REVIEW ARTICLE

Current treatment challenges in the COVID-19 pandemic

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ABSTRACT

Infection with SARS-CoV-2, responsible for COVID-19, has spread all over the world since the beginning of 2020. Healthcare providers and researchers have been overwhelmed not only by the rapid diffusion of the disease resulting in a pandemic with more than 4 million cases of death, but also by the lack of therapeutic options. After more than 1 year, the knowledge on COVID-19 has increased thanks to the enormous effort of the scientific community. To date, some algorithms of management have been adopted. While asymptomatic or mildly symptomatic patients should receive only a symptom-based treatment and clinical monitoring when necessary, inpatients could be candidates for antiviral treatment due to fully symptomatic disease. Corticosteroid treatment should be limited to patients with severe disease, particularly those with respiratory failure or acute respiratory distress syndrome. Since the main clinical features of COVID-19 are hypoxemia and dyspnea, oxygen therapy remains the cornerstone of managing more severe cases. In this context, the first-line approach should be represented by low-flow oxygen delivery via a nasal cannula or, more frequently, via a face mask with a known fraction of inspired oxygen. When low-flow oxygen fails to significantly improve oxygen saturation, oxygen therapy using a high-flow nasal cannula is recommended. The current challenges in the treatment of COVID-19 include the need to define the role of convalescent plasma and monoclonal antibodies as well as to identify the optimal target and time for anticoagulation. In this review, we highlight the main aspects of these challenges in light of recent updates.

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Introduction SARS-CoV-2 was first detected at the end of 2019 in Wuhan, the capital city of Hubei Province in China. Since then, the infection has spread all over the world, leading to a pandemic.[1,2] The disease caused by SARS-CoV-2, namely, COVID-19, has so far resulted in more than 4 million deaths. With very limited scientific and clinical knowledge about the disease, national health systems worldwide have been put under enormous pressure. As a result, healthcare providers have been overwhelmed by a multitude of patients with COVID-19 of varying severity, without access to effective treatment.[3,4]

In the absence of established therapeutic regimens, early risk stratification has been the first approach for the management of COVID-19, with the aim to facilitate patient allocation according to disease severity and available resources.[5-7] Subsequently, with the improvement of the clinical and pathophysiological knowledge on COVID-19, research quickly focused on therapeutic strategies. With more and more robust data available, either supporting or discouraging the use of what was an empiric treatment, scientific societies could come up with new recommendations[8] and updates have been subsequently released.[9]

Nevertheless, although different treatment strategies have been proposed, the optimal care of patients with COVID-19 remains controversial.[10]

In this short review, we provide an overview of the most recent evidence on the pharmacological management of patients with COVID-19, with a focus on associated pneumonia. We also describe the current challenges in the treatment of COVID-19. Finally, the pros and cons of the reported therapeutic options are discussed.

Corticosteroids The rationale for the administration of corticosteroids in patients with COVID-19 is based on the pathophysiological features of the disease. As in other viral pneumonias (eg, severe acute respiratory syndrome and avian influenza), severe inflammatory response during SARS-CoV-2 infection may play a pivotal role in the development of organ failure. As a matter of fact, severe COVID-19 is characterized by an acute pneumonic reaction with diffuse alveolar damage, interstitial infiltrates, and microthrombi.[11-13] Thus, the aim of steroid treatment in this setting is to reduce the burden of the inflammatory response, limiting "self-harm" in the body.[9] Moreover, these drugs might exert a positive effect on hemodynamic instability, as suggested in the case of septic shock.[14]

Nevertheless, over the first months of the pandemic, corticosteroid use was discouraged, or at least not recommended, for the treatment of COVID-19 patients. This was mostly due to the lack of reliable data, as explained in the first version of the 2020 Surviving Sepsis Campaign (SSC) guidelines.[8] At the time of the publication, only one small non–peer-reviewed study was available, showing that the use of methylprednisolone could reduce oxygen therapy duration and improve radiological findings.[15] Thus, the SSC panel preferred to adopt a cautious approach and did not recommend the routine use of corticosteroids in COVID-19 patients with respiratory failure but without acute respiratory distress syndrome (ARDS).[8]

