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Awaiting a cure for COVID-19: therapeutic approach in patients with different severity levels of COVID-19

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SUMMARY

COVID-19 is an unpredictable infectious disease caused by SARS-CoV-2. The development of effective anti-COVID-19 vaccines has enormously minimized the risk of severe illness in most immunocompetent patients. However, unvaccinated patients and non-responders to the COVID-19 vaccine are at risk of short- and long-term consequences. In these patients, the outcome of COVID-19 relies on an interplay of multiple factors including age, immunocompetence, comorbidities, inflammatory response triggered by the virus as well as the virulence of SARS-CoV-2 variants. Generally, COVID-19 is asymptomatic or mildly symptomatic in young people, but it may manifest with respiratory insufficiency requiring mechanical ventilation in certain susceptible groups of patients. Furthermore, severe SARS-CoV-2 infection induces multiorgan failure syndrome by affecting liver, kidney heart and nervous system.

Since December 2019, multiple drugs have been tested to treat COVID-19, but only a few have been proven effective to mitigate the course of the disease that continues to cause death and comorbidity worldwide. Current treatment of COVID-19 patients is essentially based on the administration of supportive oxygen therapy and the use of specific drugs such as steroids, anticoagulants, antivirals, anti-SARS-CoV-2 antibodies and immunomodulators. However, the rapid spread of new variants and the release of new data coming from the numerous ongoing clinical trials have created the conditions for maintaining a continuous updating of the therapeutic management of COVID-19 patients. Furthermore, we believe that a well-established therapeutic strategy along with the continuum of medical care for all patients with COVID-19 is pivotal to improving disease outcomes and restoring healthcare care fragmentation caused by the pandemic. This narrative review, focusing on the therapeutic management of COVID-19 patients, aimed to provide an overview of current therapies for (i) asymptomatic or mildly/moderate symptomatic patients, (ii) hospitalized patients requiring low-flow oxygen, (iii) high-flow oxygen and (iv) mechanical ventilation.

Keywords: COVID-19, SARS-CoV-2, therapy, ventilation, steroid, anticoagulant, tocilizumab, convalescent-plasma, monoclonal antibody, antiviral.

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INTRODUCTION

COVID-19 is a potentially deadly disease that has affected more than 400 million people worldwide and caused more than 5.5 million deaths [1]. The virus is characterized by a primary

tropism for the respiratory system, but it can lead to sepsis, prothrombotic state, kidney injury, liver injury and neuronal disorders in the most severe forms of the disease [2-8]. Age and burden of comorbidities (i.e., hypertension, obesity, metabolic disease, cardiovascular disease, chronic lung disease, renal disease) are the most relevant determinants for poor outcomes [9-11]. Indeed, risk factors of severe disease rise steadily with age, with more than 80% of deaths occurring in adults older than age 65 years [12]. The prognosis of COVID-19 is also greatly influenced by health-care access, COVID-19 vaccination status as well as the virulence of the virus [13-15]. However, despite the unprecedented developmental activity in diagnostics and vaccines, there is still a large unmet medical need to improve clinical outcomes of unvaccinated patients and vaccine non-responders.

The evolving data on treating COVID-19 patients and the different spectrum of disease severity hampers the process of identifying a unified therapeutic strategy for the treatment of COVID-19 [16, 17]. In addition, in a setting of healthcare crisis, there is the perception of fragmentation of care, especially among physicians not directly involved in the management of these patients. In light of this background, we propose an overview of the evidence-based therapeutic strategy aimed to provide a continuum of care ranging from delivery of primary care for asymptomatic infection to the delivery of advanced care for severe acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. This narrative review provides up-to-date insights into the management of

