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REVIEW ARTICLE

Infectious Disease

Early management of critically ill patients with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is associated with a severe acute respiratory condition requiring respiratory support and mechanical ventilation. Based on the pathophysiology and clinical course of the disease, a therapeutic approach can be adapted. Three phases have been identified, in which different strategies are recommended in a stepwise invasiveness approach. In the second or acute phase, patients are frequently admitted to the ICU for severe pneumonia and hypoxemia with evidence of a proinflammatory and hypercoagulable state. This stage is an opportunity to intervene early in the disease. Medical strategies and mechanical ventilation should be individualized to improve outcomes.

KEYWORDS
acute respiratory distress syndrome, coronavirus, COVID-19, critical illness

1 | INTRODUCTION

In December 2019, the first cases of a serious respiratory disease caused by a novel virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in the city of Wuhan, China. The disease, named coronavirus disease 2019 (COVID-19), is associated with a severe acute respiratory condition requiring intensive care in ≈5% of confirmed cases.[1] Critical care is an integral component of the global response to this emerging disease because of its rapid spread throughout the world, unlike previous epidemics of acute respiratory infections (SARS, Middle East respiratory syndrome [MERS], influenza A H7N9, and influenza A H1N1). Despite a much higher case-fatality rate for SARS (9.6%) and MERS (34.4%), COVID-19 (2.3%) has led to more total deaths because of the large number of cases.[2] Also, COVID-19 seems to be more transmissible (reproductive number (R0) about 3.32).[3] Of those who deteriorate and require mechanical ventilation compared with H1N1 patients, the COVID-19 patients appear to have less severe disease.[4] The concern about the COVID-19 lies in the number of patients admitted, exceeding the limits to the emergency department and intensive care generating a crisis in management.[5,6]

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2 | CLINICAL CHARACTERISTICS OF CRITICALLY ILL PATIENTS

The criteria for admission to the ICU vary by hospital depending on the capacity and resources available. According to data derived from the experience in China, 6% of the cases are classified as critical and 14% as severe.[7] In reports from the Lombardy region of Italy, up to 16% of hospitalized patients have required admission to the ICU.[8]

Most patients admitted to the ICU are older and have comorbidities such as hypertension, cardiovascular disease, and chronic obstructive pulmonary disease (COPD).[9] The main indication for admission is acute hypoxemic respiratory failure (70%), followed by septic shock (15%).[10] The mortality rate of critically ill patients is high and varies from 20% to >90%.[11]

3 | PATHOGENESIS

According to published findings and to clinical observations of patients with COVID-19, hypotheses on the pathogenesis of SARS-CoV-2 infection have been proposed, but the exact pathogenesis is still controversial. Most experts agree that the illness can be divided in phases.[12–14]

Once the virus enters the body through the mucous membranes of the upper respiratory tract, it reaches the peripheral circulation through the lungs, causing a first viremic phase. In this phase, symptoms of fever and cough predominate. The virus has a predisposition for organs that express angiotensin-converting enzyme 2 (ACE2) receptors, such as the lungs, heart, kidney, and gastrointestinal tract.[12,14]

A second, acute phase or pneumonia phase occurs between days 7 and 14 after the onset of symptoms. Here, the lymphocyte count begins to decrease because of a reduction in B lymphocytes, which can hinder the production of antibodies. This is when a second attack is produced by the activation of an uncontrolled inflammatory response. Although the concept of the cytokine storm is still controversial because of lower levels of proinflammatory cytokines compared to other acute conditions,[15] there is no doubt that the inflammatory response plays an important role in the pathogenesis of COVID-19.[16] Endothelial damage is considerable and is characteristic at this stage of the disease; it may be the principal determinant of microvascular dysfunction, inflammation, and a procoagulant state.[17,18] This is supported by observations of significant increases in inflammatory markers such as C-reactive protein (CRP), ferritin, and proinflammatory cytokines.[19] In addition, an unusual hypercoagulable state is characterized by prolonged prothrombin time and elevated D-dimer.[12] Lodigiani et al reported an incidence of 27.6% of thrombotic complications in critically ill patients with COVID-19, and 2.2% of patients met the criteria for disseminated intravascular coagulation.[20]

