# Coronavirus disease 2019–what do we know so far?

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The syndrome caused by coronavirus disease 2019 (COVID-19) has led to a wide spectrum of disease severity, and this has conferred immense pressures on hospitals worldwide, particularly within critical care. Given the rapid surge in clinical data from millions of people infected and the overwhelming scientific quest, we, the clinicians, need accurate evidence regarding the management of this disease. WHO has named this disease spectrum as COVID-2019. We seek to provide a comprehensive review of the fast-evolving literature including diagnosis, management, and novel therapies that are indicated in the management of COVID-19.

**Keywords:**
coronavirus, coronavirus disease 2019, review, venous thromboembolism

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## Introduction

The global pandemic that has occurred as a consequence of the novel severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) has caused chaos worldwide, leading to more than 400 000 deaths (at the time of writing) and significant economic downturn. This new deadly contagion has an estimated overall mortality rate of 2%. This pandemic has led to immense surge in demand on critical care services in most nations. The stretch on resources and the necessary expansion of critical care into alternative areas of the hospital have required redeployment of clinical staff. The substantial increase in workload as a result of increased critical care admissions of patients requiring advanced respiratory support demands a standardized approach to patient management. This approach must be current and backed by the existing knowledge and expertise but also a fast-evolving evidence base, to deliver high-quality care that is consistent when patients are managed by multiple clinicians of varying background. To commensurate with the evolving situation, we at Basildon University Hospital compiled a local resource to support our colleagues. This document is informed by existing guidance specific to coronavirus disease 2019 (COVID-19) as well as best available evidence from non-COVID-19-infected patients.

### Clinical characteristics

SARS-CoV-2 is an enveloped RNA COVID, thought to have originated in bats and transmitted to humans via an as-yet unidentified animal vector. 'SARS-CoV-2' relates to the virus, which causes the clinical illness known as 'COVID-19.' For clarity, this disease process has been referred to as 'COVID-19' by WHO. Transmission is via contaminated surfaces, where the virus may live for 4 days [1], or via droplets, which travel up to 2 m from an infected individual. The incubation period is typically 5 days but may range from 1 to 14 days, with viral shedding occurring 12–24 h before presentation of symptoms [2]. COVID-19 presents as a spectrum and is highly infectious, with an $R_0$ estimated to be around 2.5 [3]. Individuals may be asymptomatic and therefore pass the disease unknowingly to others, leading to potential exponential growth of case numbers with catastrophic effect. Of the cases presenting with symptoms, 80% will have either a fever (temperature >37.8°C) or nonproductive cough. Median duration of viral shedding was 20.0 days in survivors, but SARS-CoV-2 was detectable until death in nonsurvivors. The longest observed duration of viral shedding in survivors was 37 days [4]. The remainder may present with dyspnea, nonspecific symptoms (myalgia, headache, anorexia, and lethargy), anosmia, or ageusia. Less commonly, COVID-19 can present with gastrointestinal symptoms or acute confusion. Among those with COVID-19, 15% will require hospital admission and 5% will require critical care. COVID-19 can produce an atypical viral pneumonitis, characterized by hypoxemia with relatively compliant lungs and also a more classical acute respiratory distress

syndrome (ARDS). Two phenotypes of lung involvement have been described: L-type and H-type [5]. L-type is characterized by low elastance, low ventilation-to-perfusion ratio (V/Q), low lung weight, and low lung recruitability. L-type may improve or transform to H-type. H-type is characterized by high elastance, high right-to-left shunt, high lung weight, and high recruitability. Other nonrespiratory organs may also be affected: acute kidney injury (AKI), liver dysfunction, and cardiac dysrhythmia. Data from the Intensive Care National Audit and Research Centre (ICNARC) [6] indicate that males aged 50 years and older, who are overweight and have comorbidity (e.g. cardiovascular disease, diabetes mellitus, chronic respiratory disease, hypertension, malignancy, or chronic kidney disease) are making up the majority of patients with COVID-19 requiring critical care admission.

### Diagnosis

COVID-19 presents as a wide-spectrum disorder, and a high index of suspicion is required with all patients encountered. History may reveal a classical clinical picture of 5–7 days of fever, myalgia, and cough followed by worsening dyspnea. Loss of taste and smell were recently added as additional diagnostic symptoms. Physical examination is limited to minimize the chances of contamination; the patient may be cyanosed or demonstrate an increased work of breathing. Vital signs show an elevated respiratory rate and hypoxemia, although some patients may have $SpO_2$ less than 85% and not show any sign of respiratory distress. Experiments in hypobaric chambers have revealed that hypocapnic hypoxia may not usually be accompanied by air hunger; instead, patients appear calm and falsely look well. Aviation experiments have described this in hypobaric chambers, and this occurrence has been called 'silent hypoxia' [7]. Very low end-tidal $CO_2$ values in the 1.5–2.0 kPa along with a rapid respiratory rate should raise suspicion of impending prompt deterioration and decompensation in these patients.

Blood tests may show lymphopenia, mild thrombocytopenia [8], and elevated C-reactive protein. Chest radiograph findings are typically of bilateral patchy shadowing, owing to interstitial pneumonitis, and computed tomography of the chest may show patchy ground-glass appearances with subpleural shadows, reticular pattern, and reverse halo appearance. Diagnosis of COVID-19 is confirmed with reverse-transcriptase PCR of either nasopharyngeal swabs or lower respiratory isolates. It is worth noting that there appears to be a significant false negative rate (30%) with the nasopharyngeal sampling method. Serum antibody (IgM and IgG) testing has variable availability, and validation of these tests is still pending. RT-qPCR is the gold standard for detection of pathogens because of their high sensitivity and specificity. RT-LAMP (reverse transcription loop-mediated isothermal amplification) assays to detect genomic RNA of SARS-CoV-2. RT-LAMP is a one-step nucleic acid amplification method, shown to be quicker and promising [9].

Several markers have been shown to be associated with increased disease severity; these include high neutrophil/lymphocyte ratio, hypoalbuminemia, elevated troponin, elevated D-dimer, fibrinogen, elevated ferritin, and rising C-reactive protein (may indicate superadded bacterial infection or disease progression). Elevated levels of ferritin can be surrogate indicators of the presence of viruses and bacteria in the body. Unusually high levels of ferritin have suggested to indicate severe progression of the disease. The prothrombotic coagulopathic pattern observed in hospitalized COVID-19-infected patients is characterized by elevations in fibrinogen and D-dimer levels along with parallel rise in inflammatory markers. In addition, prolongation of prothrombin time and activated partial thromboplastin time has been noted in 30–40% of severe COVID-19-infected patients.