Since then, several randomized trials have been published, which investigated the effects of different steroids in patients with COVID-19. In the RECOVERY trial (Randomised Evaluation of COVID-19 Therapy), 6425 patients were enrolled and randomly assigned to receive dexamethasone at a dose of 6 mg once daily for 10 days (n = 2104) or to receive usual care alone (n = 4321).[16] In the dexamethasone group, 28-day mortality (primary outcome) was significantly lower than in the control group (22.9% vs 25.7%, respectively; age-adjusted rate ratio [RR], 0.83; 95% confidence interval [CI], 0.75–0.93]). Moreover, in patients under mechanical ventilation at the time of enrollment, dexamethasone administration was associated with lower mortality (29.3% and 41.4% for dexamethasone and control groups, respectively; RR, 0.64; 95% CI, 0.51–0.81]). Similar results were reported for patients receiving oxygen support without mechanical ventilation. The dexamethasone group showed a significantly lower 28-day mortality rate compared with controls (23.3% vs 26.2%, respectively; RR, 0.82; 95% CI, 0.72–0.94). However, a subgroup analysis of patients without the need for oxygen support at the time of randomization did not demonstrate a significant difference in primary outcome between dexamethasone and control groups (17.8% vs 14.0%, respectively; RR, 1.19; 95% CI, 0.92–1.55).[16] In a subsequent meta-analysis evaluating 1703 critically ill patients with COVID-19, the 28-day mortality rate was lower in patients receiving corticosteroids than in those receiving either standard of care or placebo (32% vs 40%, respectively; summary odds ratio [OR], 0.66; 95% CI, 0.53–0.82; $P < 0.001$).[17]

It should be noted that most studies performed in this setting did not focus on the adverse effects of corticosteroid administration. However, due to the severity of COVID-19, the short-term mortality benefits outweighed the risks of adverse events. Therefore, according to the most recent literature, corticosteroid use should be limited to more severe cases (particularly patients requiring oxygen support), while it is not recommended in patients without the need for oxygen therapy.[9]

Antivirals Several antivirals, such as lopinavir / ritonavir and darunavir, have been evaluated for the treatment of COVID-19, but the results of clinical trials failed to demonstrate their efficacy.[18,19] On the other hand, remdesivir showed some encouraging benefits in the treatment of COVID-19. Remdesivir is a nucleotide analogue that inhibits viral RNA–dependent RNA polymerase of coronaviruses, including SARS-CoV-1 and Middle East respiratory syndrome coronavirus.[20] The results of a meta-analysis including almost 7000 hospitalized patients with COVID-19 showed that remdesivir did not reduce the need for mechanical ventilation or mortality when compared with standard of care or placebo. These results were influenced by the heterogeneity of studies including patients with COVID-19 irrespective of disease severity. Nevertheless, remdesivir reduced the time to recovery from severe COVID-19,[21] and this beneficial effect was later confirmed by the SARSTer study.[22] The Solidarity trial failed to demonstrate a significant mortality reduction among patients treated with remdesivir vs standard of care. However, lower mortality was observed among patients who did not require mechanical ventilation at baseline.[23] In the ACTT-1 (Adaptive COVID-19 Treatment Trial), patients treated with remdesivir were discharged from the hospital or weaned off oxygen support earlier than those treated with placebo. Moreover, remdesivir reduced the time to recovery among patients who required low-flow oxygen at baseline and who received treatment within 10 days from symptom onset. Yet, even this trial failed to demonstrate a reduction in mortality, although the group of remdesivir-treated patients who

required low-flow oxygen showed significantly lower mortality.[20] Modest results were obtained with the use of remdesivir among inpatients with nonsevere COVID-19.[24] Finally, when administered with baricitinib, a Janus kinase inhibitor used for the treatment of rheumatoid arthritis, remdesivir appeared to reduce the recovery time, particularly among patients receiving high-flow oxygen or noninvasive ventilation.[25]