In the third phase of the disease, if the patient's immune system is competent, in most cases the virus will be effectively suppressed, and the patient enters a recovery or convalescence phase. In certain patients, possibly more likely in those with comorbidities, the immune system cannot control the acute phase, perpetuating the inflammatory response.[12] These patients present with severe symptoms, entering a critical condition characterized by organ failures requiring mechanical ventilation and organ support, with an increased risk of mortality (reaching 50%).[1]

4 | THERAPEUTIC APPROACH

Based on the pathogenesis of the SARS-CoV-2 virus, we suggest that the treatment for COVID-19 should be based on the phase and time of symptom onset (Figure 1). The opportunity to intervene is between the first and second phases, when there is evidence of a predominantly proinflammatory and hypercoagulable state.[21]

4.1 | Viremic phase

At the time of symptom onset, antiviral therapy is the potential treatment. Currently, multiple treatments with potential activity against SARS-CoV-2 are being evaluated, and some of these treatments are available for other indications.

4.1.1 | Remdesivir

Remdesivir is a nucleotide analog with in vitro activity against SARS-CoV-2.[22] It was recently authorized in the United States for children and adults with severe illness. The suggested dose is 200 mg intravenously on the first day, followed by 100 mg intravenously every 24 hours for 10 days. The clinical evidence is limited owing to insufficient clinical trials. The preliminary results of a multinational randomized study of 1063 patients treated with remdesivir showed a faster recovery time (mean of 11 days vs 15 days for placebo, $P < 0.001$) and association with a trend toward lower mortality but without statistical significance (8% vs 11.6% on placebo, $P = 0.059$).[23]

4.1.2 | Hydroxychloroquine and chloroquine

These drugs inhibit SARS-CoV-2 in vitro, and it seems that hydroxychloroquine has greater antiviral activity.[24] The data published so far are limited, with important methodological problems, and do not suggest a clear benefit. In an observational study of ≈1400 patients with COVID-19, hydroxychloroquine was used in 811 patients and was associated with an increased risk of intubation or death (hazard ratio [HR] 2.37; 95% confidence interval [CI], 1.84–3.02).[25] A Brazilian multicenter, randomized, open-label, controlled trial of 667 hospitalized patients with mild to moderate COVID-19 and showed no improvement of clinical status neither the use of hydroxychloroquine alone nor

