min.$^{42}$
- It is difficult to tolerate a flow rate > 4 L/min due to dryness and pressure caused by the flow.$^{43}$
- Oxygen concentration delivered varies from 24-40% depending on the patient’s inspiratory flow rate (i.e., respiratory rate and tidal volume).
SIMPLE FACE MASK

- Simple face masks deliver an oxygen concentration between 40-60%.\(^4\)
- Oxygen concentration delivered can be changed by increasing or decreasing the oxygen flow between 5 and 10 L/min.
- **Simple face masks should not be used at flow rates $< 5 \text{ L/min}$.**\(^4\) If the patient inspiratory flow rate is higher than the gas flow rate from the mask, the exhaled air may not be adequately flushed from the mask, causing increased resistance to breathing and a possible rebreathing with CO\(_2\) build up within the mask.

Courtesy of the British Thoracic Society
HIGH CONCENTRATION RESERVOIR MASK (NON-REBREATHING MASK)

- High concentration reservoir masks are designed to have an additional 600-1000 mL of gas within the reservoir bag to increase the delivered oxygen concentration.46
- Most are non-rebreathing masks where the exhaled air exits the side of the mask through one-way valves and prevent rebreathing of CO₂.
- A non-rebreathing mask delivers oxygen concentration around 80% (between 60-90%) when set at a flow rate of 10-15 L/min.45 The delivered oxygen concentration is variable depending on the mask fit and the patient’s breathing pattern.
- The reservoir should be filled with oxygen before the mask is placed on the patient.47
- The reservoir bag mask must be used with a minimum of 10 L/min oxygen flow rate. If the patient is in respiratory distress and is breathing fast and hard with high inspiratory flow rate, the oxygen flow rate from the reservoir needs to match it to be sufficient and effective. If not, the bag may collapse and the patient’s oxygenation may be compromised. To be effective, the reservoir bag should not deflate by more than 60% with each breath.

USING OXYGEN FROM TWO SOURCES

Consider the use of oxygen from double sources in resource limited settings such as 10 L/min through the face mask in addition to 4 L/min through nasal prongs.4

VENTURI OXYGEN MASK

- Venturi masks give an accurate concentration of oxygen regardless of oxygen flow rate
- Therefore, they are suitable for those at risk of CO₂ retention in whom an exact and consistent concentration of oxygen therapy is required to inform careful adjustment of oxygen therapy later if necessary.
- The oxygen concentration remains constant as the adaptor within the Venturi valve dilutes the gas flow into the mask with air entrained through it.
- The mask can be attached to different Venturi valves that are available in 24%, 28%, 31%, 35%, 40% and 60% concentrations. The valves are colour coded and the minimum suggested flow rate is written on each Venturi valve and as shown in the above figure.42

Courtesy of the British Thoracic Society
**Monitoring**
Patients should have their observations observed for at least 5 min after starting or changing the oxygen therapy. The exact requirements for monitoring will depending on the clinical condition of each patient. **Saturations are usually measured after one hour of oxygen therapy and then every four hours. Stable patients should be monitored four times a day.**

**Titration**
Oxygen can be titrated up or down depending on the level of oxygen saturation at the time of presentation. The proposed oxygen escalation/de-escalation pathway is as in the following page. If the oxygen saturation is not maintaining at the target saturation range despite being on 15 L/min non-rebreather reservoir mask, then a more advanced respiratory support either in the form of non-invasive ventilation or invasive mechanical ventilation, if available, is needed depending on the level of hypoxia (PaO2:FiO2 ratio), the patient's general condition and observations (see details in the respiratory support section). If the patient is not for further escalation of care due to co-morbidities and frailty, palliative care therapy should be discussed and offered (see details in the palliative care section).
COVID-19 OXYGEN SUPPLEMENTATION PATHWAY

People without COPD: Aim SaO2 > 93%

- Nasal prongs 1 L/min
- Nasal prongs 2 L/min
- Nasal prongs 4 L/min
- Simple face mask 5-6 L/min
- Simple face mask 10 L/min
- Reservoir mask 15 L/min

At risk of CO2 retention: COPD, lifelong smoker, morbid obesity Aim SaO2 88-92%

- Venturi Mask 24% (blue) 2-3 L/min
- Venturi Mask 28% (white) 4-6 L/min
- Venturi Mask 35% (yellow) 8-12 L/min
- Venturi Mask 40% (red) 10-15 L/min
- Venturi Mask 60% (red) 12-15 L/min

Consider oxygen from two sources in resource-limited settings, eg 4 L/min through nasal cannulae and 10L/min through the face mask
AWAKE PRONE POSITIONING

Rationale
The early prone positioning in sedated and intubated patients with moderate to severe acute respiratory distress syndrome (ARDS) is an established alveolar recruitment method to improve oxygenation and reduce mortality.\(^50,51\)

Lung injury with features of acute respiratory distress syndrome (ARDS) is a principal phenomenon in severe COVID pneumonitis. Internationally, observations of critical care clinicians treating the COVID patients in critical care have reported that those with moderate to severe ARDS appear to respond well to invasive ventilation in the prone position, leading to prone ventilation being recommended in international guidelines for the management of COVID-19.\(^52\)

Given the improvement in mechanically ventilated patients, it is extrapolated that prone positioning in conscious COVID-19 patients requiring basic respiratory support, may also be beneficial in improving oxygenation, reducing the need for invasive ventilation, and potentially even reducing mortality.\(^53\)

The physiological principles underpinning the postulated benefits are

▪ Reduced ventilation perfusion mismatching and hypoxaemia (by preventing over-inflation of the ventral alveoli and atelectasis of the dorsal alveoli; reducing the compression from the heart and the diaphragm)
▪ Reduced shunt (by eliminating preferential perfusion to dorsal alveoli with gravitational gradient, making perfusion pattern relatively constant while lung aeration becomes more homogenous)
▪ Recruitment of the posterior lung segments due to reversal of atelectasis
▪ Improved secretion clearance

Indications
▪ Consider prone positioning once oxygen supplementation is required.