Anti–interleukin-6 The rationale for using anti–interleukin-6 is the inhibition of the inflammatory pathway sustained by high levels of inflammatory markers (such as D-dimer and ferritin) as well as proinflammatory cytokines (including IL-6) associated with severe COVID-19.[26] Among IL-6 inhibitors, tocilizumab has been most widely studied in patients with COVID-19. A meta-analysis of 8 randomized trials including patients hospitalized for COVID-19 demonstrated lower all-cause mortality rates in tocilizumab-treated individuals compared with those who received placebo or standard of care.[27] Major evidence comes from an open-label trial that enrolled patients with suspected or confirmed COVID-19 with hypoxia and C-reactive protein levels higher than 75 mg/l. In this cohort, tocilizumab reduced the progression to mechanical ventilation or death. Moreover, better outcomes were reported among patients who received concomitant corticosteroid treatment.[16] However, these results are in contrast to the findings of other trials that failed to demonstrate benefits for tocilizumab in terms of mortality and clinical symptoms.[28,29] Therefore, expert recommendations and international guidelines on tocilizumab vary greatly. The National Institute of Health recommends adding tocilizumab to dexamethasone in hospitalized patients with COVID-19 requiring high-flow oxygen support or noninvasive ventilation and showing evidence of clinical progression or elevated levels of inflammatory markers.[30] A similar approach using a combination of tocilizumab and corticosteroids has been suggested by the Infectious Diseases Society of America for the treatment of inpatients with COVID-19 presenting with progressive severe or critical disease and systemic inflammation.[31]

Convalescent plasma and monoclonal antibodies The use of convalescent plasma from patients who recovered from COVID-19 has been proposed to provide passive antibody-based immunization, particularly in patients with deficient antibody production (eg, due to treatment with anti-CD20 monoclonal antibodies).[32] However, despite this promising physiopathological insights, the available literature does not support the use of convalescent plasma in patients with severe disease. In fact, randomized trials including inpatients did not demonstrate a clear benefit when compared with placebo or standard of care, either in terms of the length of hospital stay or in ventilation use.[33] On the other hand, some observational studies reported that the administration of convalescent plasma with higher antibody titers in the early stages of COVID-19 was associated with a lower 30-day mortality rate.[34]

More recently, monoclonal antibodies have been developed with the aim to neutralize the SARS-CoV-2 spike protein, thus preventing viral binding to host cells.[35] Casirivimab and imdevimab are recombinant human immunoglobulin G1 (IgG1) monoclonal antibodies approved by the Food and Drug Administration for the treatment of adult and pediatric patients with mild-to-moderate COVID-19, as well as individuals at high risk of progression to severe COVID-19. Limited benefits have been reported for patients with severe COVID-19.[36] Although the combination of antibodies led to a reduction in viral load, particularly in patients who have not yet mounted an immune response, further research is needed to confirm clinical benefits.[37] Another monoclonal antibody studied is bamlanivimab, a neutralizing IgG1 antibody directed against the SARS-CoV-2 spike protein. A randomized clinical trial demonstrated a direct antiviral activity of bamlanivimab, with a reduction in viral load and COVID-19-related hospitalization.[38]

Other therapies Several other agents have been also evaluated in the setting of COVID-19. Baricitinib (a Janus kinase inhibitor) in combination with remdesivir has been approved for the treatment of COVID-19 patients who require oxygen or ventilatory support.[39] More recent evidence has demonstrated its effectiveness independently of concomitant remdesivir administration.[40] Emerging data show that baricitinib may reduce mortality in selected patients with severe disease who receive concomitant dexamethasone treatment. These findings support the results from randomized trials showing that baricitinib plus remdesivir reduced the time to recovery, even in patients who were on high-flow oxygen or noninvasive ventilation at baseline.[25,40,41]

Interferons act by modulating the immune response, and interferon beta was reported to inhibit SARS-CoV-2 replication in vitro.[42] However, so far, no clinical data have indicated benefits of using interferon beta for the treatment of severe COVID-19. Interferon therapy had no significant effects on 28-day mortality when compared with standard of care.[23]

Observational studies reported the use of IL-1 inhibitors (eg, anakinra) to be associated with lower COVID-19 mortality.[43,44] However, these beneficial results were not confirmed by a randomized trial in which anakinra was used in combination with usual care vs usual care alone in hospitalized patients with mild-to-moderate COVID-19.[45]

Anticoagulants and antithrombotics The characteristic feature of COVID-19 is a prothrombotic state with massive activation of blood coagulation, reflected by high D-dimer concentrations,