### Lung ultrasound

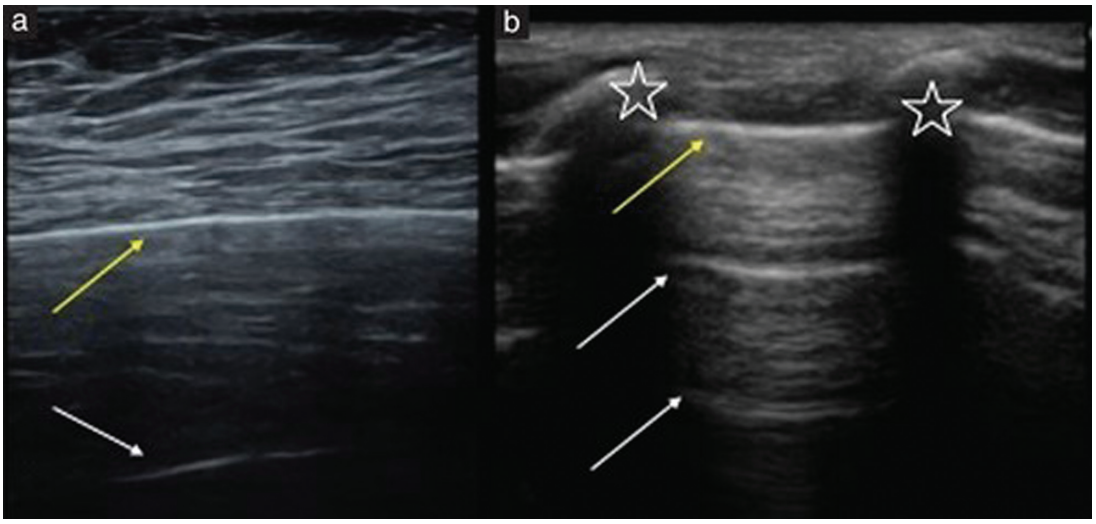
Volpicelli [10] are convinced that lung ultrasounds should be done for all patients presenting in emergency department with flu-like symptoms for diagnosing and screening COVID-19-infected patients. Bedside lung ultrasound is simple and easy to learn with multiple advantages such as low cost, high accuracy, low risk, and radiation free. Sweeping the curvilinear probe over different zones over the chest will allow us to identify a variety of pathologies in the COVID-19-infected lungs.

In a normally aerated lung, the only detectable structure is the pleura, visualized as a highly hyperechoic horizontal line (pleural line). Reflection of the ultrasound beam determines the appearance of hyperechoic, parallel, horizontal artefacts (A-lines), indicating normal inflated peripheral lung if combined with 'sliding' of the pleural line (Figs 1–3).

#### *Pathological B-lines*

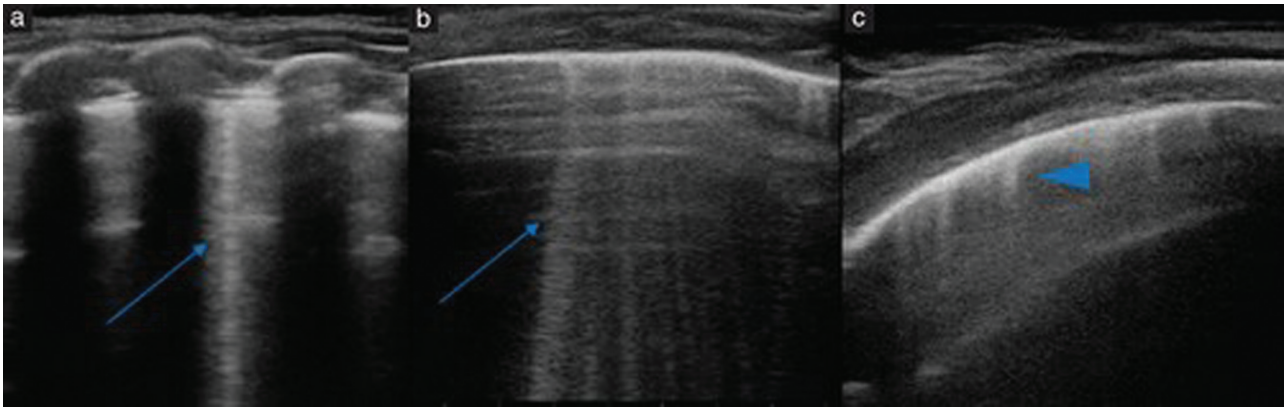
When the lung loses normal aeration but is not completely consolidated (e.g. in viral pneumonia), it

**Figure 1**




Ultrasound images of normal lung. (a) Probe positioned in intercostal space; visible are pleural line with no interruption (yellow arrow) and A-line (white arrow) due to reverberation of pleural line. (b) Probe positioned longitudinally; visible are ribs with posterior shadowing (image), pleural line (yellow arrow) and A-lines (white arrows).

**Figure 2**




Ultrasound images in patients with pneumonia, showing 'B-lines' (arrows and arrowhead). These appear as hyperechoic vertical line(s) touching bottom of screen, resembling a comet tail (a), multiple thickened hyperechoic lines (b) or short lines arising from the pleura (c).

generates different shapes and lengths of vertical artefacts, usually called B-lines. The B-lines possibly reflect the different shaped and sized acoustic channels generated by the altered peripheral air space in pathological conditions [11].

*Viral pneumonic consolidation*

In these circumstances, the involved area of the lung loses its air and becomes a solid organ that can be evaluated by ultrasound in the same way as any other organ (e.g. the liver). The consolidation appears as an irregular hypoechoic area. In pathology such as COVID-19 pneumonia, advanced ARDS, or bronchiolitis, the lung may present only small subpleural consolidations.

