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## Position paper

## Therapeutic strategies for severe COVID-19: a position paper from the Italian Society of Infectious and Tropical Diseases (SIMIT)

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## ABSTRACT

**Scope:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become pandemic, reaching almost one million death worldwide. At present standard treatment for coronavirus disease 2019 (COVID-19) is not well defined because the evidence, either from randomized or observational studies, with conflicting results, has led to rapid changes in treatment guidelines. Our aim was to narratively summarize the available literature on the management of COVID-19 in order to combine current evidence and interpretation of the data by experts who are treating patients in the frontline setting.

**Methods:** The panel conducted a detailed review of the literature and eventual press releases from randomized clinical trials for each possible available treatment. Inductive PubMed search waws performed for publications relevant to the topic, including all clinical trials conducted. The result was a flowchart with treatment indications for patients with COVID-19.

**Implications:** After 6 months of a pandemic situation and before a possible second coronavirus wave descends on Europe, it is important to evaluate which drugs proved to be effective while also considering that results from many randomized clinical trials are still awaited. Indeed, among treatments for COVID-19, only glucocorticoids have resulted in an association with a significant decrease in mortality in

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Remdesivir (GS-5734) is a nucleoside analogue prodrug displaying *in vitro* inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2 [7]. Preliminary data showed that remdesivir was superior to placebo in shortening the time to recovery but did not show a significant difference in mortality [8]. In a subsequent retrospective cohort study comparing 312 patients with severe COVID-19 who received remdesivir with 818 matched patients, remdesivir was associated with significantly greater recovery and 62% reduced odds of death versus standard-of-care treatment [9]. A RCT involving hospitalized patients with confirmed SARS-CoV-2 infection did not show a significant difference between a 5-day course and a 10-day course of remdesivir, and a clinical improvement of 2 points or more on the ordinal scale occurred in 64% of patients in the 5-day group and in 54% in the 10-day group [10]. Finally, data from the ACTT-1 double-blind RCT has been recently published [11]. The study, conducted on 1062 patients, showed that patients who received a 10-day course of remdesivir had a shorter time to recovery than those receiving placebo (10 vs. 15 days,  $p < 0.001$ ) and were more likely to have clinical improvement at day 15. No significant difference in term of mortality was detected at day 29. The magnitude of effect was significantly greater among patients receiving oxygen via a mask compared to those not receiving oxygen or needing noninvasive or invasive mechanical ventilation [11]. Of importance, the interim results from the Solidarity Trial endorsed by World Health Organization (WHO) found that remdesivir had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients with COVID-19 [5]. Although the magnitude of benefit on mortality is still to be defined, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) issued an emergency use authorization of the drug for COVID-19 treatment. At present remdesivir is approved by the Italian Medicines Agency (AIFA) for COVID-19 patients with pneumonia needing oxygen supplementation but not for patients needing high-flow oxygen, noninvasive or invasive mechanical ventilation or extracorporeal membrane oxygenation [12].

Data about favipiravir and ribavirin are limited [13].

#### *Hydroxychloroquine therapy*

Hydroxychloroquine (HCQ) was one of the first drugs used worldwide to treat COVID-19. The first observational French study, which was strongly criticized, reported enthusiastic results, with HCQ associated with azithromycin for the treatment of COVID-19 [14]. Since then, no clear evidence of the efficacy of this drug against SARS-CoV-2 has been published. At present we know that HCQ does not substantially reduce symptom severity in outpatients with early mild COVID-19 [15], and there is a dearth of evidence to support the efficacy of HCQ in preventing COVID-19 [16]. A RCT conducted in patients with mild to moderate COVID-19 pneumonia showed no impact on 15-day clinical improvement of HCQ, either alone or in combination with azithromycin [17]. Moreover, both the RECOVERY and SOLIDARITY trials discontinued the HCQ arm because no benefits of this drug over the standard of care was detected [4,5,18].

International guidelines such as the US National Institutes of Health and the Infectious Diseases Society of America COVID-19 treatment guidelines recommend against the use of chloroquine or HCQ for the treatment of COVID-19 [19,20].

#### *Anticoagulant therapy*

COVID-19 has been associated with vascular inflammation, endothelial dysfunction and a hypercoagulable state that may predispose the subject to haemostatic abnormalities such as

arterial thrombosis or thromboembolic disease [21]. This condition has been associated with poor outcomes, especially in patients with a severe disease [22]. This has fueled interest in the use of heparin for its anticoagulant and anti-inflammatory activity.

Data from a retrospective study in China showed that anticoagulant therapy with low-molecular-weight heparin (LMWH) seems to be associated with a better outcome, reducing 28-day mortality of patients with sepsis-induced coagulopathy score of  $\geq 4$  or D-dimer more than sixfold of the upper limit of normal [23]. Results from a large US cohort of COVID-19-hospitalized patients confirmed that systemic anticoagulant treatment could be associated with improved outcomes [24]. A study conducted on 4389 hospitalized COVID-19 patients found an approximately 50% reduced hazard of in-hospital mortality and a 30% reduced hazard of intubation compared to patients without anticoagulant therapy [25].

At present several RCTs are ongoing in order to assess doses, risk and benefits of anticoagulant therapy ([ClinicalTrials.gov](https://clinicaltrials.gov)). In the meantime, many scientific societies have released interim guidance for the management of thromboembolism and anticoagulation therapy [26–29]. This is a summary of current recommendations.