1) asymptomatic or mildly/moderate symptomatic patients,

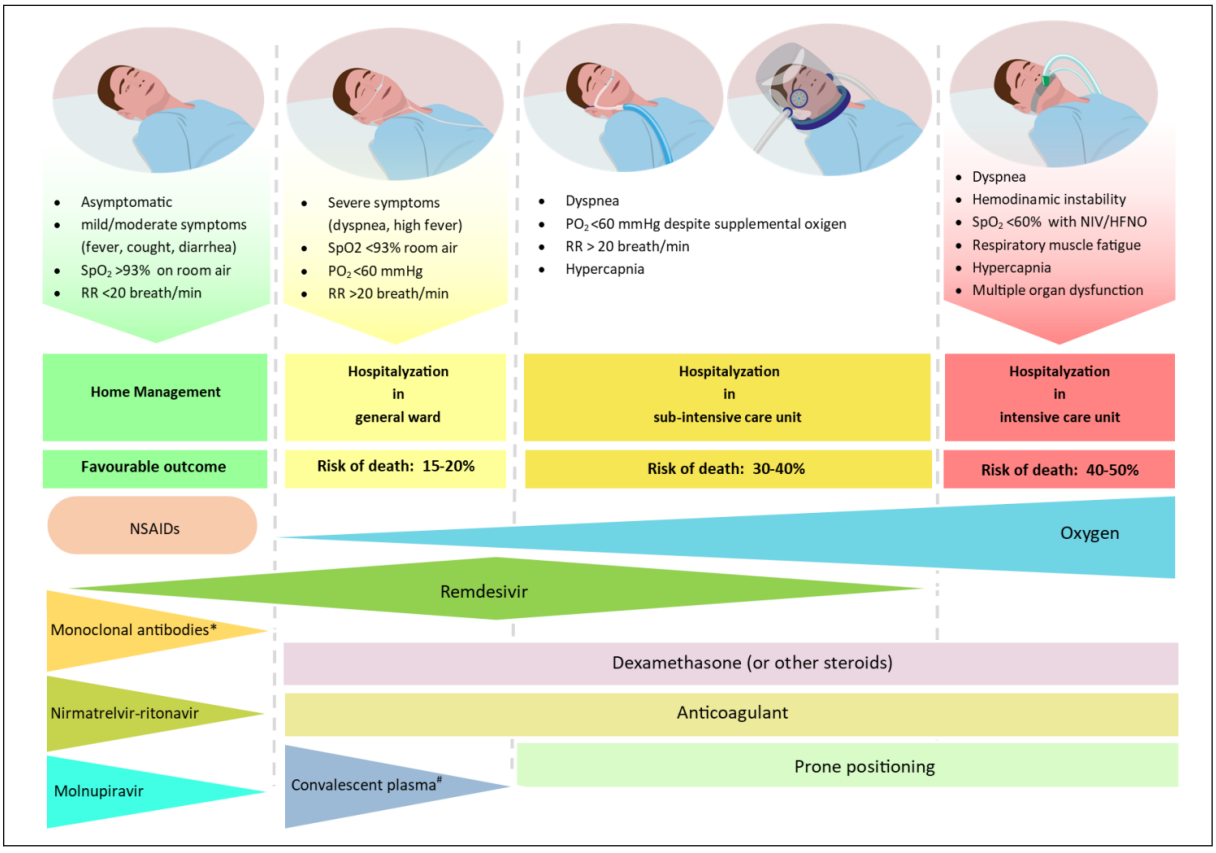

Figure 1 - Schematic representation of symptoms, treatment and outcome of patients with COVID-19 according to the disease severity. Mortality rates of COVID-19 have been extracted from data published by Tzotzos SJ et al. [75] and Grassinelli et al. [76] in unvaccinated patients.

Note: *The monoclonal antibodies available are sotrovimab, casirivimab-imdevimab, and bamlanivimab-etesevimab. The clinical efficacy of monoclonal antibodies depends on genomic characterization of SARS-CoV-2; #Plasma with high levels of antibodies.

2) hospitalized patients requiring low-flow oxygen,
3) high-flow oxygen and
4) mechanical ventilation (Figure 1).

Information sources and search strategy
We conducted a targeted search of medical and scientific literature in the following databases: "MEDLINE", "Scopus" and "Google Scholar". The terms used in our search strategy were "COVID therapy" or "COVID treatment" or "COVID management" or "COVID medicines" or "COVID guidelines". The selection of the articles was accomplished by the authors after the screening of titles and abstracts followed by the retrieval and screening of full-text articles.