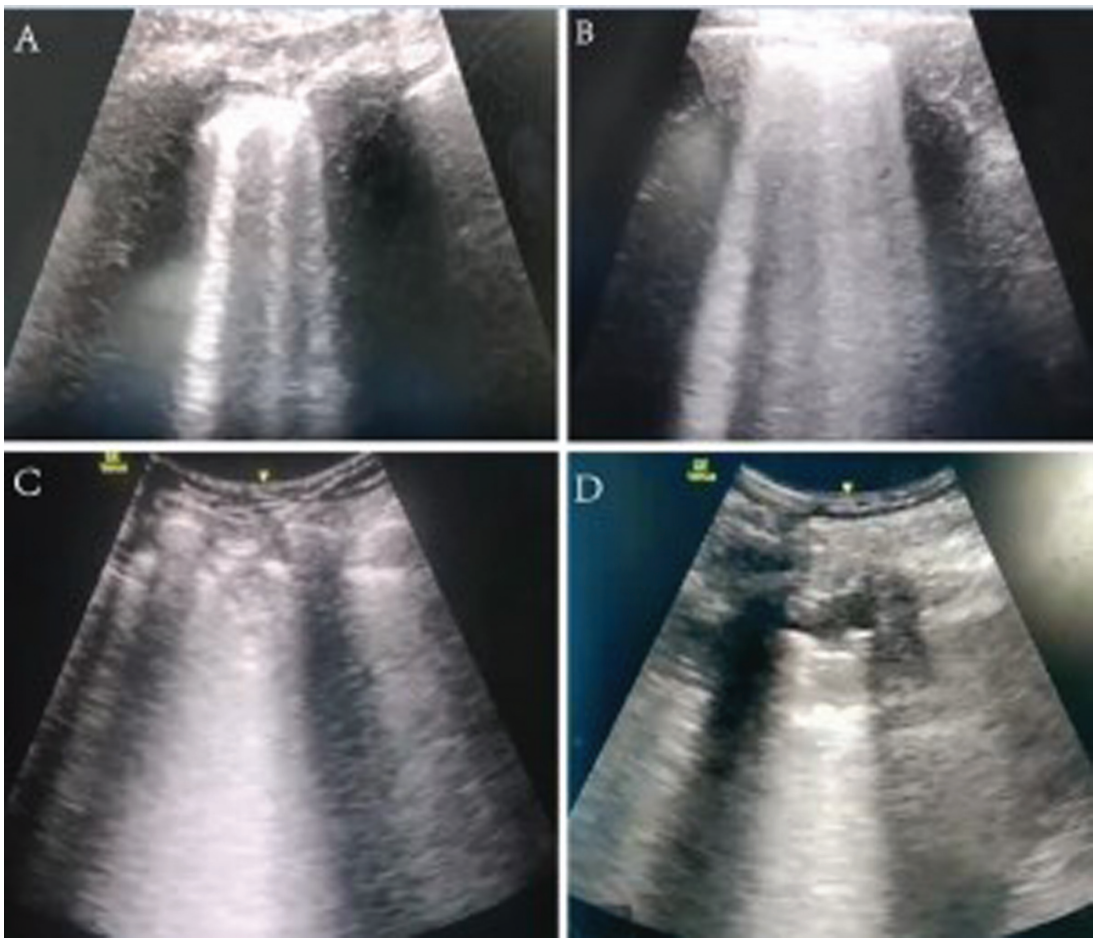
The thoracic spine sign, or spine sign (Fig. 4), on lung ultrasound is an indirect indicator of the presence of a pleural effusion or hemothorax. It represents the visualization of the vertebral bodies in the thoracic cavity above the diaphragm, which are usually not seen unless there is a fluid collection.

## Management of coronavirus disease 2019

*Oxygen therapy*

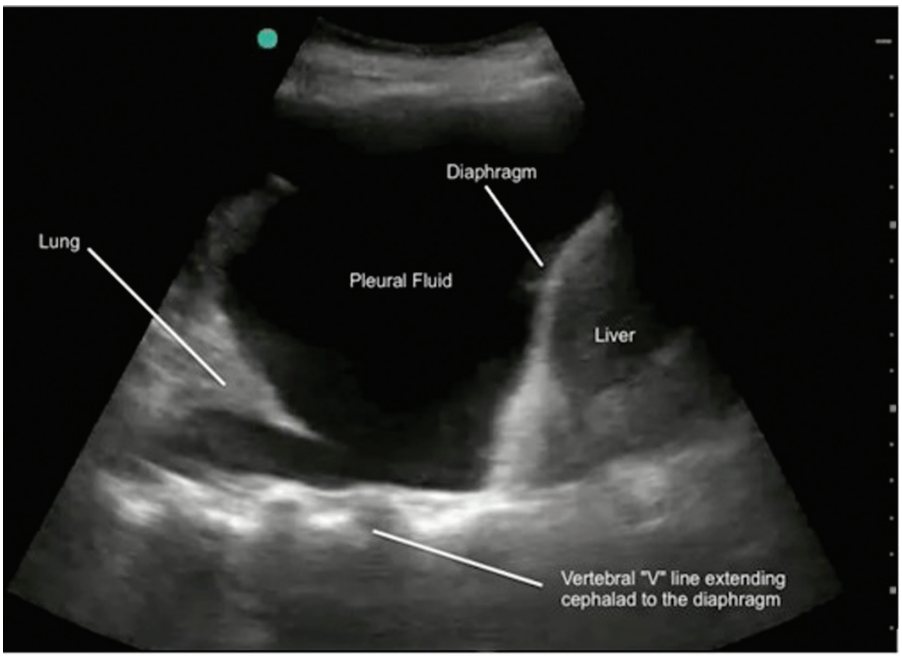
Oxygen therapy is titrated to $SpO_2$ 92–96%, avoiding hyperoxia. $SpO_2$ 90–93% is acceptable in areas with continuous pulse oximetry monitoring. Lower target $SpO_2$ ranges may be appropriate for certain patient groups such as those with chronic obstructive pulmonary disease. The use of high-flow oxygen

**Figure 3**




Typical lung ultrasonography images of nCoV pneumonia. (a) B-lines; (b) confluent B-lines; (c) small consolidations; (d) translobar consolidation.

**Figure 4**




Pleural effusion showing anechoic pleural fluid, atelectatic lung, and 'spine sign.'

delivery devices should be minimized owing to the increased demand placed on local oxygen supplies, risking failure of oxygen delivery to the clinical area. This can be difficult to predict, even if the pressure and total flow are known. Likewise, high-flow nasal oxygen devices should be avoided for the same reason, and there also exists a (debated [12]) risk of aerosolization, leading to viral contamination of the local environment.

#### Continuous positive airway pressure and noninvasive ventilation

Continuous positive airway pressure (CPAP) devices (via a nonventing face mask or helmet) may be trialled to assess whether invasive ventilation can be avoided in selected patients. Failure to respond to treatment, as evidenced by worsening gas exchange or increased work of breathing, is an indication for intubation and invasive ventilation. Patients requiring low $FiO_2$ may be suitable for low-flow CPAP devices that use entrained oxygen, to make most economical usage of local oxygen supplies. It is important to note that patients may look comfortable on CPAP during the early phase of the disease where lung compliance is near-normal. A high spontaneous minute ventilation, which may be an indicator of clinical deterioration or disease progression, may be injurious, and delayed intubation in this group may be detrimental. Noninvasive ventilation is generally not indicated in type 1 respiratory failure but may be considered in patients with type 2 respiratory failure (e.g. COPD). An appropriate antimicrobial filter should be located on the expiratory limb of any device used. Use of CPAP is aerosol generating, and there is a high risk of environmental viral contamination. Mask ventilation should be delivered in a negative or neutral pressure room. Patients may also be nursed in a cohort in restrictive access areas, called as 'red zone.' Prone positioning in awake patients can improve V/Q mismatch, oxygenation, and work of breathing, if tolerated.