Absolute contraindications\(^54\)
▪ Respiratory distress (RR ≥ 35, PaCO\(_2\) ≥ 6.5, accessory muscle use)
▪ Immediate need for intubation
▪ Haemodynamic instability (SBP < 90mmHg) or arrhythmia
▪ Agitation or altered mental status
▪ Unstable spine, thoracic injury, recent abdominal surgery

Relative contraindications
▪ Facial injury
▪ Neurological conditions (e.g. frequent seizures)
▪ Morbid obesity
▪ Pregnancy (2nd or 3rd trimesters)
▪ Pressure sores or ulcers

Positioning

![Positioning Image]

Courtesy of Sandwell and West Birmingham NHS Trust

▪ Use 1 pillow under the head, 2 pillows under the chest, 2 pillows under the pelvis and 1 pillow under the shin (as shown in the figures)
▪ The abdomen should be hanging free and not be compressed especially in obese patients.
Timing
- Change position every 1-2 hrs aiming to achieve a prone time as long as possible
- When not prone, aim to be sat at between 30-60 degrees upright
- Titrate down oxygen requirements as able but do not try to wean oxygen immediately
- 30 minutes to 2 hours lying fully prone (bed flat)
- 30 minutes to 2 hours lying on right side (bed flat)
- 30 minutes to 2 hours sitting up (30-60 degrees)
- 30 minutes to 2 hours lying on left side (bed flat)
- 30 minutes to 2 hours lying prone again
- Continue to repeat the cycle

Monitoring
Closely monitor oxygen saturations for the first 15 min with every position change

If deteriorating oxygen saturations:
- Ensure oxygen is connected to patient
- Increase inspired oxygen
- Change patient’s position
- Consider return to supine position

Discontinue if:
- No improvement with change of position
- Patient unable to tolerate position
- RR ≥ 35, looks tired, using accessory muscles
**ANTIVIRALS**

**REMDESIVIR**

Remdesivir is an intravenous antiviral adenosine analogue prodrug, originally used in the Ebola epidemic in 2013. When metabolised to its active form, it interferes with RNA polymerase and leads to premature termination of viral RNA transcription. Early in the pandemic, remdesivir was found to have antiviral effect against SARS-CoV-2 in *in vitro* and *in vivo* studies with rhesus monkeys.

Since then, several randomised controlled trials have been conducted. The largest so far are the Adaptive COVID-19 Treatment Trial (ACTT-1), funded by the National Institute of Allergy and Infectious Diseases (NIAID), and the Solidarity trial, funded and conducted by the World Health Organization. These two trials yielded varying results, causing confusion, and leading to a lack of consensus view among leading global health authorities.

ACTT-1 trial was an international, but mainly North American, double blind, randomised, placebo-controlled trial of 1000 hospitalised patients with over 500 recruited to the remdesivir arm and the rest into the placebo arm. Stratified randomisation was used to balance disease severity in both arms. The study was published in the New England Journal of Medicine (NEJM) in May 2020. It showed a reduction in time to clinical recovery by 5 days (median recovery time of 10 days as compared with 15 days among those who received placebo [95% CI, 1.12 to 1.49; P<0.001]). In a subgroup analysis, there was mortality benefit in patients requiring supplemental oxygen but not ventilation.

Solidarity trial was also an international randomised controlled trial. It had 5 trial arms, one of which was remdesivir. Most of the participants were from Asia, Africa, and Latin America. Its interim outcome was published in January 2021 in NEJM which showed no mortality benefit with the use of remdesivir compared to standard care alone (rate ratio 0.95, 95% CI 0.81 to 1.11, P=0.5). Subgroup analyses did not show any reduction in initiation of ventilation or duration of hospitalisation. At the time of publication, over 2500 participants were recruited to remdesivir arm and over 4000, to standard care arm.

Both trials used the same dose of remdesivir. The participants in both trials were hospitalised patients. However, the two trials had different primary endpoints, and thus they were powered to examine different outcomes. The primary endpoint in ACTT-1 was time to clinical recovery and it was therefore not powered for mortality. Solidarity was powered for mortality but was not designed to examine subgroups by clinical outcomes or time to clinical improvement. Only 8% of patients in Solidarity were ventilated upon enrolment, as opposed to 25% in ACTT-1. Approximately a quarter of patients in ACTT-1 received concomitant glucocorticoids whereas nearly half did in Solidarity. Time from symptom onset to randomisation was examined in ACTT-1, but similar data was not available for Solidarity.