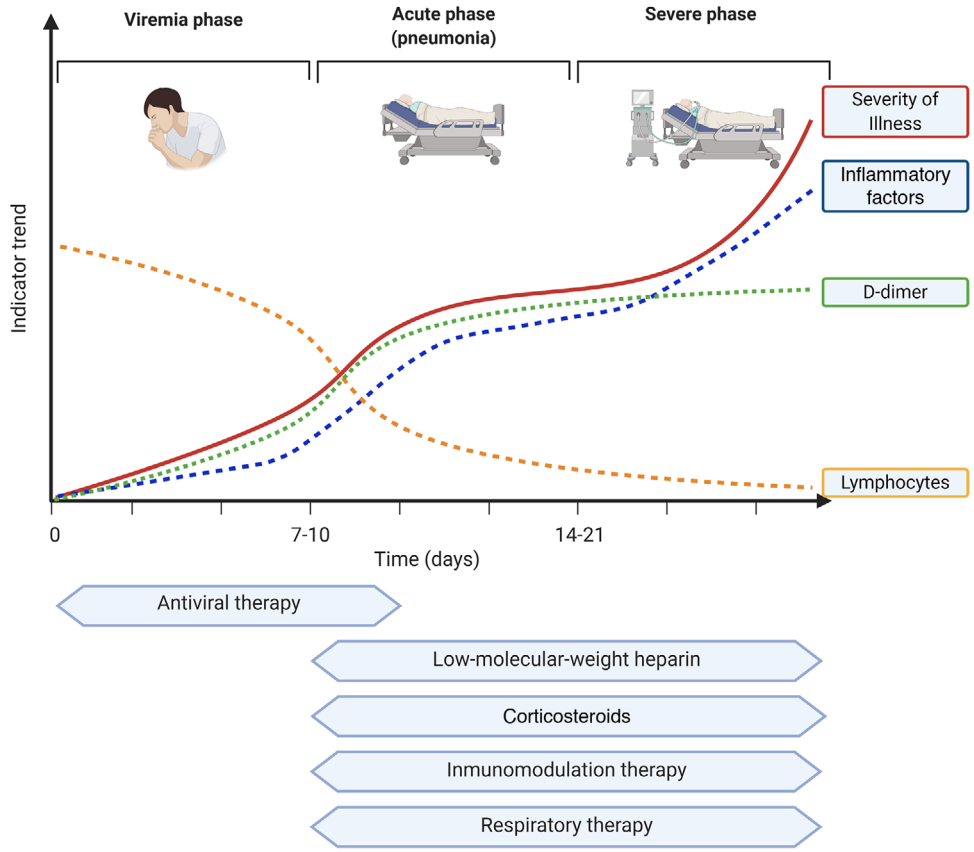

FIGURE 1 Graphic of a proposed early therapeutic approach to critically ill patients with COVID-19. Figure created with BioRender

in combination with azithromycin.[26] A recently published systematic review analyzed 4 randomized-controlled trials, 10 cohort studies, and 9 case series assessing the effects of hydroxychloroquine and chloroquine in COVID-19 and concluded that there is insufficient and often conflicting evidence on the benefits and harms of using hydroxychloroquine or chloroquine to treat COVID-19.[27]

4.1.3 | Lopinavir and ritonavir

These are enhanced protease inhibitors used for antiretroviral treatment against HIV and with demonstrated in vitro activity against MERS-CoV.[28] The results of a randomized study of 199 patients with COVID-19 showed no decrease in time to clinical improvement or mortality.[29]

4.1.4 | Other antivirals

Favipiravir is an RNA polymerase inhibitor used in Asia against influenza, but little evidence is currently available on its efficacy. Interferon beta has demonstrated evidence of in vitro activity against MERS-CoV.[30] A phase 2, multicenter, open-label, randomized trial of 127 patients showed that a triple viral combination lopinavir-ritonavir, ribavirin, and interferon beta was superior to lopinavir-ritonavir alone in the reduction of symptoms, shortened the duration of viral shedding and hospital stay, in mild to moderate COVID-19 when given within 7 days of symptom onset.[31]

4.2 | Acute phase

In this phase, the virus activates a proinflammatory response that is associated with disease severity.[32] Patients are frequently admitted to the ICU for severe pneumonia and hypoxemia in this phase. Modulating the immune response is proposed as a therapeutic approach.[33,34]

4.2.1 | Low-molecular-weight heparin

A hypercoagulable state has been described in critically ill patients with COVID-19,[20] and the rate of pulmonary microembolism is probably higher than that reported because of the difficulty of performing imaging studies in severely ill patients.[35] Tang et al described alterations in coagulation markers, especially D-dimer, that were associated with higher mortality in hospitalized patients.[36] In a prospective cohort study, Helms et al reported a rate of thrombotic complications of 16.7% in patients with COVID-19 and acute respiratory distress syndrome (ARDS), mainly due to pulmonary embolism.[37]

Low-molecular-weight heparin (LMWH) has been associated with decreased mortality in COVID-19 patients with a sepsis-induced coagulopathy score >4 and D-dimer >6 times the normal value.[38] In a recent observational study of 2773 patients hospitalized for COVID-19, the use of systemic anticoagulation was associated with lower hospital mortality, and the association with lower risk of death was stronger in patients on mechanical ventilation (adjusted HR 0.86 per day; 95% CI, 0.82–0.89; $P < 0.001$).[39]

This evidence suggests at least giving prophylactic doses of LMWH to patients admitted to the hospital who do not have contraindications. In patients with marked D-dimer elevation (>3 times the normal value), elevated inflammation markers (ferritin, CRP, interleukin-6 [IL-6]), and a critical condition (needing mechanical ventilation and in a shock state), full anticoagulation doses of 1 mg/kg LMWH every 12 hours should be considered.[40]