Asymptomatic and mildly symptomatic patients
This group of patients includes asymptomatic and mildly symptomatic patients who do not require hospital admission up to the resolution of the disease. In unvaccinated patients, asymptomatic COVID-19 accounts for approximately 40% to 45% of infections with a prevalence ranging from 6.3% to 96% across studies [18]. Natural history is favorable and treatment is unnecessary in this setting. It is worth noting that asymptomatic or paucisymptomatic patients experience a faster viral clearance than their symptomatic counterparts. Self-isolation is required to avoid the spread of the virus in the community. With this regard, the impact of asymptomatic patients in viral transmission does not appear negligible since they usually have a high viral load shedding.
In mildly symptomatic patients, fatigue, myalgia, headache, fever, cough, anorexia are the most common symptoms of COVID-19. Other non-specific symptoms may be diarrhea, anosmia, ageusia, nausea and vomiting. The standard of care relies on close monitoring of these patients to recognize a rapid worsening of symptoms or development of dyspnea that generally occurs within 11.5 days [19].
Adequate nutrition and fluid intake are recommended for all symptomatic patients to face inflammation-induced anorexia and dehydration. As a caveat, anti-SARS-CoV-2 therapeutics are of greatest benefit for nonhospitalized patients who have risk factors for progression to severe COVID-19. The key elements to prioritize treatment are: age, vaccination status, immune status, and clinical risk factors.
First-line treatment of outpatients consists of non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., acetaminophen, ibuprofen, etc.) to relieve symptoms such as fever and myalgia [20,21]. Paracetamol and inhibitors of cyclo-oxygenase-1 should be limited to a few days to avoid liver toxicity and acute kidney injury, respectively.
Remdesivir, a nucleotide prodrug of an adenosine analog, is approved for the treatment of high-risk asymptomatic outpatients. This antiviral has shown to be superior to placebo in shortening time to recovery even though the benefits on mortality and need for intubation are still unclear [22]. Remdesivir is administered intravenously in adults and adolescents (aged ≥12 years and weighing ≥40 kg) at the dose of 200 mg on the first day, followed by 100 mg once a day for two days. This antiviral is not advised in patients with a GFR of less than 30 ml/min due to a lack of clinical data. However, a cohort study of 46 patients with varying grades of kidney dysfunction, including patients with renal failure, did not show any adverse effects from remdesivir [23].
For asymptomatic patients at high risk of severe COVID-19, the administration of human anti-SARS-CoV-2 monoclonal antibodies has been shown to prevent progression to severe COVID-19 [24].
Bamlanivimab plus etesevimab, casirivimab plus imdevimab and sotrovimab received emergency use authorizations for patients aged >12 years. All these anti-SARS-CoV-2 antibodies are targeted to bind epitopes of the spike protein. Bamlanivimab plus etesevimab has in vitro activity against Alpha B1.1.7 and Delta b1.617.2; casirivimab plus imdevimab against Alpha B1.1.7, Beta B.1.351, Gamma P.1 and Delta B1.617.2; sotravimab against all the variants including Omicron B.1.1. 529.
US Food and Drug Administration (FDA) has authorized tixagevimab plus cilgavimab for pre-exposure prophylaxis of unvaccinated COVID-19 in patients and non-responders to vaccination because of immune compromise.
Prescription of monoclonal antibodies must rely on the epidemiology of COVID-19 variants because mutations in the spike protein of SARS-CoV-2 variants may escape from monoclonal antibody neutralization. Omicron variant of concern, the current dominant strain of coronavirus worldwide, is expected to be susceptible to sotrovimab, a monoclonal antibody that targets high-

ly conserved epitope of spike protein expressed by both SARS-CoV and SARS-CoV-2 [25]. Tixagevimab plus cilgavimab, seems to have 12- to 30-fold lower neutralizing activity in vitro against this variant [26].