In January 2022, Gottlieb et al. published the outcome of their PINETREE trial result in NEJM titled ‘Early Remdesivir to Prevent Progression to Severe COVID-19 in Outpatients’. It was a randomised double-blind placebo-controlled trial involving mild to moderate non-hospitalised patients with COVID-19 within 7 days of symptom onset and who had at least one risk factor for disease progression. 279 out of 562 total recruits after randomisation received 3 days of IV remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) and the rest received placebo. The primary endpoint was a composite end point of COVID related hospitalisation or death from any cause by day 28. 2 out of 279 (0.7%) in the remdesivir group compared to 15 out of 283 (5.3%) in the placebo group had COVID related hospitalisation or death giving the hazard ratio of 0.13 with a 95% confidence interval (CI) of 0.03 to 0.59 and P of 0.008. Therefore, a conclusion was drawn that ‘for those at high risk for COVID-19 progression, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalisation or death than placebo’. The limitation of the trial is for choosing hospitalisation and death as a composite primary end point thereby diluting the actual outcome of prevention of death by the medication and the number of the trial was small in comparison to population-based study such as SOLIDARITY trial. There were no other trials cited to date which had looked into a similar clinical aspect.
The following are the current recommendations from different societies.

- In the US, the National Institutes of Health (NIH) guidelines recommend the use of remdesivir in hospitalised COVID-19 patients requiring supplemental oxygen through nasal cannula. For patients who require oxygen through a high flow device or non-invasive ventilation, remdesivir plus dexamethasone may be used.
- The Infectious Disease Society of America (IDSA) guideline\(^1\) recommends the use of remdesivir among hospitalised patients with severe COVID-19 (defined as patients with SpO2 ≤ 94% on room air, or those who require supplemental oxygen). The guidelines recommend against the routine use of remdesivir in patients with COVID-19 requiring mechanical ventilation or extracorporeal mechanical oxygenation. Among COVID-19 patients without the need for supplemental oxygen and with oxygen saturation > 94% on room air, IDSA suggests against the routine use of remdesivir.
- In the UK, the National Institute for Health and Care Excellence (NICE)\(^2,3\) makes a conditional recommendation for the use of remdesivir in patients requiring low flow oxygen supplementation (nasal cannula or face mask at a flow rate up to 15 L/min). NICE does not recommend using it in patients on high flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) or invasive ventilation except in research settings.
- World Health Organization (WHO)\(^4\) guidelines recommend against remdesivir outside of clinical trials for COVID-19 of any disease severity. However, this aspect of the guidance has not been updated since 2020.
- In the US, NIH guideline recommends the use of 3-days of remdesivir in mild to moderate disease in patients with high-risk factors as a third choice after Ritonavir-boosted nirmatrelvir (Paxlovid) and Sotrovimab (both unavailable in Myanmar) but a preferred choice to Molnupiravir. In the UK, NICE guideline is in the process of updating to this effect and the Chief Medical Officer has already issued a central alert (CAS alert) to clinicians to consider the same treatment option as that of NIH.

**Recommendations**

In line with NICE, NIH and IDSA guidance, NUG COVID-19 Taskforce conditionally recommends the use of remdesivir in the following conditions:

- In severe COVID-19 infection: with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at the start of treatment) but not on mechanical ventilation, AND if presented within 10 days of symptom onset.
- We **DO NOT RECOMMEND** using remdesivir in asymptomatic patients who do not need oxygen or those who are on mechanical ventilation.
- In mild to moderate COVID-19 infection: with at least one high risk factor AND who do not require supplemental oxygen AND if presented within 7 days of symptom onset, **(NEW)**
- We **DO NOT RECOMMEND** using remdesivir in mild to moderate disease who do not have risk factors for disease progression.

We also recommend patient-centred discussion. The uncertainties, limitations in evidence base and lack of consensus among global health bodies should be explained to the patient. Ultimately, it should be an individualised clinical decision, depending on patient choice, the stage in the disease process, baseline liver and renal functions, comorbidities, and cost considerations.

**Criteria for therapy**

Remdesivir may be considered in patients with

- age ≥12 years **AND**
- body weight ≥ 40 kg **AND**
- confirmed COVID-19 infection **AND**
- Within 7 days of onset of symptoms in mild to moderate severity with at least one high risk factor OR within 10 days of symptom onset in severe disease.

**Contraindications**

- Known hypersensitivity to remdesivir or any component of the formulation
- Estimated glomerular filtration rate (eGFR) < 30 mL/minute
- Alanine aminotransferase (ALT) > 5 times the upper limit of normal at baseline
• Asymptomatic patients who do not require oxygen or who do not have risk factors for disease progression

**Pregnancy and lactation**
As pregnancy is one of the risk factors which can progress to severe disease, remdesivir should not be withheld from pregnancy if it is otherwise indicated.3

There are no data on the use of remdesivir in lactating mothers. Since remdesivir undergoes extensive first-pass metabolism, infants are unlikely to absorb clinically important amounts of remdesivir from breastmilk2 However, systemic exposure to metabolites could result from breastfeeding. Reassuringly, no adverse effects were documented in the small number of infants who received remdesivir for treatment of Ebola virus infection or COVID-19.60,61

**Dose**
For patients with pneumonia requiring supplemental oxygen (severe infection):
• 200 mg IV loading dose on day 1 followed by 100 mg IV once daily for a maximum of 5 days in total.62,63
For patients who do not require supplemental oxygen and are at increased risk of progression to severe COVID-19 (mild to moderate infection):
• 200 mg IV loading dose on day 1 followed by 100 mg once daily for 3 days in total.