4.2.2 | Steroids

Steroids decrease systemic and pulmonary inflammation, but they also inhibit the immune response and, in the context of viral pneumonia, might delay viral elimination.[41] The most recent strong example is the 2019 systematic review and meta-analysis of observational studies of influenza pneumonia, where higher mortality was observed in patients receiving steroids (relative risk [RR] 1.75; 95% CI, 1.3–2.4; $P = 0.0002$), as was a longer ICU stay (mean difference 2.1; 95% CI, 1.2–3.1; $P < 0.0001$) and a higher rate of bacterial or fungal infections (RR 2.0; 95% CI, 1.0–3.8; $P = 0.04$).[42] Along with the little prospective evidence on the management of severe forms of COVID-19, the guidelines issued by the Surviving Sepsis Campaign panel included a weak recommendation for the use of steroids in patients with COVID-19 on mechanical ventilation and with ARDS.[43]

One of the main arguments against the use of steroids is their delay in eliminating the virus. In a retrospective study by Fang et al, low doses of steroid (mean dose of methylprednisolone per day of 38 mg) had no effect on the time to viral clearance.[44] This finding may be related to the time of administration of the steroid because most patients started it ≈7 days after the onset of symptoms. In another retrospective study, Wang et al reported a faster decrease in general symptoms, improvement in oxygenation, and earlier withdrawal of oxygen therapy in patients with severe pneumonia treated with methylprednisolone at a dose of 1–2 mg/kg/day for 5 to 7 days.[45] In a subgroup analysis in another retrospective study of patients with COVID-19 and ARDS, the use of methylprednisolone was associated with a reduced risk of death (HR 0.38; 95% CI, 0.20–0.72; $P = 0.003$).[46] A recently published preliminary report of a randomized controlled open-label trial comparing dexamethasone (at a dose of 6 mg once daily for up to 10 days) to usual care, and the primary outcome was 28-day mortality, the authors found that in the dexamethasone group the incidence of death was lower among patients receiving invasive mechanical ventilation (29.3% vs 41.4%; rate ratio, 0.64; 95% CI, 0.51–0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs 26.2%; rate ratio, 0.82; 95% CI, 0.72–0.94).[47] Another recently published randomized clinical trial that included 149 patients was terminated early because of no significant difference in the primary outcome between low-dose hydrocortisone versus placebo.[48]

The evidence of steroids in COVID-19 is growing and guidelines are reconsidering their use, including the World Health Organization.[33] Based on specific evidence, COVID-19 patients are recommended low steroid doses (dexamethasone 6 mg once daily or 1 mg/kg of methylprednisolone 1 daily) for short periods in specific situations. The benefit will be greater during the acute phase (7–10 days after symptom onset), when the adaptive immune phase begins and the inflammatory response increases. Patients with severe pneumonia, hypoxemia, intubation, and ARDS have the clearest clinical indication to administer steroids. Some researchers recommend using inflammatory markers as part of the indications and to titrate the steroid dose.[49,50]

4.2.3 | Immunomodulatory therapy

Immune response-modulating drugs have been considered as potential treatment strategies in COVID-19.

Tocilizumab is a monoclonal antibody that binds and blocks the IL-6 receptor.[51] It is commonly used in autoimmune diseases such as rheumatoid arthritis and juvenile idiopathic arthritis. In severe forms of COVID-19, the exaggerated immune response leads to severe respiratory failure; in these cases, inhibition of IL-6 could decrease the response in the acute phase. Evidence of the efficacy of tocilizumab is low because of poor study designs and lack of clinical trials, but clinical experience in China seems to support its use.[52] A case–control study in France suggests that tocilizumab can reduce the rate of ICU admissions and mortality in patients with severe SARS-CoV-2 pneumonia.[53] In small retrospective studies, improvement in biochemical parameters of inflammation and in oxygenation have been observed, with a reduction in ventilatory support.[54,55] In a prospective study in patients with severe COVID-19 and ARDS taking tocilizumab, respiratory parameters improved.[56] In the setting of rheumatoid arthritis, the standard recommended dose of tocilizumab is a first dose of 4–8 mg/kg (maximum dose of 800 mg).[51] The considerations for the use of tocilizumab are patients diagnosed with severe to critical COVID-19 and high blood IL-6.[52]