#### Mechanical ventilation

Patients requiring mechanical ventilation are nursed in restricted access area, by staff wearing enhanced personal protective equipment (i.e. respirator face mask – FFP3 standard, eye protection, long sleeved fluid resistant gown, and gloves). An antimicrobial filter is placed on the expiratory limb or ventilator exhaust. One must note that filters represent an airflow obstruction when saturated with moisture, and regular assessment and replacement is advised. Heated humidifiers can cause rapid saturation of in-line filters, and the combination should be used with caution. Dry circuits with heat–moisture exchange filters can cause secretion build-up and obstruction of endotracheal tubes. Regular nebulized saline and mucolytics may be useful but can also contribute to circuit obstruction through saturation of filters and salt crystal build-up within ventilator expiratory blocks. In-line suction systems should be used. Inadvertent ventilator circuit disconnections should be avoided by ensuring all connections are 'tight.' Manual ventilation using a Mapleson C circuit (or equivalent) should be avoided, owing to concerns about aerosol generation and infection risk. Patient requiring advanced respiratory support may overwhelm critical care resources, including ventilators, necessitating the usage of anesthetic machines to provide mechanical ventilation for COVID-19-infected patients. There are several issues specific to the use of anesthetic machines: in-line suction systems may trigger ventilator to stop owing to collapse of the bellows; ensure end-tidal capnography sampling is taken from the 'ventilator side' of the viral filter; and heat–moisture exchange filters may become rapidly saturated with water vapor when a circle system with soda lime is used.

Ventilator strategy should be guided by disease phenotype. Low pulmonary elastance or L-type often demonstrates normal compliance (>50 ml/$cmH_2O$), and recruitment may not be required. Target tidal volume of 8 ml/kg (based on ideal body weight) and positive end expiratory pressure 8–10 cm/$H_2O$. Neuromuscular blockade is advised in cases of ventilator desynchrony, high spontaneous minute ventilation, or $FiO_2$ more than 0.7. Consideration should be made of pulmonary vasodilators (e.g. Nebulized epoprostenol) to improve V/Q mismatching where available owing to loss of hypoxic pulmonary vasoconstriction. Improvements in oxygenation can often be achieved by proning, which is considered a rescue maneuver (Table 1). High pulmonary elastance or H-type management follows that is common to severe ARDS: lung-protective ventilation (tidal volume 4–6 ml/kg ideal body weight), conservative fluid management to reduce lung edema, neuromuscular blockage, lung recruitment manoeuvres (e.g. positive end expiratory pressure escalation), and prone positioning.

#### Refractory hypoxemia

Prone position is considered if $PaO_2/FiO_2$ less than 20 kPa; this should commence within first 72 h of critical care admission. Prone positioning should be maintained for 16 h in the first instance and then for 12 h for subsequent turns. Continued proning/

**Table 1 Ventilation strategies in patients with coronavirus disease 2019 infection**

| Mechanical ventilation strategies for COVID-19 patients | Target for volume-control ventilation | Targets for pressure-control ventilation |
|---|---|---|
| Sedation with neuromuscular blockade if $FiO_2$ >0.7 | $SpO_2$ 88–95% | $SpO_2$ 88–95% |
| Vt 4–8 ml/kg IBW | $PaO_2$ >8 kPa | $PaO_2$ >8 kPa |
| Start PEEP 8 $cmH_2O$ | pH >7.25 (permissive hypercapnia) | pH >7.25 (permissive hypercapnia) |
| RR 16–26/min (if pH <7.25, increase RR up to 30/min) | $P_{plateau}$ <28–30 cm.$H_20$, Vt 4–8 ml/kg IBW ($P_{plateau}$ <32 $cmH_2O$ if BMI >30) | Pressure support (PS) 15 $cmH_2O$ over PEEP 10 $cmH_2O$ (allow PS 12–18 $cmH_2O$ if BMI >30) |
| | RR 16–26/min | RR 16–26/min |

COVID-19, coronavirus disease 2019; IBW, ideal body weight; PEEP, positive end expiratory pressure; Vt, tidal volume.

**Table 2 Criteria to assess suitability for extubation in coronavirus disease 2019-infected patients**

| Ventilation criteria | Hemodynamic criteria | Neurological criteria | Investigations |
|---|---|---|---|
| $FiO_2$ <0.4 | Low-dose vasopressors (e.g. noradrenaline <0.5 mcg/kg/min) | Awake | CXR stable or improving |
| PEEP <8 $cmH_2O$ | Systolic BP >90 mmHg or mean arterial pressure >60 mmHg | Follows commands | PaO2 >8 kPa on $FiO_2$ 0.4 |
| PS <10 $cmH_2O$ | Stable cardiac rhythm | Effective cough | pH >7.3 |
| No respiratory distress | No significant tachycardia | Not aggressive or agitated | |
| Minimal secretion load | No fever | No significant neuromuscular weakness | |
| | | Pain adequately controlled | |

CXR, chest radiograph; PPEP, positive end expiratory pressure.

supination cycles should be continued until oxygenation improves. Extracorporeal membrane oxygenation (ECMO) may be considered if there is no improvement or deterioration in the prone position, demonstrated by $PaO_2/FiO_2$ less than 8–10 kPa, $PaCO_2$ more than 8 kPa, or pH less than 7.25. Currently, there is lack of evidence as to whether ECMO will improve survival, so we cannot recommend ECMO in COVID-19 ARDS.

### Extubation

Criteria to assess suitability for extubation (Table 2) follow similar principles to that of non-COVID-19-infected patients. COVID-19 has been associated with the incidence of laryngeal edema, and a cuff leak test is recommended before attempting extubation, and any suspicion should delay extubation for 24–48 h. Corticosteroid therapy, for example, dexamethasone, may be started 12–24 h before extubation, and nebulized adrenaline is administered immediately after extubation.

### Management of infection

Patients admitted with features in keeping with COVID-19, awaiting confirmation, are commenced on empirical broad-spectrum antibiotic therapy. Recommended treatment options in our institution as first-line therapy are ceftriaxone 2 g intravenous OD and clarithromycin 500 mg intravenous BD. Clarithromycin is ceased on confirmation of COVID-19. As second-line therapy or those with severe penicillin allergy, levofloxacin 500 mg intravenous BD is considered. These agents were selected based on local flora and reduced frequency of dosing, to ease burden on nursing staff preparing intravenous medications. Antibiotic therapy is limited to 5 days, unless clinical evidence or organisms detected on sampling suggest otherwise. All admissions to critical care should have a routine HIV test. Surveillance of secondary infection is mandatory for patient mechanically ventilated for more than 7 days. Empirical treatment of nosocomial infection is with piperacillin/tazobactam 4.5 g intravenous QDS (meropenem 1–2 g intravenous TDS for mild penicillin allergy, and vancomycin infusion and ciprofloxacin 400 mg intravenous BD for severe penicillin allergy) alongside sending endotracheal aspirates, blood cultures, and consideration of any indwelling lines or catheters. Consideration should also be made for possibility of fungal (*Candida* spp. is common, *Aspergillus* spp. to a lesser extent) and viral (cyclomegalovirus, *Herpes simplex*, and Adenovirus spp.) infection in those who have received prolonged mechanical ventilation (>10 days).

Routine corticosteroids are not recommended. However, where patients require corticosteroids for other indications (either at replacement doses for

known adrenal insufficiency or as a treatment for another underlying condition such as asthma or COPD), they should not be withheld.