**Dosing adjustment**
Renal impairment: the use of the drug is not recommended in eGFR < 30 mL/min
Hepatic impairment: the use of the drug is contraindicated in patients with baseline ALT ≥ 5 times the upper limit of normal.

**Administration**
Each vial should be reconstituted with 19 mL of water for injections, then diluted in 250 mL of 0.9% normal saline, and given over 30-120 minutes.

**Monitoring**
Monitor renal and liver functions at baseline and on completion of treatment. Consider also checking during the treatment if baseline functions are not normal.
Stop the treatment if
• ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (may resume when ALT becomes <5 times the upper limit of normal)
• ALT elevation accompanied by signs or symptoms of liver inflammation or
• increasing conjugated bilirubin, alkaline phosphatase, or INR
• eGFR < 30 mL/min
MOLNUPIRAVIR

Molnupiravir is an oral antiviral pro-ribonucleotide drug that has a broad antiviral action against RNA viruses. It incorporates into the virus RNA causing viral RNA mutation and death. The phase 3 MOVe-OUT trial showed that the oral antiviral resulted in a relative risk reduction of 30% in the composite primary outcome of hospitalisation or death at day 29.80

Molnupiravir is currently being assessed by the WHO for consideration in the new guideline. The Medicines and Healthcare products Regulatory Agency (UK) announced on 4 November 2021 that the drug is safe and effective at reducing the risk of hospitalisation and death in people with mild to moderate COVID-19 who are at increased risk of developing severe disease. It has a lower efficacy than the other treatment options. Therefore, the NIH guideline, stressed that molnupiravir should be considered ONLY when other options such as remdesivir cannot be used and it should be initiated as soon as possible within 5 days of symptom onset in those aged ≥ 18 years.

Molnupiravir being a mutagenic agent, there is a theoretical risk of the drug getting into the human cells, incorporating into DNA and causing mutation. However, based on the currently available negative and equivocal genotoxicity data of molnupiravir and the fact that the course is only for 5 days, Food and Drug Association of the US concluded that the risk of genotoxicity is low.

**Indications**

- Patients with mild to moderate COVID-19 infection who are at high risk of infection progression AND Remdesivir is not available or not tolerated AND
- Present within 5 days of symptoms onset AND
- Aged > 18 years

**Dose**

The recommended dose is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days. Treatment must not be extended beyond 5 days. It should be started as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset.

**Side effects**

Diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%).

**Cautions in pregnancy and lactation**

Molnupiravir is NOT RECOMMENDED for use in pregnant patients due to concerns about foetal toxicity that are based on data from animal studies.

However, when preferred therapies are not available, pregnant people who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risk, particularly those who are beyond the time of embryogenesis (i.e., >10 weeks' gestation).

Based on the lack of data on the use of molnupiravir in lactating people and the potential for adverse effects in the infant from molnupiravir exposure, the current recommendation is to avoid feeding an infant breast milk during molnupiravir treatment and for 4 days after the final dose.72

**Cautions in patients with childbearing potential**

Patients of childbearing potential should be counselled about abstaining from sex or using reliable contraception for the duration of therapy and for up to 4 days after receiving molnupiravir.

Reproductive toxicity has been reported in animal studies of molnupiravir may be mutagenic during pregnancy.72

Men of reproductive potential who are sexually active with individuals of childbearing potential should abstain from sex or use a reliable method of contraception for the duration of treatment and for at least 3 months after the last dose of molnupiravir.72
IMMUNOMODULATORY AGENTS

Rationale
A hyper-responsive immune system with excessive inflammatory response to the SARS-CoV-2 viral infection is observed in COVID-19 infection and is thought to be a key underlying immunopathology leading to severe disease and multi-organ damages. The interleukin-6 receptor antagonist (anti-IL6) such as tocilizumab and Janus Kinase (JAK) inhibitor such as baricitinib both show effectiveness in reduction of inflammation as an additional immunomodulator to corticosteroids in the treatment of severe COVID-19 infection.

Criteria for therapy
Current evidence suggests that baricitinib or tocilizumab may be considered in patients who

▪  are on or have completed a course of corticosteroids AND
▪  have no evidence of a bacterial or viral infection (other than COVID-19) AND
▪  have not had another anti-IL6 during the present illness AND
▪  have a CRP of ≥75 mg/litre AND
▪  are within 48 hours of starting higher flow rate oxygen therapy (>10 L/min oxygen flow rate), continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation

Contraindications
▪  Known severe allergic reactions to baricitinib or other JAK inhibitors (or tocilizumab or other monoclonal antibodies)
▪  Active tuberculosis infection
▪  Suspected active bacterial, fungal or viral infection (in additional to COVID-19)
▪  High procalcitonin level

▪  Have received oral antirejection or immunomodulatory drugs including baricitinib or tocilizumab within past 3 months
▪  Any serious medical conditions (severe haematological, renal or liver function impairment)
▪  Active diverticulitis, inflammatory bowel disease, other symptomatic GI diseases
▪  Absolute neutrophil count <1000/mL
▪  Platelet count < 50,000/mL

Points to consider:
▪  There are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19. There is insufficient evidence to recommend one drug or class of drugs over the other (i.e., JAK inhibitors and anti-IL6 receptors). Treatment decisions should be based on drug availability, patient’s comorbidities, logistical constraints of intravenous administration and cost.
▪  Baricitinib or tocilizumab should only be given in combination with corticosteroids. It is reasonable to assess a patient’s clinical response to corticosteroids before deciding whether adding baricitinib or tocilizumab as a second immunomodulatory drug is necessary.
▪  It is recommended against the use of baricitinib in combination with tocilizumab for the treatment of COVID-19 due to the potential additive risk of infection secondary to potent immunosuppressive effects of both drugs.
▪  Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids. Many clinicians would initiate treatment for strongyloidiasis empirically with or without testing in patients from areas where Strongyloides is endemic.