Baricitinib is a Janus kinase inhibitor that has anti-inflammatory effects by inhibiting the release of cytokines. It is approved for use in rheumatoid arthritis. In addition, baricitinib seems to have an antiviral effect by affinity inhibition of the AAK1 protein of AT2 cells in the lung, reducing the endocytosis of SARS-CoV-2.[57] For this dual anti-inflammatory and antiviral effect, baricitinib has been proposed as a treatment for COVID-19. Cantini et al published a pilot study of the safety and clinical impact of baricitinib added to ritonoavir-lopinavir in 12 patients with moderate COVID-19 and reported clinical and respiratory function improvement and a significant decrease in CRP in the first week of treatment without adverse effects, in comparison to standard therapy (ritonavir-lopinavir plus hydroxychloroquine).[58] The greatest concern with baricitinib is the increased risk of reactivation of latent infections such as tuberculosis and hepatitis B.

Other types of immunomodulatory therapy, such as intravenous immunoglobulin or recombinant interferon, have uncertain value because of the absence of scientific evidence of efficacy in COVID-19.[34]

4.2.4 | Management of acute respiratory failure

The most frequent complication of COVID-19 is acute hypoxemic respiratory failure. The mechanisms of hypoxemia are diverse and include pulmonary edema, vascular microthrombosis, and impaired ventilation/perfusion (V/Q). The recommended objective is to maintain oxygen saturation at 92%–96%.[43] It is possible that in most patients it is only necessary to use supplemental oxygen at low flows (nasal cannula, simple mask, or mask with reservoir). The challenge is patients with rapid and progressive deterioration in whom the choice of strategies such as a high-flow nasal cannula (HFNC), noninvasive mechanical ventilation (NIMV), and early intubation is controversial.

HFNC have been effective in hypoxemic respiratory failure, reducing the need for intubation and mortality compared to NIMV.[59] In patients with COVID-19, the HFNC failure rate was 41% to >60% among patients with PaO_2/FiO_2 <200 mmHg,[60] which is a higher rate than in patients with non-COVID hypoxemic respiratory failure (failure rate of 40% and 35% in patients with PaO_2/FiO_2 below 200 mmHg).[59] Some case series indicate a sustained improvement in oxygenation when combining HFNC and prone positioning in awake patients with COVID-19.[61] There is less evidence for NIMV in hypoxemic respiratory failure, and it is probably reserved for patients with a history of COPD, respiratory failure with hypercapnia, and/or cardiogenic pulmonary edema. There is a risk of aerosolization with either of the 2 devices; and, if used, health personnel should wear the optimal personal protective equipment, and negative pressure isolation rooms should be available at the hospital.[62]

4.2.5 | Early intubation

The decision to intubate a patient is difficult, even more so in extreme situations such as this pandemic, where resources such as ventilators are limited. An apparently frequent form of presentation called "silent hypoxemia" is described in patients with COVID-19, characterized by low arterial oxygen content in the absence of respiratory symptoms. This phenomenon is poorly documented in the literature and is based on physiological concepts described elegantly by Dr. Martin Tobin.[63] Intubation and initiation of mechanical ventilation should be considered part of the treatment and not as rescue therapies in patients with progressive deterioration. Delaying intubation until the late phases, when the inflammatory response is exacerbated with multiple-organ failure, probably explains the high mortality reported worldwide. When the respiratory drive is not reduced after the administration of supplemental oxygen or with non-invasive support, respiratory efforts in spontaneous ventilation increase the stress on the tissue and increase capillary leakage, causing patient self-induced lung injury.[64,65] As suggested in some observational studies when the patient is on mechanical ventilation, there are no changes in lung compliance over time and the patient also presents with higher respiratory drive that predicts relapse of respiratory failure with higher need for neuromuscular blockers. Thus, self-inflicted lung injury during spontaneous ventilation is one of the main determinants for deterioration.[66–68]

The indication for early intubation from the Chinese Society of Anesthesiology is respiratory failure (tachypnea ≥ 30 per minute, low oxygenation with PaO_2/FiO_2 <150 mmHg) that does not improve after 2 hours of therapy with high-flow oxygen or noninvasive ventilation.[69] Other expert authors recommend intubation in patients with high respiratory drive and at high risk of patient self-inflicted lung injury.[70] This allows the equipment to be prepared for the procedure, the medical staff to have the appropriate protective equipment, the most experienced operator to be recruited, bag-mask ventilation to be preferably avoided, a rapid induction sequence to be applied, and video laryngoscopy to be used. It also prevents progressive lung damage ("ventilator-induced lung injury [VILI] vortex") and unnecessary exposure of personnel to viral transmission.[71]