Recently, two novel antivirals, nirmatrelvir-ritonavir (300/100 mg BID for 5 days) and molnupiravir (800 mg BID for 5 days) have been authorized for the treatment of COVID-19. Briefly, ritonavir-boosted nirmatrelvir is a protease inhibitor currently being assessed in phase 3 trials for its safety and efficacy. An interim analysis (data not shown) documented that ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 89% compared to placebo in patients, who do not require initiation of supplemental oxygen, treated within three days from symptom onset [27]. This agent must be prescribed in patients aged ≥18 years and it is contraindicated in patients with GFR<30 ml/min or severe hepatic impairment, moreover, the interaction of ritonavir with other drugs should be taken into account before its prescription. Molnupiravir, a nucleoside analog that inhibits SARS-CoV-2 replication, has been shown to reduce the risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19 in a randomized trial [28]. Molnupiravir is contraindicated in people aged <18 years due to bone and cartilage toxicity and during pregnancy and lactation. Female contraception is needed for the entire treatment course and 4 days after while for males is contraception is needed for the entire treatment course and 90 days after.

There are many home-based testings aimed to identify outpatients requiring advanced medical care. Monitoring of oxygen saturation by peripheral oximetry is a rapid and effective modality to assess respiratory function with minimally invasive instrumentation. Dyspnea has low predictive accuracy for hypoxia in COVID-19, therefore, exertional desaturation test (e.g., classical or modified six-minute walking test) has been advocated as a useful instrument to detect patients with a poor functional capacity [29]. Adequate physician's guidance is necessary to interpret resting and exertional oxygen saturation which threshold has been set to 93% in non-chronic obstructive pulmonary disease (COPD) patients. More importantly, the recognition of a mismatch between respiratory distress and objective evidence of peripheral hypoxia, probably due to underlying prominent pulmonary perfusion defect, is of crucial importance in order to supply oxygen therapy to patients with moderate hypoxemia (40 to 59 mmHg) despite relatively mild respiratory discomfort (silent hypoxia) [30].

Beyond oxygen desaturation, dyspnea, respiratory muscle effort, fever, respiratory rate >20 breaths per minute are main determinants of the hospital visit, especially if these symptoms develop in subjects at high risk of progressing to a serious illness.

Symptomatic patients with low oxygen requirement

Once established the severity of hypoxemia (mild or moderate) oxygen therapy should be promptly delivered. The initial approach to the hypoxemic patient consists in providing oxygen with low-flow devices such as a nasal cannula or simple face mask. These systems deliver oxygen flow rates at a maximum of 15 liters per minute which is lower than patients' inspiratory demand (approximately 30 L during quite breathing).

Current standard treatment consists of combination corticosteroids, prophylactic anticoagulants and remdesivir unless they are contraindicated. International recommendations suggest titrating oxygen to a target peripheral oxygen saturation (SpO_2) ≥90%, ideally, the target of SpO_2 should be between 90% and 96%. A lower target (88%-93%) is warranted in patients with concomitant COPD. Oxygen can be provided using simple nasal cannulas or facial masks with oxygen flow up to around 5-6 L O_2/minute. If the desired SpO_2 is not achieved and clinical status does not improve, oxygen delivery can be increased by using a non-rebreathing mask. This type of mask is equipped with a reservoir bag filled with 100% oxygen. The non-rebreathing mask requires an oxygen flow of at least 10-15 L/min and provides a higher fraction of inspired oxygen (FiO_2) (about 80%) compared to a rebreathing mask or facial mask.

The requirement of supplemental oxygen is a clinical indication for the use of corticosteroids in COVID-19. The administration of corticosteroids has led to the paradigm shift in the clinical management of COVID-19 [31]. The findings coming from the RECOVERY trial, a large multicentric randomized trial, have shown that intravenous dexamethasone at the dosage of 6 mg/daily for 10 days reduces 28-day mortality [32]. Similar re-

sults, albeit not conclusive, have been reported with hydrocortisone in fixed-dose (50 mg [or 100 mg] every 6 hours) or shock-dependent course (50 mg every 6 hours) in patients with severe COVID-19 enrolled in the REMAP-CAP trial [33]. However, some aspects of corticosteroid therapy in COVID-19 patients remain unclear. In particular, a significant proportion of patients with severe COVID-19 requiring oxygen support has a period of hospitalization longer than 10 days and probably a higher dose of corticosteroid may be helpful to modulate the COVID-driven inflammatory response [34]. Although data on other corticosteroids are more limited than those for dexamethasone, reasonable alternatives at equivalent doses include methylprednisolone 32 mg, prednisone 40 mg, or hydrocortisone 150 mg. It is important to note that there is not a clear benefit to administering corticosteroids to non-hypoxemic patients