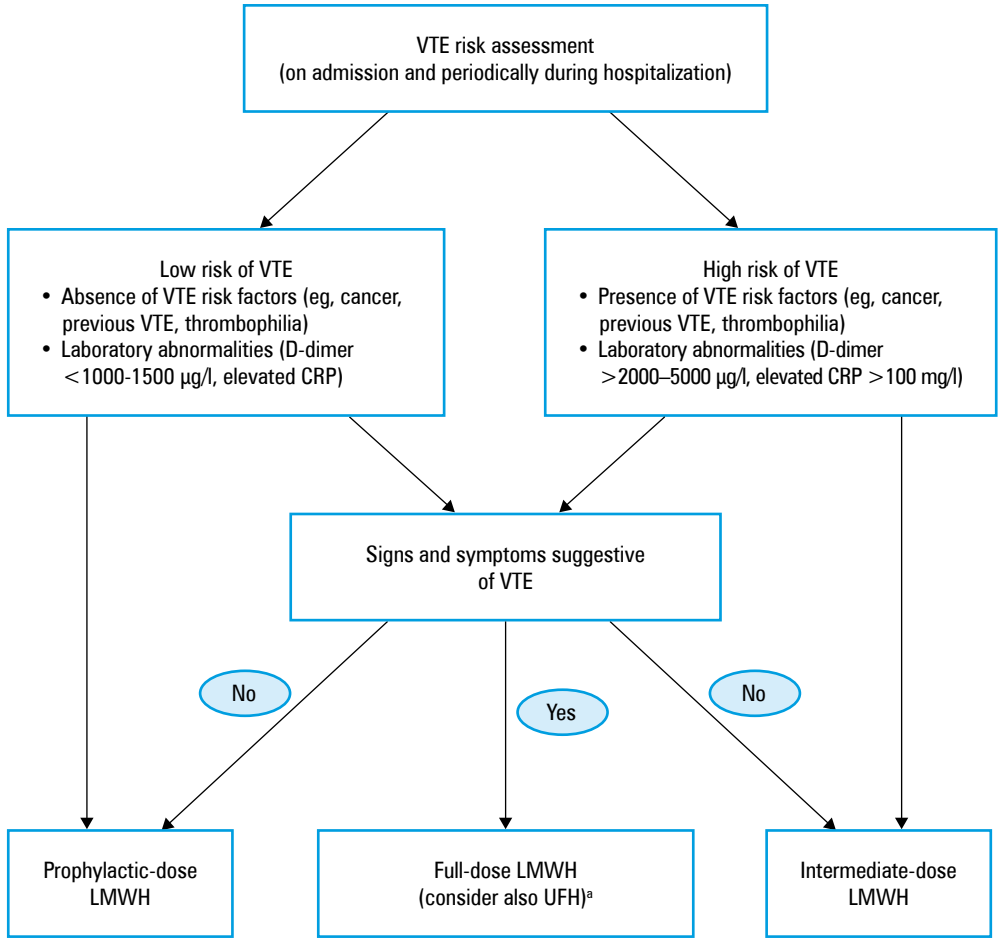

FIGURE 1 Proposed algorithm of pharmacological thromboprophylaxis in hospitalized patients with COVID-19
a Given the recent evidence from randomized trials published in August 2021,[65,66] a therapeutic dose of LMWH could be considered in all not critically ill hospitalized COVID-19 patients, especially in those with high D-dimer levels
Abbreviations: CRP, C-reactive protein; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism

platelet activation, formation of neutrophil extracellular traps, and generation of antiphospholipid antibodies, all leading to venous thromboembolism.[46] Numerous reports published since the beginning of the pandemic have documented a high rate of venous thromboembolism (VTE), ranging from 17% to 69%.[47-52] Currently, the mean rate of VTE in inpatients with COVID-19 is estimated at 9% (95% CI, 5%–13%) and 21% in the intensive care unit (ICU).[53] The most common manifestation of VTE is pulmonary embolism, with an estimated rate of 8% (vs 3% for deep vein thrombosis).[53-56] The risk of VTE during hospitalization of COVID-19 patients was reported to increase at D-dimer concentrations higher than 2500 ng/ml (OR, 6.79; 95% CI, 2.39–19.30), platelet count higher than 450 000/µl (OR, 3.56; 95% CI, 1.27–9.97), and C-reactive protein levels higher than 100 mg/l (OR, 2.71; 95% CI, 1.26–5.86).[57]