4.2.6 | Mechanical ventilation

COVID-19 pneumonia seems to have special characteristics that make it different from classic ARDS, as described by Gattinoni et al.[72] Using computed tomography (CT) imaging, it has been possible to characterize COVID-19 ARDS (CARDS) as a continuum on which the initial phase presents with low elastance (high compliance) with low lung weight and low oxygenation. In this "Type L" disease, lung damage is mainly interstitial, and on CT it appears as a ground-glass pattern. Patients may present with "silent hypoxemia" without presenting deterioration, but for various reasons they may progress to a characteristic type of ARDS. "Type H" CARDS, with high elastance (low compliance), appears on CT as consolidations, and the lung weight is high. These types of CARDS are the extremes of a continuous spectrum of lung disease caused by the virus. It is also important to consider endothelial damage, pulmonary vasculature dysregulation, and the hypercoagulability state that produces micro- and macrothrombosis, leading to alterations in ventilation-perfusion, which are also determinants of the mechanical ventilation strategies.[73]

The objectives of ventilation are to minimize VILI and to reduce and distribute the pulmonary and vascular stress. Lung protective ventilation is based on a low tidal volume (Vt) of 4–8 mL/kg of predicted weight and maintaining airway pressures at safe levels (peak pressure ≤ 35 cmH_2O, plateau pressure ≤ 30 cmH_2O).[74] Because of the changing compliance over the phases of CARDS, the best strategy for the programming, and titration of the positive end-expiratory pressure (PEEP) is probably to seek the best compliance with the lowest PEEP possible.[75] Titrating the PEEP by oxygenation as recommended in classic ARDS ($PEEP/FiO_2$ table) is probably a bad strategy in the initial phases of CARDS, because the main condition is V/Q alterations due to increased dead space, and, despite improvement in oxygenation after