BARICITINIB

▪  Baricitinib is a Janus kinase (JAK) inhibitor which prevents phosphorylation of proteins involved in the signalling of immune activation and inflammation. Immune suppression induced by JAK inhibitors potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19.
▪  The COV-BARRIER trial was a randomised placebo-controlled trial in which 1,525 hospitalised patients with COVID-19 and ≥1 high inflammatory markers were randomised either to receive 4 mg of oral baricitinib or placebo in addition to the standard care for up to 14 days (or until hospital discharge). Although there was no
difference in the primary composite endpoint of progression to high-flow oxygen, NIV, mechanical ventilation or death between the baricitinib arm and the placebo arm, all-cause mortality by Day 28 was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality for baricitinib (hazard ratio 0.57; 95% CI, 0.41 – 0.78; P = 0.002).65

- The difference in mortality was most noticeable in the subgroup of 370 patients receiving high-flow oxygen or NIV at baseline (17.5% in the baricitinib arm vs. 29.4% in the placebo arm; hazard ratio 0.52; 95% CI, 0.33-0.80; P = 0.007). The occurrence of adverse events in both arms was comparable.
- The ACTT-2 trial informed that baricitinib used in combination with remdesivir improved time to recovery in hospitalised patients with COVID-1966. The effect was most pronounced in patients who were receiving high-flow oxygen or NIV. However, patients receiving corticosteroids were excluded from the ACTT-2 trial, limiting the generalisability of the findings.

**Dosage, route and duration**

It is given orally for a total of 14 days or until hospital discharge, whichever is first.

The dosage is dependent on the renal function.

- 4 mg PO once daily if renal function is normal (with eGFR ≥60 mL/min/1.73 m2)
- 2 mg PO once daily if renal impairment is mild (with eGFR 30 to <60 mL/min/1.73 m2)
- 1 mg PO once daily if renal impairment is moderate (with eGFR 15 to <30 mL/min/1.73 m2)
- It is not recommended if renal impairment is severe (with eGFR <15 mL/min/1.73 m2)

**Adverse effects**

The data of side effects are from long term use and it is uncertain whether it is applicable to the short-term use in COVID-19 infection

- Infections (typically respiratory and urinary tract infections)
- Reactivation of herpes viruses
- Myelosuppression
- Transaminase elevations
- Gastrointestinal perforation (rare)

**Pregnancy**

There is paucity of data on the use of JAK inhibitors in pregnancy.

**TOCILIZUMAB**

- The interleukin-6 receptor antagonist (anti-IL6), tocilizumab, inhibits the inflammatory pathway responsible for the release of pro-inflammatory cytokines associated with severe COVID-19 disease.
- The Randomised Embedded Multifactorial Adaptive Platform trial for Community Acquired Pneumonia (REMAP-CAP trial), with nearly 400 patients in each trial arm, has shown that tocilizumab group has a significantly improved 90-day survival compared to that of the control group (hazard ratio 1.61, 95% confidence interval 1.25 to 2.08).67
- The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial33 in the UK, a randomised controlled trial with more than 2000 patients in each trial arm, has demonstrated that tocilizumab, when given in combination with a systemic corticosteroid (such as dexamethasone), reduces the risk of death by about one third in patients with severe COVID-19 requiring oxygen. The study also shows that tocilizumab shortens the time of recovery and reduces the need for ventilation.
- Some observational studies have not identified an associated clinical benefit68 or improved survival69-71 with tocilizumab.
- Decision to initiate the treatment should only be made by a clinician.

**Dose**

Single dose of 8 mg/kg by intravenous infusion. The total dose should not exceed 800 mg. A second dose could be given 12-24 hours later if the patient’s condition has not improved.

- Body weight > 40 and ≤ 65 kg: 400 mg
- Body weight > 65 and ≤ 90 kg: 600 mg
- Body weight > 90 kg: 800 mg

**Dosing adjustment**
- Renal impairment: no dose adjustment is needed.
- Hepatic impairment: caution in patients with baseline ALT ≥ 5 times the upper limit of normal.
- Pregnancy: although data for use in pregnancy is limited, there is currently no compelling evidence that tocilizumab is teratogenic or fetotoxic. An individualised decision should be made between the patient, obstetrician and physician.