Vitamin D: there is evidence that vitamin D supplementation enhances the function of the immune system and reduces the risk of developing respiratory infection [13]. As well as this, it appears that high levels of vitamin D reduce the severity of respiratory infection [14]. The precise mechanism by which vitamin D exerts its protective effect against infection is unknown. Vitamin D is nonetheless known to play a role in the immune system where it influences antigen presentation, innate immunity, and T-cell function [15]. Vitamin D also affects the expression of angiotensin-converting enzyme 2 (ACE2), the functional receptor for the SARS-CoV-2 [16]. Many trusts in the UK have started vitamin D supplementation in COVID-19-infected patients along with therapeutic dosing of vitamin D in proven deficiency.

#### Acute kidney injury

AKI occurs in ~17–45% of patients admitted to critical care units with COVID-related organ failure. AKI in COVID-19 appears to be a multifactorial process, driven by virus-mediated injury, cytokine storm, angiotensin II pathway activation, complement activation, hypercoagulation, and microangiopathy interacting with common and known risk factors for renal failure [17].

Patients of COVID can present with high insensible losses owing to fever and are often in fluid deficit, owing to self-isolation at home with symptoms in the time preceding admission to hospital. Initial judicious fluid resuscitation should be attempted to replenish intravascular volume. Overzealous fluid restriction is not recommended.

The indications for renal replacement therapy (RRT) for AKI remain the same regardless of the COVID-19 status of any given patient. The conventional indications to start RRT include life-threatening hyperkalemia, refractory fluid overload, severe metabolic acidosis, etc. In all cases, maximal medical management should be considered before attempting RRT, including loop diuretics (oral or intravenous) for fluid overload, potassium binders as per National Institute of Clinical Excellence guidance, and other measures to manage acute hyperkalemia in hospitalized patients with COVID-19. Sodium bicarbonate (oral or intravenous) in severe metabolic acidosis [18] may be considered.

#### Venous thromboembolism prophylaxis

A prothrombotic phenomenon is common, characterized by high fibrinogen, D-dimer, and prothrombin time, despite thrombocytopaenia. All COVID-19-infected patients should receive pharmacological venous thromboembolism (VTE) prophylaxis, unless platelet count is less than $30\,000\,\mu l^{-1}$ or there is evidence of active bleeding. In the absence of bleeding, coagulopathy is not an absolute contraindication for VTE prophylaxis, unless the platelet count is less than $30\,000\,\mu l^{-1}$ for prophylactic or less than $50\,000\,\mu l^{-1}$ for therapeutic anticoagulation. On admission to hospital, blood tests for full blood count, urea and electrolytes, liver function tests, clotting profile, and D-dimers should be sent, and anticoagulation should follow the guidance in Table 3. D-dimer should be repeated every 48 h or whenever there is a clinical deterioration and the anticoagulation plan reviewed.

Mechanical thromboprophylaxis should be considered for patients with platelet count less than $30\,000\,\mu l^{-1}$. For patients established on novel oral anticoagulants for preexisting conditions, consider changing to low-molecular-weight heparin (LMWH) if clinical deterioration or rising D-dimer, as there is some evidence that LMWH has better efficacy. Patients should remain on VTE prophylaxis for two weeks following discharge from hospital (Tables 4 and 5).

Heparin resistance may occur and is defined as failure to achieve adequate activated partial thromboplastin time ratio 2–2.5, despite titration of unfractionated heparin. This is commonly encountered as filter thrombosis with patients receiving RRT via continuous venovenous hemofiltration. Troubleshooting of this issue should include antithrombin III levels and heparin-induced thrombocytopaenia screening. Unfractionated heparin may be replaced by LMWH with anti-Xa levels, target 0.6-1.0 IU/l, or with systemic anticoagulation by a direct thrombin inhibitor such as Argatroban.

#### Nutrition

Energy and protein targets should be set as per current local practice. Adjustments to feeding plan should be made for propofol, glucose, and citrate to avoid overfeeding. One must consider protein supplementation in patients who are unable to meet protein targets owing to significant contribution of non-nutritional calories. Prokinetics should be considered for those patients with high gastric residual volume (GRV), alongside consideration of potential interactions with other commonly used drugs in critical care [e.g. metoclopramide/

**Table 3 Guidance for venous thromboembolism prophylaxis in coronavirus disease 2019-infected patients**

| | | |
|---|---|---|
| D-dimers <1000 | | |
| Creatinine clearance >30 ml/min | Standard weight adjusted VTE prophylaxis | <50 kg enoxaparin 20 mg OD 50–100 kg enoxaparin 40 mg OD 100–150 kg enoxaparin 40 mg BD >150 kg enoxaparin 60 mg B |
| For creatinine clearance < 30 ml/min | UF heparin 5000 U SC BD | |
| D-dimers >1000 | | |
| Creatinine clearance >30 ml/min | Double the dose of standard weight adjusted VTE prophylaxis | <50 kg enoxaparin 20 mg BD 50–100 kg enoxaparin 40 mg BD 100–150 kg enoxaparin 80 mg BD >150 kg enoxaparin 120 mg BD |
| Creatinine clearance <30 ml/min | 50 100 kg UF heparin 5000 U SC TDS 100–150 kg UF heparin 10 000 U SC BD >150 kg UF heparin 12 500 U SC BD | |
| For all patients with severe COVID-19 at presentation requiring assisted ventilation in ITU, with D-dimers >1000, or proven VTE | | |
| Consider full therapeutic anticoagulation if creatinine clearance >30 ml/min Creatinine clearance <30 ml/min or requiring renal replacement therapy | Enoxaparin 1.5 mg/kg OD If the bleeding risk is higher, treatment can be given in two divided doses or if progressive rise in D-dimers consider 1 mg/kg BD with monitoring anti-Xa 0.5–1 IU/ml | |
| | UF heparin, target APTT:R 2–2.5 If difficult to administer UF heparin and monitor APTT (poor venous access/patient not in ITU set up, enoxaparin 1 mg/kg SC OD – but monitor anti-Xa at least once in 2–3 days (anti-Xa level 0.5–1.0 IU/ml) If platelet count less than <30, avoid anticoagulation until counts improve and consider mechanical prophylaxis (e.g. intermittent calf compression device) | |

APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; UF, unfractionated; VTE, venous thromboembolism.

**Table 4 Guidance on venous thromboembolism prophylaxis for coronavirus disease 2019-infected patients following discharge**

| | |
|---|---|
| Category 1–no proven VTE | |
| CrCl >30 ml/min Weight >60 kg Age <80 years | Apixaban 5 mg BD or enoxaparin 0.5 mg/kg |
| CrCl 15–30 ml/min Weight <60 kg Age >80 years | Apixaban 2.5 mg BD |
| CrCl <15 ml/min | Enoxaparin 0.5 mg/kg for 10–14 days, measure anti-Xa level of longer treatment required (target 0.2–0.4 IU/l) |

VTE, venous thromboembolism.