Thromboprophylaxis with heparins, preferably low-molecular-weight heparin (LMWH), was recommended in all hospitalized patients with COVID-19 unless there are absolute contraindications.[58-60] Despite the lack of high-quality evidence, several experts suggested that higher heparin doses than those used for standard prophylaxis should be administered in severe COVID-19, while an intermediate- or therapeutic-dose strategy could be considered in COVID-19 patients with obesity, prothrombotic conditions, or high D-dimer concentrations with a rapid increase during hospitalization (FIGURE 1).[59] However, it has been shown that dose escalation of heparin could result in a significantly higher rate of clinically relevant hemorrhagic episodes without reducing the rates of thromboembolism or mortality among hospitalized patients with COVID-19.[47] Recently, the INSPIRATION trial (Intermediate-dose vs Standard Prophylactic Anticoagulation and Statin vs Placebo in ICU Patients With COVID-19) showed that the use of intermediate vs standard prophylactic dose of LMWH is not associated with a reduced risk of VTE or arterial thrombosis, requirement for extracorporeal membrane oxygenation, or mortality.[61] The same was observed for major bleeding and thrombocytopenia.[61] Therefore, similar to thromboprophylaxis in hospitalized patients prior to the COVID-19 pandemic, this strategy seems to reduce the risk of VTE but, most likely, not the risk of death.

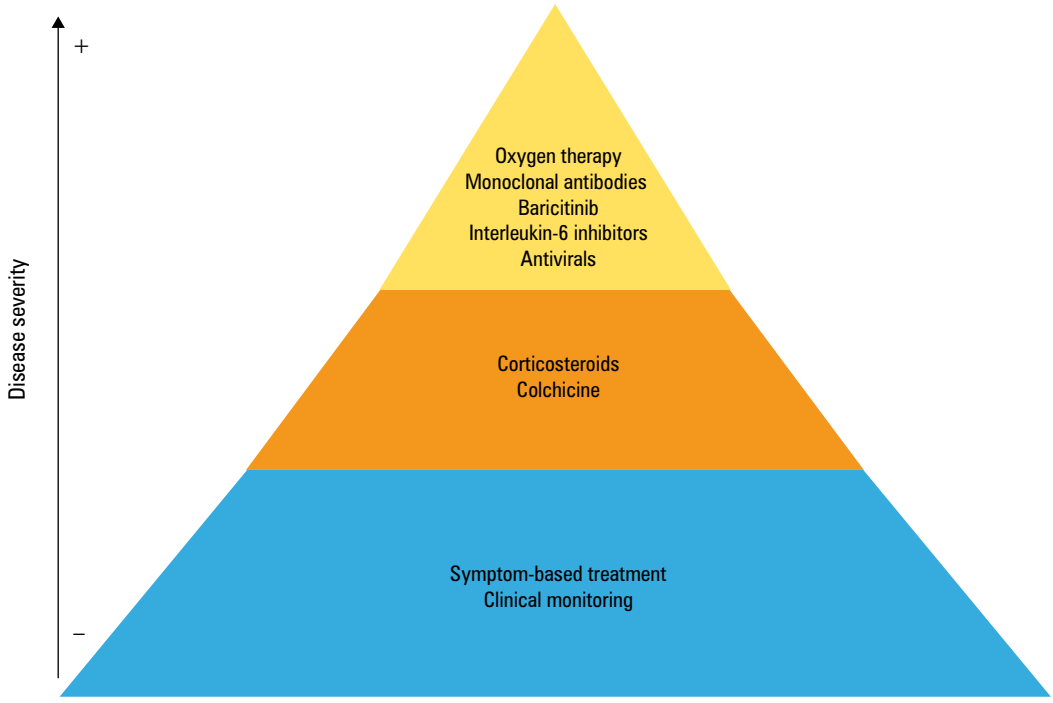

FIGURE 2 Simplified therapeutic strategies in patients with COVID-19

Major bleeding occurs in about 5% of patients receiving thromboprophylaxis, and the balance between thrombosis and bleeding should be regularly assessed, especially if higher LMWH doses are administered in COVID-19 patients. The rate of major or clinically relevant nonmajor bleeding was reported at 24 per 100 person-months compared with 6.9 per 100 person-months in patients receiving standard prophylactic-intensity anticoagulation.[62] In critically ill patients with COVID-19, two-thirds of major bleeding events were observed in those receiving therapeutic anticoagulation.[47] Despite platelet activation in COVID-19 patients, low-dose aspirin is not recommended for thromboprophylaxis due to elevated bleeding risk unless antiplatelet agents are required for other indications.