**Administration**
The drug should be diluted in 100 mL of 0.9% NaCl and given over 60 minutes.

**Adverse reactions**
- **Serious and sometimes fatal infections due to various bacterial, viral, fungal and opportunistic pathogens**
- Increased serum ALT/AST or serum bilirubin
- Infusion-related reaction (mild fever, chills, nausea, headache, pruritus, dizziness, chest pain, shortness of breath, palpitation, hypotension, shock)
- Hypertension, peripheral oedema
- Skin rash, Steven-Johnson syndrome
- Diarrhoea, nausea, gastric ulcer, gastritis, oral mucosa ulcer, stomatitis, upper abdominal pain, weight gain, GI perforation, pancreatitis
- Leucopenia, neutropenia, thrombocytopenia
**BREATHING/RESPIRATORY SUPPORT**

The most fundamental treatment in COVID-19 pneumonitis is to improve oxygenation into the body and to prevent tissue hypoxaemia and subsequent tissue damage. When the COVID-19 pneumonitis is severe, low flow oxygen supplementation alone may not be adequate. Further escalation of respiratory support to high flow nasal cannula oxygen (HFNC or HFNO) therapy, non-invasive ventilation such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) or invasive mechanical ventilation may be necessary if available and appropriate. The suggested respiratory support escalation pathway, if facilities and resources are available, is as shown in the following page.
COVID-19 RESPIRATORY SUPPORT PATHWAY

Proven or likely COVID-19

\[ \text{SaO}_2 \geq 93\% \text{ on air} \]

Test for exertional desaturation (\( \geq 3\% \) drop in \( \text{SaO}_2 \)) with 1 min sit to stand test or 40-step test

\[ \downarrow < 3\% \]

Unlikely to need any respiratory support

\[ \downarrow \geq 3\% \]

Close monitoring of \( \text{SaO}_2 \)

\[ \text{SaO}_2 < 93\% \text{ on air} \]

Oxygen therapy to achieve \( \text{SaO}_2 \geq 93\% \)

Awake proning

\[ \text{SaO}_2 \geq 93\% \text{ with } <40\% \text{ FiO}_2 \] (approx. 10L) \( \text{O}_2 \)

Continue monitoring

Continue proning

\[ \text{SaO}_2 < 93\% \text{ with } <40\% \text{ FiO}_2 \] (approx. 10L) \( \text{O}_2 \)

\[ 1 \text{ FiO}_2 \text{ to 60\%} \] (Approx. 15L)

Continue proning

Consider trial of CPAP (with PEEP 10 cm \( \text{H}_2\text{O} \)) and \( \text{FiO}_2 \) 60\%

or

Consider HFNC

\[ \text{SaO}_2 \text{ in target range?} \]

\[ \text{NO} \]

Clarify escalation plan

Appropriate for escalation

Intensive care
Mechanical ventilation

Not appropriate for escalation

CPAP or HFNC available

1PEEP to 12 cm\( \text{H}_2\text{O} \)
1\( \text{O}_2 \)
Proning
Side positioning

CPAP or HFNC not available

Proning
Side positioning
Highest possible \( \text{O}_2 \)
Palliation

\[ \text{YES} \]

Continue monitoring

Continue proning
NON-INVASIVE VENTILATION
CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

Rationale
A CPAP machine can deliver positive pressure (and oxygen when attached to an oxygen source) via a tightly fitting mask and can splint open the alveoli in the lungs that are collapsed. With this mechanism, CPAP can achieve ‘alveolar recruitment’ and improves the overall oxygenation.73

CPAP is used commonly for obstructive sleep apnoea in domiciliary setting. It may also be used in an acute setting for pneumonia with type 1 respiratory failure in intensive care units as a bridging measure to borrow some time for intensivists while preparing for intubation. During the first wave of the pandemic, noticeably in Italy and the US, the intensive care units were overwhelmed with patients needing to be intubated. This led to the use of CPAP in severe to critically ill COVID patients with type 1 respiratory failure on respiratory/medical wards outside the intensive care facilities as a bridging tool pending intubation. It was found that some such patients had improved with CPAP treatment and avoided intubation.

This finding is later supported by the study from Lawton et al.74 and the preliminary data from the RECOVERY-RS trial (RECOVERY Respiratory Support trial),75 a landmark NIHR supported multicentre UK trial, that compared standard oxygen therapy, CPAP and high flow nasal oxygenation (HFNO) in COVID-19 patients. The outcome of the trial, presented (yet to be published in a peer-reviewed journal) in August 2021, demonstrated that the number who needed mechanical ventilation or died within 30 days was significantly fewer in the CPAP group when compared with that of the conventional oxygen therapy group and of the HFNO group. The trial used an adaptive randomised controlled design and included over 1200 hospitalised patients who required increasing oxygen above FiO2 of 40%. It showed 1 person would avoid needing invasive ventilation for every 12 people treated with CPAP, instead of standard oxygen therapy, in those needing increasing oxygen.

In severe to critically ill COVID patients with type 1 respiratory failure who remain hypoxic despite high flow oxygen supplementation and who do not need immediate intubation, using CPAP as a treatment for intubation avoidance and as a bridging step before intubation has now become common practice.

CPAP, however, is not a replacement of mechanical ventilation. If the patient is in severe ARDS with very low PaO2:FiO2 ratio or in severe respiratory distress, the patient must be considered for immediate assessment of mechanical ventilation if clinically appropriate and if intubation is an available option.

Treatment criteria in places with resource constraints
- Consider CPAP, when available, in patients who need > FiO2 60% (approx. 15 L/min) oxygen supplementation to maintain oxygen saturation ≥ 93% and do not require immediate intubation.