**Table 5 Management of proven venous thromboembolism in coronavirus disease 2019 patients following discharge**

| | |
|---|---|
| Category 2–proven VTE | |
| No contraindication to oral anticoagulants | Contraindication to oral anticoagulants |
| CrCl >15 ml/min – Apixaban 5 mg BD | CrCl >30 ml/min – enoxaparin 1.5 mg/kg |
| CrCl <15 ml/min – warfarin | CrCl <30 ml/min – enoxaparin 1 mg/kg (anti-Xa level 4 h after third dose, target 0.4–0.8 IU/l) |

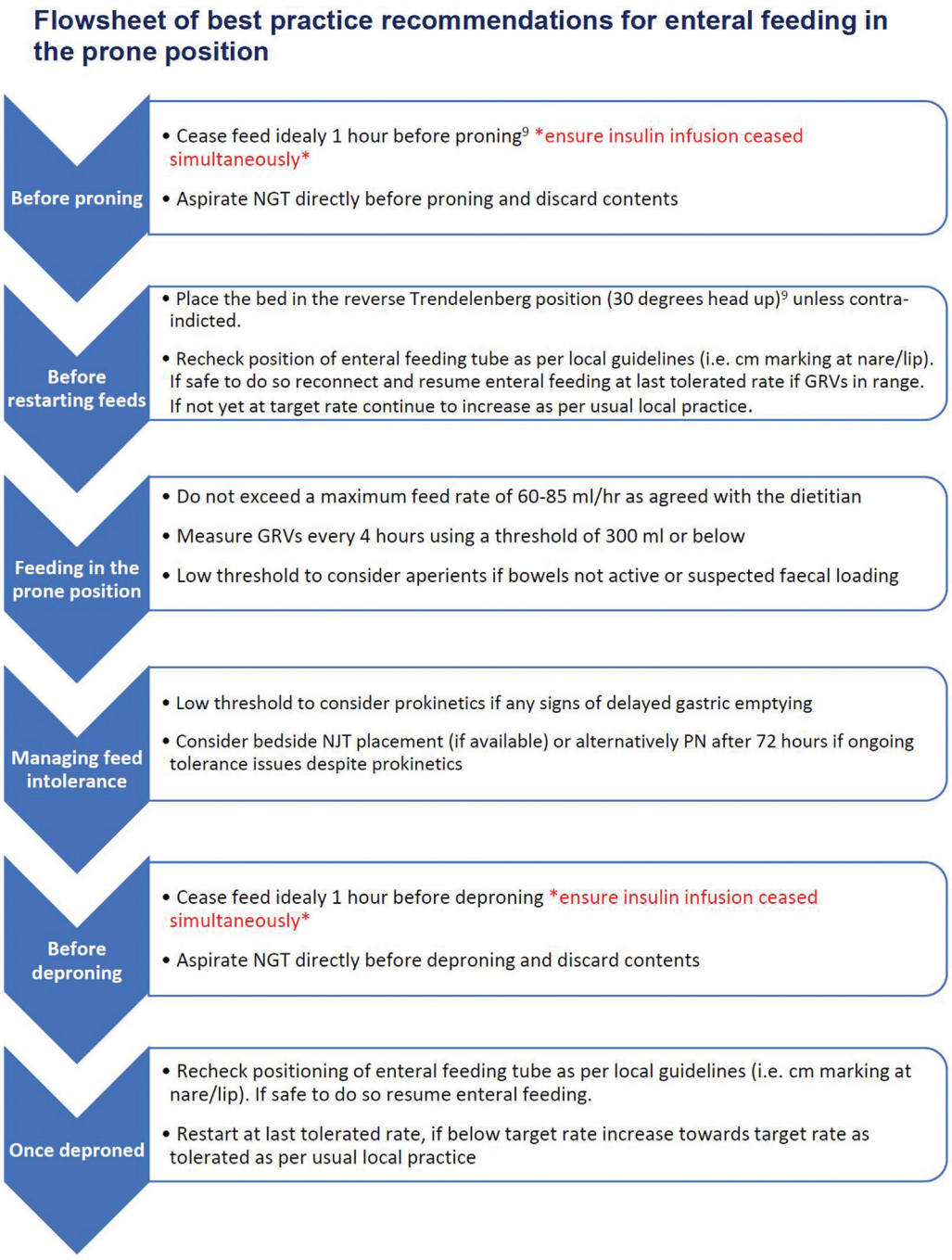
VTE, venous thromboembolism.

erythromycin with hydroxychloroquine (HCQ)/amiodarone]. Postpyloric tube placement is preferable, and parenteral nutrition should be considered if ongoing high GRV.

Enteral feeding should be continued while in the prone position, unless there are concerns regarding gastrointestinal intolerance (e.g. high GRVs). If GRV is more than 300 ml in 4 h, reduce feeding rate. Where possible, avoid 2 kcal/ml enteral feeds as these may exacerbate high GRV, although it is acknowledged that these may be required for the management of potassium or fluid restrictions.

The Intensive Care Society and Association of UK Dieticians recommend the use of a nutrition flow chart (Figs 5 and 6) [20].

**Figure 5**




Management of enteral feeding whilst in the prone position, adapted from joint ICS and Association of UK Dieticians guideline for enteral feeding in the prone position. ICS, Intensive Care Society.