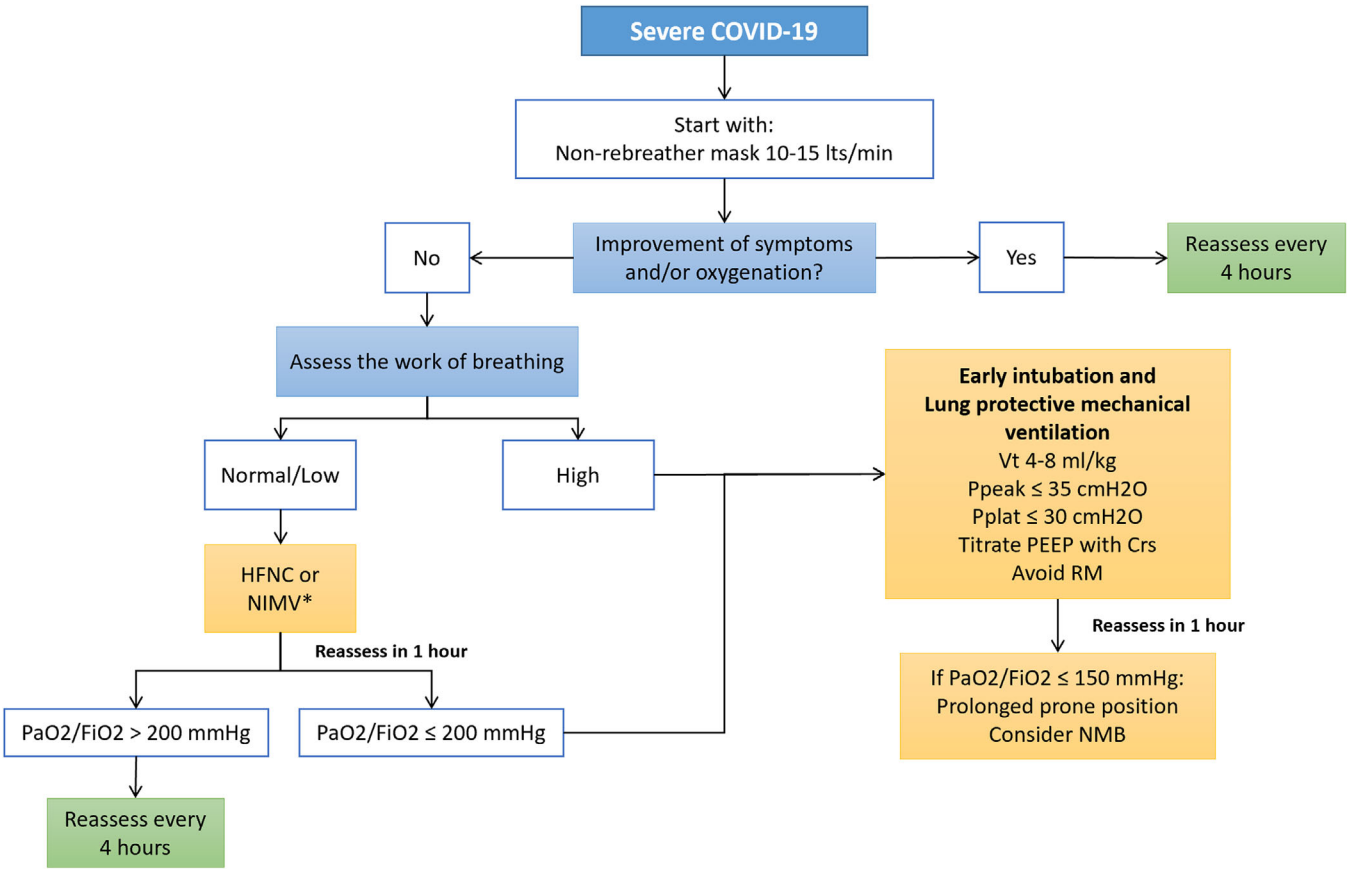

FIGURE 2 COVID-19, coronavirus disease 2019; HFNC, high-flow nasal cannula; NIMV, noninvasive mechanical ventilation; NMB, neuromuscular blockers; PEEP, positive end-expiratory pressure; RM, recruitment maneuvers; Vt, tidal volume

the increase in PEEP, the dead space will increase in lockstep and will lead to lung overdistension with an increased risk of stress and strain injury to the healthy lung.[76]

It is important to avoid alveolar recruitment strategies since they have been associated with increased mortality in patients with ARDS, and low recruitment potential has been observed in CARDS.[77,78] Using the prone position in $PaO_2/FiO_2 \leq 150$ mmHg for at least 16 hours redistributes pulmonary blood flow and is the safest form of pulmonary recruitment to open areas of collapse in dependent lung regions.[79] The use of continuous prone positioning for >24 hours is safe and is probably more beneficial in these patients for reducing procedures needed because of changes in position.[80]

Mechanical ventilation in CARDS is complex, and owing to the heterogeneity of the pulmonary pathology, pulmonary protection strategies should be individualized to improve outcomes (Figure 2).

5 | CONCLUSIONS

With the rapid increase in the number of COVID-19 cases, health services are being overburdened to provide adequate care.[5,6] This has had an important impact on the proportion of deaths among critically ill patients. Therefore, each ICU must adapt and create care protocols for critically ill patients with COVID-19 according to its own needs and resources.[81]

There is a rapidly expanding knowledge regarding COVID-19 treatment. To date, the current clinical evidence supports the use of remdesivir as an antiviral; it should be started in the viremic phase, preferred for patients hospitalized and receiving oxygen to prevent further deterioration. In severe and critical cases, it is recommended to start low corticosteroid dose and LMWH as early as possible to limit the acute phase. Other immunomodulatory agents like tocilizumab or baricitinib have limited evidence to recommended systematic use when managing respiratory failure is essential to monitor hypoxemia and the patient's respiratory effort and not delaying intubation. The cornerstone of care remains supportive and high-quality intensive care.

It is important to keep in mind that the mechanisms of SARS-CoV-2 viral injury are time dependent. Therefore, early and systematic interventions could be the key to decreasing the proportion of patients with severe COVID-19 who need mechanical ventilation and individualizing mechanical ventilation strategies in critically ill patients could decrease mortality.

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