Patients who experienced VTE during hospitalization for COVID-19 should be treated with LMWH. Oral anticoagulants could be used during hospitalization in those patients with less severe COVID-19 given the absence of potent drug-drug interactions. Duration of anticoagulation after discharge should be individualized based on the assessment of VTE recurrence risk, but the minimal duration is 3 to 6 months. In COVID-19 patients who do not require hospitalization, thromboprophylaxis should not be routinely prescribed, except those at high risk of VTE (eg, patients with previous VTE, those receiving chemotherapy, and those with known thrombophilia). Thromboprophylaxis should not be routinely prescribed also in patients who are discharged home, as it offers benefit only in selected cases. However, these patients should undergo routine VTE risk assessment. The IMPROVE VTE score has been proposed for the assessment of VTE risk after discharge. Current studies indicate that the risk of VTE in COVID-19 patients at discharge is similar to or slightly higher than that in the corresponding period of 2019 in patients discharged after hospitalization for acute diseases. Roberts et al[63] reported that the OR of thrombosis within 42 days from discharge in patients with COVID-19 was 1.6 (95% CI, 0.6–3.1). In a study by Engelen et al,[64] screening for VTE 6 weeks after COVID-19 hospitalization revealed very low incidence of VTE (<1%) in a group of 146 patients, of whom only 28% received thromboprophylaxis despite the fact that one-third still had elevated D-dimer levels.[64] Postdischarge pharmacological prophylaxis should not be longer than 2 to 6 weeks.

The collaborative international platform trials ATTACC (Antithrombotic Therapy to Ameliorate Complications of COVID-19), REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia), and ACTIV-4 (Anti-thrombotics for Adults Hospitalized With COVID-19) compared the safety and efficacy of therapeutic- vs standard-dose thromboprophylaxis in randomly assigned hospitalized patients with COVID-19. In August 2021, two studies were published which suggested that therapeutic daily heparin doses could be beneficial in noncritically ill patients but not in critically ill cases.[65,66] The optimal thromboprophylaxis protocol remains to be established.[67]

Oxygen therapy Since the main clinical features of SARS-CoV-2 infection are hypoxemia and dyspnea,[68] oxygen therapy is the cornerstone of the management of severe COVID-19 cases (FIGURE 2).[69] From a clinical perspective, as

the onset of dyspnea can be relatively late, during the first days of the disease, the patient can present with reduced oxygen saturation (SpO_2) by pulse oximetry, without shortness of breath despite progression of the infection.[70] Different studies estimated that the lag between symptom onset and the development of dyspnea is 7 days on average.[71,72] However, after that, the progression to ARDS is much faster, with a median of 2.5 days.[70-72]

Typically, the respiratory pattern of COVID-19 is characterized by hypoxemic respiratory failure, with different degrees of severity, up to an ARDS pattern. In this regard, the severity of COVID-19 has been classified into 2 major categories:[9] severe and critical. Severe disease is defined as COVID-19 with clinical signs of pneumonia (fever, cough, dyspnea, tachypnea) and one of the following: respiratory rate higher than 30 breaths/min, severe respiratory distress, or SpO_2 lower than 90% on room air. Critical disease refers to COVID-19 with the presence of ARDS or respiratory failure requiring ventilation, sepsis, or septic shock.