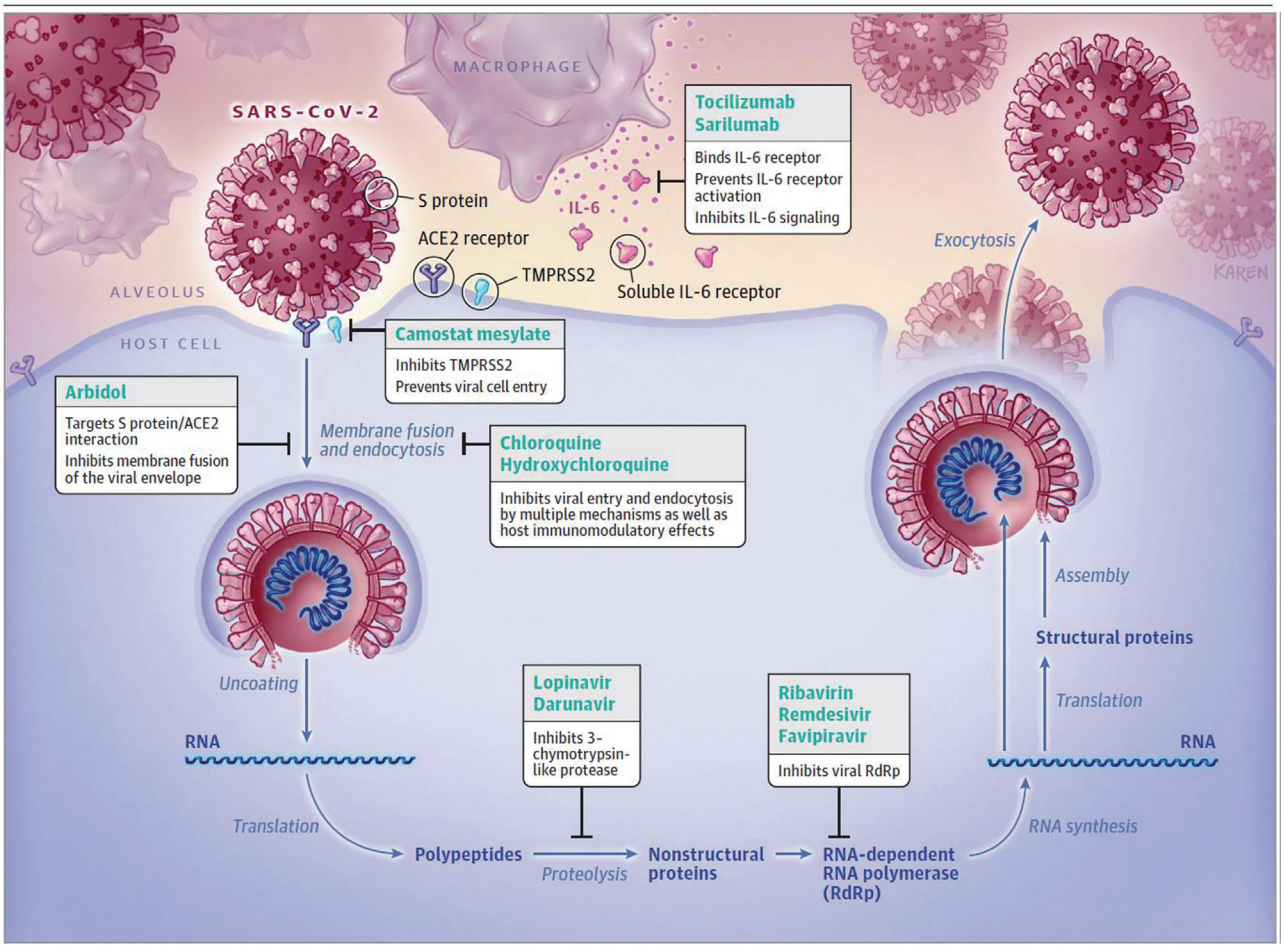
### Cardiovascular complications associated with coronavirus disease 2019 infection

Systemic inflammation can destabilize vascular plaques, while the viral illness increases cytokine activity, increasing cardiac demand, similar to influenza [21]. Recent research has suggested that the virus may also cause direct damage to the heart using ACE2 receptors located within the cardiac tissue [22].

### Acute myocardial injury and myocarditis

Acute myocardial injury with an elevated troponin level may occur in 22–31% of those admitted to the ICU. Acute myocarditis poses significant diagnostic challenge in COVID-19-infected patients and presents with chest pain, dyspnea, dysrhythmia, and acute left ventricular dysfunction [23]. Echocardiographic evaluation is more likely to demonstrate a focal wall motion abnormality with active, significant, acute coronary syndrome, whereas

**Figure 6**




Schematic represents virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease.

Reproduced from Sanders *et al*. [19].

severe forms of COVID-19-related myocarditis will show either no wall motion defects or global wall motion dysfunction.

### Acute heart failure and cardiomyopathy

Acute heart failure and cardiomyopathy may be present in COVID-19-infected patients with an incidence of 23 and 33%, respectively. Cautious fluid administration must be considered in the background of right heart failure in addition to ARDS.

### Dysrhythmias

A range of dysrhythmias have been encountered in patients with COVID-19 infection. Most frequently, sinus tachycardia is seen in such patients, resulting from multiple, simultaneous causes (hypoperfusion, fever, hypoxia, anxiety, etc.) [24].

### Current clinical treatment experience and ongoing research

The WHO guidance emphasizes the role of supportive care based on severity of illness, ranging from symptomatic treatment for mild disease to evidence-based ventilatory management for ARDS and early recognition and treatment of bacterial infections and sepsis in critically ill patients. Routine use of corticosteroids is not recommended, although exception is made in the instance of clinical trial participants. They recommend to not routinely give systemic corticosteroids for treatment of viral pneumonia outside clinical trials and state 'investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials.' The WHO recently launched a global 'mega-trial' called SOLIDARITY with a pragmatic design that will randomize confirmed cases into either standard care or one of four active treatment arms [remdesivir, chloroquine (CQ) or HCQ, lopinavir/ritonavir, or lopinavir/ritonavir plus interferon-β) based on local drug availability [25].

### Chloroquine and hydroxychloroquine

CQ and HCQ have a long-standing history in the prevention and treatment of malaria and the treatment

of chronic inflammatory diseases including systemic lupus erythematosus and rheumatoid arthritis [26]. CQ and HCQ appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells [19,27]. However, there are legitimate concerns that CQ and HCQ could excessively dampen the immune response, thereby leading people more susceptible to SARS-CoV-2. The Randomized Evaluation of COVID-19 therapy (RECOVERY-NCT04381936) is randomizing HCQ, lopinavir-ritonavir combination, low-dose dexamethasone, azithromycin, tocilizumab (interlukin-6 blocker), and placebo as part of treatment for COVID-19 infection.

Currently, there are multiple international clinical trials looking into the efficacy of CQ and HCQ as prophylaxis in health care workers. Some studies in India by Indian Council of Medical Research have shown encouraging results with HCQ in preventing the onset of disease in health care workers.

#### Lopinavir/ritonavir and other antiretrovirals

Lopinavir/ritonavir, a US Food and Drug Administration approved oral combination agent for treating HIV, demonstrated in-vitro activity against other novel coronaviruses via inhibition of 3-chymotrypsin-like protease [28,29]. No published SARS-CoV-2 data exist for lopinavir/ritonavir [30]. A systematic review of ritonavir for the treatment of SARS and MERS found limited available studies, with most of these investigating SARS. Clinical studies in SARS were associated with reduced mortality and intubation rates, but their retrospective, observational nature prevents definitive conclusions. The timing of administration during the early peak viral replication phase (initial 7–10 days) appears to be important because delayed therapy initiation with lopinavir/ritonavir had no effect on clinical outcomes [31,32].

Early reports of lopinavir/ritonavir for the treatment of COVID-19 are mostly case reports and small retrospective, nonrandomized cohort studies, making it difficult to ascertain the direct treatment effect of lopinavir/ritonavir [31,32]. Although additional randomized control trails of lopinavir/ritonavir are ongoing (RECOVERY-NCT04381936), the current data suggest a limited role for lopinavir/ritonavir in COVID-19 treatment.

#### Ribavirin

Ribavirin, a guanine analog, inhibits viral RNA-dependent RNA polymerase. Its activity against other nCoVs makes it a candidate for COVID-19 treatment. However, it is in-vitro activity against SARS-CoV was limited and required high concentrations to inhibit viral replication, necessitating high-dose and combination therapy. Patients received either intravenous or enteral administration in previous studies [33]. No evidence exists for inhaled ribavirin for nCoV treatment, and data with respiratory syncytial virus suggest inhaled administration offers no benefit over enteral or intravenous administration [34].