Contraindications
- Pneumothorax suspected or visible on chest x-ray
- Fixed upper airway obstruction or open tracheostomy site
- Low GCS <14
- Confusion/agitation/severe cognitive impairment
- Primary ventilatory failure (such as post respiratory arrest)
- Bowel surgery or bowel obstruction
- Inability to protect own airway
- Profuse vomiting or copious respiratory secretions
- Haemodynamically unstable
- Facial burns/trauma/recent facial or upper airway surgery

CPAP delivery requirement
- Ideally CPAP should only be given in a hospital setting where close monitoring and continuing care can be provided.
- CPAP should only be initiated, titrated, and weaned by trained and experienced operators.
- For patients who are for full escalation of treatment, there should be a continuous collaboration with intensive care clinicians for timely assessment and transfer to the intensive care facility if the patient becomes tired or fails to respond to CPAP treatment. A sustained positive response to CPAP treatment is usually noticeable within 2-3 days [the median time to intubation for CPAP patients in the RECOVERY- RS trial was 2.2 days (95% CI 1.0 to 4.6)].
- Patient should be isolated in a single room or grouped only with other patients who are also on CPAP/BiPAP, to limit high viral load exposure to others who are not on the machines.
- Staff and carers should wear full PPE while caring for patients on CPAP. CPAP treatment is classed as an aerosol generating procedure (AGP) with potentially high viral dispersion.

**Initiation**
- Well fitted face mask, full face mask or helmets could be used.
- Only a non-vented mask with an exhalation port should be used to minimise viral dispersion.
- Check whether the circuit is compatible with a non-vented mask.
- Viral filters should be placed appropriately on the expiratory circuit and changed regularly.
- Oxygen should be delivered at the mask end.
- The example circuit set up is shown below.
Consider starting at a positive end-expiratory pressure (PEEP) of 10 cmH₂O with FiO₂ of 60% (10-15 L/min oxygen).²⁶ If Vₜ (tidal volume) can be measured, consider adjusting the pressure to keep Vₜ between 500 to 1,000 mL to prevent lung injury. Can start at a lower pressure if tolerance is an issue, to give patients time to acclimatise to CPAP.²⁷ Avoid using very low pressure, such as ≤ 5 cmH₂O, to prevent rebreathing.

- Put mask on the face first before switching on the machine and switch off the machine first before taking off the mask to reduce viral droplet dispersion.

**Monitoring**
- Continuous monitoring of oxygen saturation is required.
- Observations should be made every 15 minutes in the first hour of the commencement. If stable, monitoring can be reduced to hourly later.
- ECG monitoring if possible.
- Prone positioning can be performed whilst on CPAP treatment, but very close observation should be made on oxygen saturation, mask leak and circuit disconnection.
- Consider doing an ABG after 1 hour of treatment.

**Troubleshooting**
- Persistent hypoxaemia
  - Check circuit and oxygen connection
  - Increase oxygen incrementally to achieve target oxygen saturations
  - If the patient obese, an increased PEEP may help.
  - Re-evaluate pneumothorax

- Mask leak
  - Small volume leaks are acceptable (> 60 L/min)
  - Consider alternative mask

- Asynchrony with machine
  - Consider using the Flex mode
  - Consider using a ramp when incrementally increasing the PEEP

- Uncooperative/agitated patient
  - It may be necessary to hold the mask in place until the patient is able to tolerate.
  - Consider cautious sedation under close monitoring

- Hypotension
  - Consider cautious IV fluid

**Other considerations**
- Consider IV fluids if not fluid restricted. Patients are less able to drink whilst on CPAP.
- Consider nasal padding (using dermal pad) for soreness or an alternative interface.
- Ensure regular mouth care and pressure care.
- Monitor for gastric distension and ask for medical review if significant or painful.
- Ensure adequate sleep, patient positioning, physiotherapy, skin integrity, nutrition and hydration

**Escalation and weaning**
- If there is no improvement in clinical condition or on ABG, increase CPAP pressure to 12 cmH₂O with 15 L/min entrained oxygen. Reassess in 1 hour. If ABG shows deterioration or if patient is tiring and clinically deteriorating, consider immediate consultation with intensive care clinician if the patient is for escalation.
- If there is improvement in clinical condition or on ABG, wean CPAP. Weaning is patient dependent, and some patients may tolerate quicker weaning, and some may need weaning over a long period. A typical weaning in COVID pneumonia respiratory failure will take over 5 days to prevent alveolar de-recruitment as below:
  - Day 1: allow only meal breaks, such as 15-20 minutes for 3 times. Keep on high flow oxygen during the meal breaks
  - Day 2: allow longer meal breaks during daytime, such as 1 hour for 3 times
  - Day 3: allow 2-hour breaks for 3 times during daytime
  - Day 4: CPAP only during afternoon nap and at night-time
  - Day 5: CPAP only at night-time
The use of adapted domiciliary machines
During the first peak of COVID pandemic, there was shortage of standard CPAP machines in the hospitals around the world. Some hospitals resorted to unlicensed use of domiciliary CPAP, normally designed for treatment of obstructive sleep apnoea at home. The concerns for such usage were that the home CPAP machines were not designed for continuous use and the actual amount of entrained oxygen delivered may not be reliable. When tested in the lab, approximately 10L/min oxygen or above was needed to be effective for CPAP used at 10 cmH₂O pressure, and 15L/min oxygen supplementation appeared adequate for CPAP usage at any pressure. So far there have been no reported safety incidents related to use of domiciliary CPAP in this way.