As mentioned above, ARDS is a typical complication of COVID-19 progression, with numerous features overlapping those of ARDS from other causes, such as a reduction in lung compliance.[73] However, compared with ARDS from other causes, the risk of barotrauma seems slightly increased.[74]

Peripheral oxygen saturation Peripheral oxygen saturation monitoring is crucial in the management of COVID-19 patients. At the onset of the disease, plethysmography allows clinicians to noninvasively detect deterioration in respiratory exchange, even in patients with mild symptoms.[75,76] In fact, the first update of the SSC guidelines on the management of patients with COVID-19 suggested starting supplemental oxygen administration when SpO_2 is lower than 92% and recommended supplemental oxygen administration when SpO_2 is lower than 90%. The recommended target is SpO_2 not higher than 96%.[9]

Oxygen administration The first-line therapy in patients with acute respiratory failure is low-flow oxygen administration via a nasal cannula or, more frequently, via a face mask with a known fraction of inspired oxygen (FiO_2).[69] The Novara-COVID Score, one of the earliest validated prognostic scores in the setting of COVID-19, has been designed to evaluate the patient's response to oxygen therapy administered at a FiO_2 of 50%.[5,6]

When low-flow oxygen fails to significantly improve SpO_2 and gas exchanges, oxygen therapy using a high-flow nasal cannula is recommended.[9] This device allows the administration of high flows of humidified oxygen (up to 70 l/min), with a FiO_2 of up to 100%.[77-79] Recent studies on COVID-19 patients have yielded interesting results. Wendel Garcia et al[80] investigated 351 patients with COVID-19 and reported that an early trial of high-flow nasal cannula might be the most balanced initial respiratory support, as it was associated with a reduction in the intubation rate compared with low-flow oxygen therapy, without impact on ICU mortality. However, it is important to note that the optimal management of respiratory failure in patients with COVID-19 should follow a structured protocol in order to anticipate possible complications[69] and the need for mechanical ventilation.[81]

Another therapeutic option in patients with respiratory failure is oxygen delivery using noninvasive positive pressure ventilation (NIPPV). By recruiting collapsed alveoli, this strategy improves gas exchange and hemodynamic performance.[77] Moreover, it reduces the patient's respiratory effort. In patients with COVID-19, NIPPV using a full-face mask (or even a dedicated helmet) rather than a nasal mask is suggested to reduce the risk of particle dispersion.[69] Also, the use of continuous positive airway pressure is suggested for the initial management of COVID-19 patients requiring oxygen support, using the lowest effective pressures (eg, 5–10 cmH_2O).[82] However, the current guidelines provide a weak recommendation on the use of NIPPV in patients with COVID-19 when high-flow nasal cannulas are not available, in the absence of urgent need for endotracheal intubation. The SSC panel recommends close monitoring to avoid delays in endotracheal intubation, similar as in the management of patients with ARDS.[9] In this context, Wendel Garcia et al[80] showed that NIPPV failure and the subsequent need for invasive mechanical ventilation were associated with increased ICU length of stay and mortality. Thus, when a trial of NIPPV is adopted, close monitoring of the respiratory status and early intubation in case of worsening are recommended.[9]

Awake prone positioning Prone positioning is one of the therapeutic strategies currently used in patients with ARDS, as this technique improves the hemodynamic performance of both ventricles. Moreover, prone positioning of a patient ameliorates respiratory gas exchange by reducing ventilation-perfusion mismatches.[83] Therefore, the method has been proposed in patients with COVID-19 with the aim to reproduce these beneficial effects and thus avoid the need for intubation. Some interesting findings were reported.[84,85] In a study by Coppo et al,[86] prone positioning was associated with a significant improvement in the ratio of arterial oxygen partial pressure to FiO_2 compared with the supine position. However, more research is needed to confirm these results. The use of prone positioning is currently not recommended by the SSC guideline update in awake nonintubated patients with COVID-19.[9]

Conclusions The spectrum of therapies for COVID-19 has been evolving rapidly. Currently, a severity-based approach should be considered. While asymptomatic or mildly symptomatic patients should receive only a symptom-based treatment and clinical monitoring, hospitalized

patients with fully symptomatic disease could be candidates for antiviral treatment. Corticosteroid administration should be reserved for more severe cases, particularly those with respiratory failure or ARDS. Since the main clinical features of COVID-19 are hypoxemia and dyspnea, oxygen therapy remains the mainstay of treatment in patients with severe disease.

Current challenges in the treatment of COVID-19 include the need to determine the effectiveness of convalescent plasma and monoclonal antibodies as well as to identify the optimal target and timing of anticoagulation.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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