The inconclusive efficacy data with ribavirin for other nCoVs and its substantial toxicity suggest that it has limited value for treatment of COVID-19. If used, combination therapy likely provides the best chance for clinical efficacy.

#### Other antivirals

Oseltamivir, a neuraminidase inhibitor approved for the treatment of influenza, has no documented in-vitro activity against SARS-CoV-2. Umifenovir (also known as Arbidol) is a more promising repurposed antiviral agent with a unique mechanism of action targeting the S protein/ACE2 interaction and inhibiting membrane fusion of viral envelope [35].

#### Miscellaneous agents

Interferon-α and interferon-β have been studied for nCoVs, with interferon-β demonstrating activity against MERS [33,36]. Most published studies reported results of therapy combined with ribavirin and/or lopinavir/ritonavir. Similar to other agents, delayed treatment may limit effectiveness of these agents. Given conflicting in vitro and animal data and the absence of clinical trials, the use of interferons to treat SARS-CoV-2 cannot currently be recommended [37].

Camostat mesylate, an approved agent in Japan for the treatment of pancreatitis, prevents nCoV cell entry in vitro through inhibition of the host serine protease TMPRSS2 [38]. This novel mechanism provides an additional drug target for future research.

SARS-CoV-2 uses the ACE2 receptor for entry into the host cell. This discovery has stimulated discussions about whether ACE inhibitors and/or angiotensin receptor blockers may potentially treat COVID-19 or, conversely, worsen disease [39]. These drugs upregulate ACE2 receptors, which could theoretically lead to worse outcomes if viral entry is

enhanced. In contrast, angiotensin receptor blockers could theoretically provide clinical benefit via blockade of ACE2 receptors. Conflicting in-vitro data exist to determine if these agents have a detrimental or protective effect in patients with COVID-19. Pending further research, clinical societies and practice guidelines are recommending continuing therapy for patients already taking these agents [40,41].

#### Remdesivir

Remdesivir, formally known as GS-5734, is a monophosphate prodrug that undergoes metabolism to an active C-adenosine nucleoside triphosphate analog. Remdesivir is believed to be a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cell. The agent was discovered amidst a screening process for antimicrobials with activity against RNA viruses, such as Coronaviridae and Flaviviridae.

A phase 3 randomized study to evaluate the safety and antiviral activity of remdesivir (GS-5734) in participants with severe COVID-19 and adaptive COVID-19 treatment trial (ACTT – NCT04280705) is underway looking at the effectiveness of the new antiviral remdesivir.

#### Favipiravir

Favipiravir, previously known as T-705, is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate. The active agent inhibits the RNA polymerase, halting viral replication. Most of favipiravir's preclinical data are derived from its influenza and Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses [42].

### Adjunctive therapies

At present in the absence of proven therapy for SARS-CoV-2, the cornerstone of care for patients with COVID-19 remains supportive care, ranging from symptomatic outpatient management to full intensive care support. However, three adjunctive therapies that warrant special mention are corticosteroids, anti-cytokine or immunomodulatory agents, and immunoglobulin therapy.

#### Corticosteroids

The rationale for the use of corticosteroids is to decrease the host inflammatory responses in the lungs, which may lead to acute lung injury and ARDS. However, this benefit may be outweighed by adverse effects, including delayed viral clearance and increased risk of secondary infection.

#### Anti-cytokine or immunomodulatory agents

Monoclonal antibodies directed against key inflammatory cytokines or other aspects of the innate immune response represent another potential class of adjunctive therapies for COVID-19. The rationale for their use is that the underlying pathophysiology of significant organ damage in the lungs and other organs is caused by an amplified immune response and cytokine release, or 'cytokine storm' [43]. IL-6 appears to be a key driver of this dysregulated inflammation. Thus, monoclonal antibodies against IL-6 could theoretically dampen this process and improve clinical outcomes. Tocilizumab, a monoclonal antibody IL-6 receptor antagonist, is Food and Drug Administration approved to treat RA and cytokine release syndrome following chimeric antigen receptor T-cell therapy.

#### Immunoglobulin therapy

Another potential adjunctive therapy for COVID-19 is the use of convalescent plasma or hyperimmune immunoglobulins [44]. The current trial includes hyperimmune plasma for critical patients with COVID-19 (COV19-PLASMA-NCT04356534). The rationale for this treatment is that antibodies from recovered patients may help with both free virus and infected cell immune clearance.

#### Vaccination in coronavirus disease 2019

Bacillus Calmette-Guerin was developed as a vaccine against tuberculosis, but studies have shown its ability to induce potent protection against other infectious diseases, the so-called nonspecific effects. There is an ongoing trial (NCT04328441) looking into 1500 participants with a hypothesis that Bacillus Calmette-Guerin vaccination can reduce health care worker absenteeism during the epidemic phase of COVID-19.

A phase I/II single-blinded, randomized, multi-center study to determine efficacy, safety, and immunogenicity of the candidate COVID-19 vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers aged 18–55 years is underway. There are four study groups, and it is anticipated that a total of 1112 volunteers will be enrolled. Volunteers will participate in the study for ~6 months [a study of a candidate COVID-19 vaccine (COV001): NCT04324606].

### Prognosis and conclusion

COVID-19 has produced a pandemic of such a scale that has never ever been faced in a generation, and outcomes globally show considerable variability. The

overall mortality predicted is believed to be around 2%. The outcome depends on multiple variables and factors. The latest data on COVID-19-infected patients from ICNARC in the UK show that men were twice more likely to get severe COVID-19, and BAME (Black African Asian Minority ethnicity) patients had disproportionately higher mortality rates, in comparison to whites. Overall, survival after admission to critical care is 50%, but among patients receiving advanced respiratory support, 55% died, and those receiving advanced respiratory support plus RRT had a 75% mortality rate [6]. It is of note that despite growing familiarity of COVID-19 through increasing case numbers and novel therapies, the mortality rate in patients of all ages receiving advanced respiratory support has remained consistently at 50%, indicating the severity of the disease process.

Current research projects may reveal a novel and effective treatment for patients with COVID-19, but until then the only treatment with an evidence base remains to be supportive care. In a quest for definitive treatment for COVID-19, science is in the process of reinventing the efficacy of old drugs such as the CQ, macrolides, colchicine, Chinese herbals, anti-HIV drugs, and many others. Even the briefest of literature search reveals that journals have been inundated with COVID-19-related publications. Even more, what of the future? There is suggestion that SARS-CoV-2 will become an endemic organism, akin to influenza; should that become the case, we will continue to diagnose and treat cases of COVID-19 for years to come. Lastly, if the world population were to develop an immune response via symptomatic or asymptomatic infection at some point, then the COVID-19 era may become a forgotten tale for the next generation.

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