BI-LEVEL POSITIVE AIRWAY PRESSURE (BIPAP)

- BiPAP involves delivery of two distinct pressures for inspiration and expiration: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). EPAP is similar to the PEEP pressure of CPAP, and it helps prevent alveolar collapse on expiration. IPAP provides additional pressure on EPAP during inspiration to achieve effective ventilation.
- BiPAP helps ease the patient’s work of breathing and is useful in patients with type 2 respiratory failure.
- However, in COVID pneumonia, as in any type of pneumonia, type 1 respiratory failure (hypoxia without hypercapnia) is to be expected. If type 1 respiratory failure transforms into a type 2 respiratory failure (hypoxia with hypercapnia), it usually means that the patient is tiring. At that stage, if the patient is for full escalation of care, then immediate mechanical ventilation should be considered. If intubation is not available or feasible, then BiPAP may be considered as a matter of last resort. There is no proven benefit of BiPAP in this situation.
- There is a chance, however, that the type 2 respiratory failure is due to co-existing conditions such as COPD and obesity hypoventilation in addition to COVID pneumonia. These conditions may be previously undiagnosed. In such cases, a trial of therapy with BiPAP may be of benefit and should be considered.
HIGH FLOW NASAL CANNULA (HFNC)
HIGH FLOW NASAL OXYGENATION (HFNO)

HFNC can deliver FiO\(_2\) up to 1.0 (100% oxygen) in 50-60L/min flow rate.

- It can also deliver warmed and humidified oxygen.
- It is comfortable especially for those in ‘air hunger’.
- It is also convenient during mealtimes.
- It consumes a large amount of oxygen. It is therefore not possible for home use. Even in hospital setting, the number of patients that can be treated with HFNC may be limited by oxygen availability.
- It cannot deliver high pressure into the lungs and cannot reduce the work of breathing.
- Data from the RECOVERY-RS trial suggests that there is no improvement in outcomes (avoidance of mechanical ventilation or reduction in 30-day mortality) in HFNC patients when compared to patients treated with conventional oxygen therapy (unadjusted odds ratio 0.97; 95% CI 0.73 to 1.29, P=0.85).
- However, it has a role\(^{13,49,80}\) in delivery high flow oxygenation, weaning from CPAP (eg during mealtimes for a rest from CPAP), as a bridging before mechanical ventilation and for comfort in palliative therapy.

Courtesy of Veoflow®
ANTIBIOTICS

▪ In mild COVID-19 disease, routine and prophylactic use of antibiotics are not recommended.
▪ In moderate COVID-19 disease, use antibiotics only if there is clinical suspicion of a co-existing bacterial infection.
▪ In severe and critically ill COVID-19 cases, use empirical antibiotics in accordance with the likely pathogens, and stop if the markers, such as procalcitonin, do not indicate secondary bacterial infection.

Points to consider
▪ The choice of antibiotics should be made on individual basis, determined by clinical severity, patient’s host factors and immune status, local epidemiology on common pathogens and antibiotic resistance pattern.
▪ The choice of antibiotics for patients in the community will be different to that for patients on hospital wards or in intensive care facilities, and from one part of the country to another.

⚠︎ Do not use broad spectrum antibiotics unless it is essential to do so.

▪ Antibiotic resistance due to non-selective and inappropriate use of antibiotics is a major national and international problem which extends beyond COVID-19 pandemic and will cost lives for years.

According to the UK data during the first wave and second wave of the COVID-19 pandemic, there was only 10% co-infection of COVID-19 virus with a bacterial pathogen in patients. The injudicious use of co-amoxiclav antibiotics in the UK hospitals during the first wave of the pandemic has led to the emergence of co-amoxiclav resistant bacterial strains in several regions.

▪ When antibiotics are considered necessary, give them only for the recommended duration. Extend the course, only if necessary, and after careful consideration on the risks and benefits not only for the patient but also for the whole population.
▪ Stop the antibiotics if the markers for bacterial infection, such as procalcitonin, are available, reliable and are not indicating a bacterial cause.
▪ Azithromycin, although still useful as an antibiotic in treating co-existing bacterial infection when indicated, is proven to be not effective as an anti-inflammatory drug for COVID-19 viral infection (RECOVERY trial outcome).
PALLIATIVE CARE

Severe and critically ill COVID-19 patients may deteriorate despite appropriate and optimal treatment. When all the reversible causes are ruled out, and the patient is not suitable for further escalation of care such as mechanical ventilation and the patient is clearly dying, then the focus of care should be solely on comfort and dignity. The fact that the patient is approaching the end of life should be communicated with (the patient, if feasible and appropriate to the local context) and the family or those important to the patient, with consent, in an open, honest and sensitive manner.

In the context of resource constraints and limited availability of controlled medications such as morphine, midazolam or lorazepam, intramuscular usage of the following drugs can be considered:

- Haloperidol, for restlessness and agitation,
- Metoclopramide or ondansetron, for nausea and vomiting and
- Hyoscine butylbromide (Buscopan), for respiratory tract secretions.
REFERENCES


83. SIGN. Scottish Palliative Care Guidelines: end of life care guidance when a person is imminently dying from COVID-19 lung disease. 2020.