There is evidence that inflammation and virus-induced endothelial damage increase the risk for arterial and venous thrombotic events. Cerebrovascular, pulmonary, coronary, and other micro-and macrovascular thrombotic complications have been documented in patients who died of COVID-19. Furthermore, thrombotic complications, including lung embolism, occur up to 37% of the hospitalized patients despite prophylactic anticoagulation [35, 36]. Indeed, if the physician recognizes a consistent discrepancy between symptoms and radiology reports, pulmonary embolism needs to be excluded.

Anti-thrombotic protocols are extremely heterogeneous and recommended doses of anticoagulation range from prophylactic to therapeutic anticoagulation. To date, the dilemma between the superiority of therapeutic and prophylactic regimens remains to be explored and requires larger trials before drawing firm conclusions. In particular, the French Working Group on Perioperative Hemostasis and the French Study Group on Thrombosis and Hemostasis have proposed anticoagulation dose escalation in subjects with obesity (BMI≥30), high oxygen demand, need for mechanical ventilation, severe inflammatory syndrome (e.g., fibrinogen >8g/L), hypercoagulability (e.g., D-dimers >3000 ng/ml) [37].

For normal-weight patients the prophylactic dose of anticoagulant is enoxaparin 4000U subcutaneous (SC) once daily, fondaparinux 2.5 mg SC once daily or calcium heparin 5000U SC twice daily.

For patients with kidney impairment, dose of heparin should be adjusted according to the creatinine clearance. Low molecular weight (LMW) heparin should be halved in patients with a creatinine of less than 30 ml/min albeit, the risk of LMW accumulation can occur also beyond this cut-off; unfractionated heparin is generally reduced by 30% in dialysis and older patients [38].

Remdesivir is part of the armamentarium in patients with pneumonia requiring supplemental oxygen. In this group of patients, total duration of treatment should be at least 5 days and not more than 10.

In the United States, high-titer convalescent plasma has been authorization among hospitalized patients with COVID-19 who have impaired humoral immunity. Nevertheless, the experience with convalescent plasma has yielded conflicting results so far. Few observational and randomized clinical trials demonstrated a benefit of high-titer convalescent plasma in hospitalized patients with COVID-19 who are early in the course of the disease or have impaired humoral immunity [39-43]. Conversely, a consistent series of randomized clinical trials clearly showed that this potential therapeutic option was ineffective in slowing the progression to severe COVID-19 and reducing the mortality irrespectively of timing or severity of the disease [44-47]. Furthermore, convalescent plasma led to serious transfusion reactions in a restricted number of subjects.

Antibiotic prophylaxis is discouraged in the absence of bacterial superinfection. Distinguishing bacterial pneumonia or sepsis from COVID-19 is challenging and imposes a high index of suspicion in case of high procalcitonin levels, productive cough and deteriorating clinical condition.

Prone positioning is a procedure valid for all patients experiencing hypoxia, even though it is applied in patients with a more severe acute respiratory syndrome. Moving from supine to prone leads to recruit the posterior lung fields and improves the ventilation-perfusion mismatch in non-intubated and intubated patients [48, 49]. Laying on own side or sitting straight up are alternatives if pronation is not feasible as occurs in obese patients.

Symptomatic patients with high oxygen requirement

The unprecedented surge of hypoxemic patients has extraordinarily increased the fragmentary

knowledge of noninvasive respiratory support strategies delivering O_2 at very high flow. These devices are used in the treatment of hypoxic patients who require controlled increments in FiO_2 Despite conflicting results on patient outcomes, non-invasive modalities such as high-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV) are a secure bridge over troubled waters for the management of severe hypoxic patients with COVID-19 when an adequate patient selection and clinical judgment is applied.

