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/
**Definition of disease severity**

<table>
<thead>
<tr>
<th>Mild illness</th>
<th>Moderate illness</th>
<th>Severe illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic without features of viral pneumonia or hypoxaemia. Common symptoms: fever (83-99%), cough (59-82%), fatigue (44-70%), anorexia (40-84%), shortness of breath (31-40%), myalgia (11-35%).</td>
<td>Clinical symptoms and signs of pneumonia (fever, cough, dyspnoea) with no features of severe pneumonia. SpO₂ &gt; 93% on room air.</td>
<td>Clinical pneumonia and one of the following (respiratory rate &gt; 30/min, severe respiratory distress or SpO₂ ≤ 93% on room air)</td>
</tr>
</tbody>
</table>

**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
- Morbid obesity
- Smoking
- Diabetes
- Hypertension
- Chronic respiratory diseases, cardiac diseases, chronic kidney disease, cerebrovascular disease
- Cancer
- Immunocompromise

**Manage according to disease severity**

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe or critically ill</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>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 antibiotics if procalcitonin is negative. Test O₂ desaturation with sitting and standing for 1 min or walking 40 steps. If desaturation</td>
<td>Admit to hospital if possible. Remember STOP</td>
</tr>
<tr>
<td>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 or intermediate dose, for 14 days (see details in the thromboprophylaxis section). O: offer oxygen therapy (target O₂ saturation &gt;93% or 88-92% if there is risk of type 2 respiratory failure). Titrate oxygen using appropriate interfaces to achieve target</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
of >3% on testing, manage as severe.

- Consider standard thromboprophylaxis.

- saturation (see flow chart in the oxygen therapy section).
- P: try prone positioning (see details in the awake prone positioning section).

**Consider STAR**

- **S**: offer respiratory 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).
- **T**: consider tocilizumab 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.
- **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).
- **R**: consider 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).

**Monitor COVID**

- **C**: circulation – beware of hypovolaemic and septic shock. Treat promptly and appropriately.
- **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, euvoemia 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.
### 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>HFNO</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>-------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>REMAP-CAP trial</td>
<td>Randomised, Embedded, Multi-factorial, Adaptive Platform</td>
</tr>
<tr>
<td></td>
<td>Trial for Community-Acquired Pneumonia trial</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</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 virus</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 organisations1,8-12. 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 (eg 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.¹ 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 (8% to 99%), cough (59% to 82%), fatigue (44% to 70%), anorexia (40% to 84%), shortness of breath (31% to 40%) or myalgia (11% to 35%).
- 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. SpO₂ > 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 SpO₂ ≤ 93% on room air

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

<table>
<thead>
<tr>
<th>Acute respiratory distress syndrome (ARDS)</th>
<th>The original definition of ARDS is based on PaO₂/FiO₂ 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 FiO₂ 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</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxygen saturations are &lt; 93% on oxygen supplementation of ≥ 6L/min of oxygen (SaO₂/FiO₂ ≤ 315)¹¹ and onset of desaturation within 1 week of new or worsening of respiratory symptoms and respiratory failure not fully explained by cardiac failure or fluid overload</td>
<td></td>
</tr>
</tbody>
</table>
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

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.

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 > R3% on testing, manage as severe.
- Consider standard thromboprophylaxis.

‘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% (eg 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.13

The REMAP-CAP (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia) trial14 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.15-17 International health organisations, therefore, have recommended the use of steroids in severe COVID-19 infection.18,19

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).13

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>
</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).20
- An RBS level up to 210 mg/dL (12 mmol/L) may be acceptable.20
Hypoglycaemia is more dangerous than hyperglycaemia. For those who may be at risk of hypoglycaemia (eg 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 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% (eg 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, eg 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 moderate, severe and critical severity.
- Consider in those with additional risk factors (eg age > 65 years, male, obesity, active cancer, previous thromboembolism, pregnancy, immobility and multiple comorbidities)
- Routine thromboprophylaxis is not recommended in mild 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.

Doses for thromboprophylaxis

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Critical</th>
</tr>
</thead>
<tbody>
<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>Signs of severe respiratory distress</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Consider standard thromboprophylaxis 21</td>
<td>Consider standard prophylactic dose or intermediate dose 22,23</td>
<td>Sepsis</td>
<td>Septic shock</td>
</tr>
<tr>
<td>No routine thromboprophylaxis</td>
<td>Consider standard prophylactic dose or intermediate dose 21</td>
<td></td>
<td></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 25.

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. LMWH/Heparin can later be switched to DOAC.