HFNO is a relatively new technique providing high oxygen flow (50-100 liters/minutes) with a high FiO2 (95-100%) through specially designed nasal cannulae. The beneficial effects of HFNO are multiple and include CO_2 clearance and reduction of the dead space thereby improving alveolar ventilation. It generates a positive end-expiratory pressure (PEEP) level, which is proportional to the flow rate and the modality of breathing (open vs close mouth breathing). Each 10 L/min increase in flow rate increases mean PEEP by 0.35 cm H_2O with open-mouth breathing and by 0.69 cm H_2O with closed-mouth breathing [50].

NIV includes CPAP (continuous positive airway pressure) and BiPAP (Biphasic Positive Airway Pressure). Facial mask (CPAP or BiPAP) has several limitations (oxygen leakage, mask intolerance) that minimize its effectiveness in hypoxic patients compared to the helmet [19]. CPAP delivers a constant flow of oxygen and generates a constant PEEP that tends to prevent alveolar collapse, increases lung volumes, and improves gaseous exchange. The initial setting requires PEEP of 10 cm H_2O and FiO_2 of 60% whereas a lower PEEP is used in patients with COPD.

BiPAP is the modality mainly used in patients who remain hypoxic with other modalities of respiratory support or experience respiratory muscle fatigue. BiPAP provides a high driving pressure coupled with a lower one. An inspiratory positive airway pressure (IPAP) is set at 12-20 cmH_20 and expiratory positive airway pressure (EPAP) at 4-5 cm H_2O. Pressure support (IPAP-EPAP) should be at least 8 cm H_20.

As the patient adapts to the assisted ventilation, pressure support should be rapidly increased to obtain tidal volumes of more than 400 ml (about 6 cc/kg) and about 6-7 liters per minute to guarantee normal ventilation. Vigilant monitoring of patients is required especially within the first hours after configuration of the parameters. A SpO_2 between 88-92% and a respiratory rate of <25 breaths per minute demonstrate a favorable response. The goal of oxygen saturation should be preferably obtained by increasing ventilation rather than increasing FiO_2. Blood gas analyzer should be performed within 1-2 hours to ensure resolution of hypoxia and exclusion of hypercapnia. The patient should be observed closely for signs of patient-ventilator asynchrony, excessive use of accessory muscles, mask leakage and discomfort.

However, it is worth noting that a high peak pressure and a high tidal volume can increase the risk of barotrauma and volutrauma in a context of a low compliant lung.

When NIV is administered, all patients should receive intensive assistance to avoid the risk of malnutrition and dehydration. Critically ill patients have increased energy requirements (25-30 kcal/kg/day) and an augmentation insensible fluid loss with perspiration (>900 ml/day) [51]. Although humidified ventilation can balance the losses that occur with hyperventilation, intravenous hydration up to 40 cc/kg/daily is often necessary for patients with no fluid intake. A routine check of serum and urine electrolytes is also advisable given the high incidence of serum electrolyte abnormalities [52].

Immunomodulators agents have been used to tame the dangerous inflammatory response experienced by critically ill COVID-19 patients [53]. Recent randomized trials suggest adjunctive use of the interleukin-6 receptor (tocilizumab or sarilumab) and Janus kinase (baricitinib) inhibitors in hospitalized adults with severe COVID-19 [54-56]. Recently, the SAVE-MORE trial showed that early administration of anakinra, a recombinant IL-1 receptor antagonist, in hospitalized patients with moderate and severe COVID-19 significantly reduced 28-day mortality [57].

As a general recommendation, anakinra (100 mg once a day by subcutaneous injection for 10 days) guided by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR) ≥6 ng/mL, tocilizumab (8 mg/kg single [or double] intravenous administration), baricitinib (4 mg orally once daily for up to 14 days) or sarilumab (400 mg as single intravenous administration) should be administered in addition to corticosteroids in patients that have progressively greater

oxygen requirements or within 24 to 48 hours of initiation of ICU-level care.