### Thromboprophylaxis

#### Drug and dose

<table>
<thead>
<tr>
<th>Thromboprophylaxis</th>
<th>Standard dosing</th>
<th>Intermediate dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin 40 mg SC OD or</td>
<td>Fonaparinux 2.5 mg SC OD or</td>
<td>Enoxaparin 40 mg SC OD or</td>
</tr>
<tr>
<td>Fondaparinux 5 mg SC OD or</td>
<td>Unfractionated heparin 5000 units SC BD or</td>
<td>Fonaparinux 5 mg SC OD or</td>
</tr>
<tr>
<td>Rivaroxaban 10mg PO OD or</td>
<td>Apixaban 2.5mg PO BD</td>
<td>Rivaroxaban 15mg PO OD or</td>
</tr>
<tr>
<td>Apixaban 2.5mg PO BD</td>
<td></td>
<td>Apixaban 2.5mg PO BD</td>
</tr>
</tbody>
</table>
Adjust dose in renal failure as below:

<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 moderate, severe and critically ill cases
- May extend up to 4 weeks if multiple risk factors for thrombosis are present
**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</td>
<td>Do not use if CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>50-100 kg: 7.5 mg in one dose or in split doses per day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 100 kg: 10 mg in one dose of in split doses per day</td>
<td></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 SpO2 > 93% in all patients\textsuperscript{30,31} except in those with high risk of CO\textsubscript{2} retention (eg in known or suspected underlying chronic obstructive pulmonary disease (COPD), life-long smoker and in morbidly obese patients) in which case, aim for SpO2 between 88 to 92%\textsuperscript{10,32}.

NASAL PRONGS

- Nasal prongs are easy and comfortable for the patient.
- Oxygen flow rate can be from 1L/min up to 6L/min\textsuperscript{33}.
- It is difficult to tolerate a flow rate > 4L/min due to dryness and pressure caused by the flow\textsuperscript{34}.
- Oxygen concentration delivered varies from 24-40% depending on the patient’s inspiratory flow rate (ie respiratory rate and tidal volume).

SIMPLE FACE MASK

- Simple face masks deliver an oxygen concentration between 40-60\%\textsuperscript{35}.
- Oxygen concentration delivered can be changed by increasing or decreasing the oxygen flow between 5 and 10L/min.
- Simple face masks should not be used at flow rates < 5L/min.\textsuperscript{36} 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\textsubscript{2} build up within the mask.
HIGH CONCENTRATION RESERVOIR MASK (NON-REBREATHEING 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.\(^{37}\)
- Most are non-rebreath masks where the exhaled air exits the side of the mask through one-way valves and prevent rebreathing of CO\(_2\).\(^{37}\)
- A non-rebreathing mask delivers oxygen concentration around 80% (between 60-90%) when set at a flow rate of 10-15L/min.\(^{36}\) The delivered oxygen concentration is variable depending on the mask fit and the patient's breathing pattern.\(^{37}\)
- The reservoir should be filled with oxygen before the mask is placed on the patient.\(^{38}\)
- **The reservoir bag mask must be used with a minimum of 10L/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, and 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.\(^{36}\)

USING OXYGEN FROM TWO SOURCES

Consider the use of oxygen from double sources in resource limited settings such as 10L/min through the face mask in addition to 4 L/min through nasal prongs.\(^8\)

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 CO\(_2\) retention in whom an exact and consistent concentration of oxygen therapy is required to inform careful adjustment of oxygen therapy later if necessary.\(^4\)
- The oxygen concentration remains constant as the adaptor within the Venturi valve dilutes the gas flow into the mask with air entrained through it.\(^33\)
- 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.\(^33\)
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 15L/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, e.g. 4 L/min through nasal cannulae and 10 L/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. 41,42

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-19.43

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.44

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** 45
- Respiratory distress (RR ≥ 35, PaCO₂ ≥ 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 (eg frequent seizures)
- Morbid obesity
- Pregnancy (2nd or 3rd trimesters)
- Pressure sores or ulcers

**Positioning**

- 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.

*Courtesy of Sandwell and West Birmingham NHS Trust*
**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
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

- \( \text{SaO}_2 \geq 93\% \) 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 \( \text{SaO}_2 \)

- \( \text{SaO}_2 < 93\% \) on air
  - Oxygen therapy to achieve \( \text{SaO}_2 \geq 93\% \) Awake proning

  - \( \text{SaO}_2 \geq 93\% \) with <40\% \( \text{FiO}_2 \) (approx. 10L) \( \text{O}_2 \)
    - Continue monitoring Continue proning

  - \( \text{SaO}_2 < 93\% \) with <40\% \( \text{FiO}_2 \) (approx. 10L) \( \text{O}_2 \)
    - \( \uparrow \text{FiO}_2 \) to 60\% (Approx. 15L) Continue proning
    - Consider trial of CPAP (with PEEP 10 cm H\(_2\)O) and \( \text{FiO}_2 \) 60\%
    - or
    - Consider HFNC

- \( \text{SaO}_2 \) in target range?
  - NO
    - Clarify escalation plan
    - Not appropriate for escalation
      - CPAP or HFNC not available
        - Proning Side positioning Highest possible \( \text{O}_2 \) Palliation
  - YES
    - Continue monitoring Continue proning
    - Appropriate for escalation
      - Intensive care Mechanical ventilation
        - \( \uparrow \text{PEEP} \) to 12 cmH\(_2\)O
          - \( \uparrow \text{O}_2 \)
          - Proning Side positioning
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 improve the overall oxygenation.46

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.47 and the preliminary data from the RECOVERY-RS trial (RECOVERY Respiratory Support trial),48 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. 15L/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.

![Example circuit set up](image)

Courtesy: British Thoracic Society
Consider starting at a positive end-expiratory pressure (PEEP) of 10 cmH₂O with FiO₂ of 60% (10-15L/min oxygen). If VT (tidal volume) can be measured, consider adjusting the pressure to keep VT between 500 to 1000 mL to prevent lung injury. Can start at a lower pressure if tolerance is an issue, to give patients time to acclimatise to CPAP. 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 12cmH₂O with 15L/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 FiO₂ 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 in delivery high flow oxygenation, weaning from CPAP (e.g. during mealtimes for a rest from CPAP), as a bridging before mechanical ventilation and for comfort in palliative therapy.
TOCILIZUMAB

Rationale
- 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).  
- The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial 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 benefit or improved survival with tocilizumab.
- Decision to initiate the treatment should only be made by a clinician.

Criteria for therapy
Current evidence suggests that 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 (>10L/min oxygen flow rate), continuous positive airway pressure, non-invasive ventilation, or invasive mechanical ventilation

Contraindications
- Known severe allergic reactions to 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 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

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
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).
**REMDESVIR**

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)\(^{64}\), funded by the National Institute of Allergy and Infectious Diseases (NIAID), and the Solidarity trial\(^{65}\), 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\(^{64}\) 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\(^{65}\) 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 summary, the two large trials had different patient characteristics, looked at different outcomes and had different results. Consequently, there is a lack of consensus among society and organisational guidelines on the use of remdesivir in COVID-19. The following are the current recommendations from different societies.

- In the US, the National Institutes of Health (NIH) guidelines\(^9\) 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\(^10\) recommends the use of remdesivir among hospitalised patients with severe COVID-19 (defined as patients with \(\text{SpO2} \leq 94\%\) 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)\(^10,11,66\) 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)\(^1\) guidelines recommend against remdesivir outside of clinical trials for COVID-19 of any disease severity.
In line with NICE, NIH and IDSA guidance, we make a conditional recommendation for the use of remdesivir in patients who are within 10 days of symptom onset and who require oxygen supplementation.

We do not recommend using remdesivir in asymptomatic patients who do not need oxygen or those who are on mechanical ventilation.

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, co-morbidities, and cost considerations.

**Criteria for therapy**
Remdesivir may be considered in patients with
- age ≥12 years AND
- body weight ≥ 40kg AND
- confirmed COVID-19 infection AND
- pneumonia requiring supplemental oxygen, but not mechanical ventilation AND
- within 10 days after symptom onset AND
- mortality is clinically judged as not too low (those are highly likely to recover without treatment with remdesivir) or too high (those are clinically judged as unlikely to survive). The 4C Mortality Score can be helpful in this assessment. (Available at [https://isaric4c.net/risk](https://isaric4c.net/risk))

**Contraindications**
- Known hypersensitivity to remdesivir or any component of the formulation
- Estimated glomerular filtration rate (eGFR) < 30mL/minute
- Alanine aminotransferase (ALT) > 5 times the upper limit of normal at baseline

**Dose**
200mg IV loading dose on day 1 followed by 100mg IV once daily for a maximum of 5 days.

**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 19mL of water for injections, then diluted in 250mL 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

Consider stopping the treatment if
- The patient clinically improves and no longer requires supplemental oxygen 72 hours after commencement of treatment OR
- The patient continues to deteriorate despite 48 hours of sustained mechanical ventilation
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

Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA 2021;325:1620-30.


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