Patients on invasive mechanical ventilation

Patients who have the potential for functional recovery can benefit from life-sustaining treatments. Once admitted, two-third of patients require invasive mechanical ventilation for the treatment of hypoxia, due principally to ARDS. Despite the first anecdotal recommendations for early intubation, there is now convincing evidence for a higher threshold for intubation, because early intubation, deep sedation, ventilator-associated pneumonia and delayed weaning from mechanical ventilation impact mortality. Clinical conditions leading to intubation include rapidly escalating oxygen requirements (<60 mmHg) despite the use of HFNO and NIV and/or muscular fatigue. Other signs of progression are hypercapnia, respiratory muscle fatigue, worsening of mental status (i.e., delirium), hemodynamic instability or multiorgan failure

ARDS and sepsis and the main causes of ICU admission in patients with COVID-19. Whereas sepsis in COVID-19 is clinically indistinguishable from other episodes of sepsis, ARDS can be specific in terms of clinical features and clinical course. A simplistic approach of COVID-19-associated ARDS describes two patterns of lung involvement [58]:

1) type L (low values of elastance, pulmonary ventilation/perfusion ratio, lung weight, and recruitability) and
2) type H (high values of elastance, right-to-left shunt, lung weight, and recruitability).

At presentation, most patients show lung involvement consistent with type L, but some of them switch to type H afterward. The causes rely on the synergistic unfavourable effects of worsening COVID-19 pneumonia and patient self-inflicted lung injury. For this subset of patients, lung-protective mechanical ventilation in conjunction with standard supportive care is the cornerstone of treatment. Ventilation strategy is based on low tidal volume, medium-high PEEP and prone position. A simplified shared ventilation strategy consists of a combination of a tidal volume of 6-8 cc/kg of ideal body weight, driving pressure <12 cmH2O and a plateau pressure ≤30 cm H2O. PEEP should be set at 8-12 cm H2O; advisable respiratory rate should range between 15 and 25 breath/minute for a target SpO2 of 92-95%, pH range of 7.30-7.42. If the PaO2/FiO2 ratio remains under 100 despite optimization of ventilator settings, prone positioning is indicated for at least 12 hours/day. The benefits of pronation defined as "oxygenation response to prone position" occur when PaO2/FiO2 ratio rises by 20% or at least 20 mmHg during the first prone position session. In patients with refractory hypoxemia, sustained inflation or stepwise increase of inspiratory pressure and/or of PEEP is considered a rescue therapy for reopening non-aerated or poorly aerated alveoli (recruitment maneuvers). Another therapeutic strategy to rescue severely hypoxic patients is extracorporeal membrane oxygenation (ECMO). This complex supportive treatment should be considered when lung-protective ventilation, pronation and neuromuscular blockade have been unsuccessful. Data from the largest cohort of severely-ill COVID-19 patients showed an estimated cumulative incidence of in-hospital mortality 90 days after ECMO initiation of 37%. Although encouraging, these results suggest caution in patients requiring mechanical circulatory support and extracorporeal cardiopulmonary resuscitation [59]. However, further studies are required to solve the conflicting results of ECMO amongst cohorts of COVID-19 patients due essentially to potential patient selection bias and different technical skills of dedicated healthcare workers. Patients requiring mechanical ventilation require a different therapeutic approach compared to non-ICU admitted patients. The therapeutic strategy is based on high-dose prophylactic anticoagulation, immunomodulators as well as high dosage steroids in the case of ARDS. ICU patients are at particularly high risk of thrombotic complications including pulmonary embolism. Notably, the diagnosis of pulmonary embolism is challenging in patients on mechanical ventilation. For these reasons, intensification of heparin treatment has been proposed in this subset of hospitalized patients. Recent data support this thesis, indeed the use of high-dose prophylactic anticoagulation has been associated with a reduction in thrombotic risk without increasing the risk of bleeding [60].

The documented benefits of corticosteroids in ARDS have also been confirmed in a prospective meta-analysis of 7 randomized clinical trials that included 1703 critically ill patients with COV-

ID-19 [61, 62]. In this study, administration of corticosteroids was associated with lower 28-day all-cause mortality compared with standard care or placebo [63].
However, the questions regarding the exact dose of corticosteroids that should be prescribed remain unanswered. Corticosteroids have been used for a prolonged period and at higher doses in patients with non-COVID-19 ARDS [64, 65]. The COVID STEROID 2 Randomized Trial evaluated whether patients with severe and critical COVID-19 may benefit from a higher dose of corticosteroid (12 mg/daily versus 6 mg/daily) than currently recommended. The findings of this study, probably underpowered to identify a significant difference, did not provide a significant survival benefit at 28 days (p=0.07) [66]. Conversely, the CODEX trial, which included only COVID-19 patients on mechanical ventilation for moderate to severe ARDS, revealed benefit from high doses of dexamethasone (20 mg daily for five days, followed by 10 mg daily for five days) [67]. More interestingly, in both these studies, high-dose corticosteroids were not associated with a higher rate of serious adverse events compared to the standard of care [66, 67]. Furthermore, the survival benefit observed in RECOVERY trial participants receiving invasive mechanical ventilation (11% mortality reduction) was comparable to the benefits observed with 200 mg of hydrocortisone for 7 days in septic shock and ARDS (9% mortality reduction) [68].
A growing body of evidence suggested that prolonged treatment and higher dose of corticosteroids provided higher immunomodulatory effects for severely-ill patients with COVID pneumonia [64]. Pulse administration of intravenous methylprednisolone (ranging 125-250 mg daily for 3 days) or pulse methylprednisolone therapy (250 to 500 mg daily for three days) followed by oral prednisone (50 mg orally every day for 14 days) were associated with a better outcome compared to the control group [69-71]. Unclear results have been reported in patients not eligible for other treatments or as rescue therapy treated with high-dose methylprednisolone pulse-therapy (1 gram daily for at least three days) [72]. Lastly, biological agents, such as tocilizumab (sarilumab) anakinra and baricitinib and sarilumab, have been authorized as adjunctive therapy to corticosteroids to prevent disease progression and death in hospitalized adults with COVID-19. The combined use of these medicaments is off-label and the safety of coadministration is uncertain. More importantly, careful monitoring for signs of systemic or invasive infectious disease (procalcitonin, β-d-glucan, serum galactomannan, liver function tests, neutropenia, HBV, herpes virus, EBV and tubercolosis screening) is required pre- and post- administration of these immunomodulators [73, 74].
Synthesizing all the available evidence and experience, therapeutic strategy in mechanically ventilated COVID-19-associated ARDS subjects should be patient-specific in order to avoid harmful effects of drugs with a narrow therapeutic index.
Overall, the prognosis of patients admitted to ICU is poor and highly conditioned by advantage age and pre-existing comorbidities. The mortality is about 40-50%, and virtually, all deceased patients have diffused alveolar damage consistent with a diagnosis of ARDS. [75, 76]. Kidney failure requiring dialysis treatment, cardiovascular collapse, and neurologic involvement are the most severe sequelae of severe COVID-19. When multiple organs have been involved the progression to multiorgan failure syndrome is inevitable.

CONCLUSIONS

Since COVID-19 identification, the increased knowledge of SARS-CoV-2 pathogenesis and the results of randomized trials have raised a higher awareness of potential therapeutic strategies against COVID-19. First of all, the development of COVID-19 vaccines has been a milestone in the therapeutic strategy against SARS-CoV-2 infection. Severe COVID-19 has indeed become a vaccine-preventable disease for most immunocompetent people. However, considering the global rate of unvaccinated people and non-responders to COVID-19 vaccination, the fight against SARS-CoV-2 is not over. In this group of patients, the disease can have a severe and progressive course with multiorgan involvement. The available armamentarium against this infection includes corticosteroids, SARS-CoV-2-neutralising monoclonal antibodies, antivirals, anticoagulants and biological drugs. The choice of these drugs relies principally on the phase of the disease according to the risk of progression and the severity of the clinical manifestations. However, given the rapid spread of emerging variants, drug shortage and

limited access to high-cost medicaments, access to updating therapeutic recommendations and therapeutic alternatives has a crucial role in the current management of patients with COVID-19.

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Authors' contributions
Conception: GA, AF.
Design of the study and draft of the manuscript: NM, MF, AF, FF, RT, EF, MM, DG.
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