- Deep venous thrombosis (DVT) prophylaxis should be prescribed for all hospitalized nonpregnant adults with confirmed or highly suspected COVID-19, regardless of DVT risk assessment score, as per guidelines for non-COVID-19 hospitalized patient, unless contraindicated (e.g. severe thrombocytopenia, active bleeding). LMWH is preferred over oral anticoagulant therapy in hospitalized patients with critical disease because of the shorter half-life, best route of administration and fewer drug–drug interactions.
- For non-critically hospitalized patients, a standard dose of LMWH is recommended.
- For severe critical patients, intermediate-dose LMWH (i.e., enoxaparin 40 mg provided subcutaneously (sc) twice daily, enoxaparin 0.5 mg/kg sc twice daily, heparin 7500 U sc three times daily or low-intensity heparin infusion) may be considered on an individual basis in patients with multiple risk factors for DVT (i.e. body mass index  $>30$  kg/m<sup>2</sup>, previous DVT, active cancer, large increase in D-dimers, severe inflammation or signs of imminent respiratory failure).
- The therapeutic dose of LMWH is not supported by evidence outside of proven DVT.
- Treatment duration recommended is until hospital discharge and for at least 7 to 14 days.
- Standard risk for bleeding should be considered before prescribing anticoagulant therapy by assessing individual potential advantages.

#### *Anti-inflammatory drugs*

Patients with SARS-CoV-2 infection may develop a so-called cytokine storm, characterized by the increase of many cytokines, mainly interleukin (IL)-1 and IL-6, which promotes the development of an acute respiratory distress syndrome [30,31].

Tocilizumab is a recombinant humanized monoclonal antibody of the IgG1 class directed against both the soluble and the membrane-bound IL-6 receptor [32]. Several observational studies have shown promising results [33–35]. In particular, a large retrospective Italian cohort study evaluated the effect of two doses of tocilizumab (administered as intravenous or sc formulation) on the outcome of patients with severe SARS-CoV-2 pneumonia (oxygen saturation  $<92\%$  in room air and a PaO<sub>2</sub>/FiO<sub>2</sub> (mm Hg) ratio of  $<250$  or a decrease in PaO<sub>2</sub>/FiO<sub>2</sub> greater than 30% in the last 24 hours). The risk of invasive mechanical ventilation/death was

reduced for participants treated with tocilizumab from fitting a Cox regression analysis adjusted for gender, age and Sequential Organ Failure Assessment (SOFA) score (adjusted hazard ratio 0.61; 95% confidence interval (CI) 0.40–0.92;  $p < 0.02$ ). The 14-day mortality rate was 20% in the standard-care group compared to 7% ( $p < 0.001$ ) in the tocilizumab group [34]. Similar results were observed in a large observational study conducted on intensive care unit (ICU) patients across the United States [35]. A recently published RCT (CORIMUNO-19-TOCI-1) conducted on COVID-19 patients with moderate to severe SARS-CoV-2 pneumonia confirmed a positive effect of tocilizumab on the composite endpoint of mechanical ventilation/death, but not on 28-day mortality [36]. Instead, the scenario could be completely different in patients whose disease is not severe. A multicentre RCT by Salvarani et al. did not confirm the efficacy of early administration of tocilizumab in COVID-19 patients with a  $\text{PaO}_2/\text{FiO}_2$  ratio between 200 and 300, and tocilizumab use had no benefit on disease progression, defined as need of ICU admission for invasive mechanical ventilation, death from all causes or clinical deterioration expressed by  $\text{PaO}_2/\text{FiO}_2$  ratio  $< 150$  [37]. Another RCT on 243 patients showed no effect for preventing intubation or death in moderately ill hospitalized patients with COVID-19 [38]. Concerning patients with more severe disease, final results from EMPACTA trials conducted on ethnical minorities have been published recently showing that tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death but did not improve survival [39]. Moreover, these favorable results were confirmed by the REMAP-CAP trial that compared tocilizumab and sarilumab to no-immunomodulators [40]. Data from other RCTs as REMDACTA and COVACTA aimed to assess the safety and efficacy of tocilizumab in patients with SARS-CoV2 pneumonia will be available in the next future [41,42]. A recent metaanalysis including preliminary results from these 2 last trials together with previous RCTs and results from observational studies demonstrated moderate-certainty evidence that tocilizumab reduces mechanical ventilation in hospitalized COVID-19 patients, while the effect on mortality needs to be assessed in further studies [43]. Concerning sarilumab, another IL-6 antagonist, a recent press release from Sanofi stated that it failed the primary endpoint in a RCT [44], but the still unpublished results of REMAP-CAP showed a similar efficacy of tocilizumab and sarilumab [40].

Anakinra is an IL-1 receptor antagonist that blocks activity of the proinflammatory cytokines IL-1 $\alpha$  and IL-1 $\beta$  and is used to treat autoinflammatory disorders at a daily dose of 100 mg sc in adult patients [45]. At present data from RCTs are not available; nevertheless, small clinical studies have been published showing an advantage of high doses of anakinra [46–48].

Concerning possible side effects of immunomodulatory drugs, despite previous cohort studies suggested a possible increased risk of infectious complications compared to standard of care including life-threatening herpes simplex reactivation [34,49], these evidences was not confirmed in subsequent randomised studies [43].

Janus kinase (JAK) 1/2 inhibitors have been also proposed as attractive candidates to treat COVID-19 as a result of their properties as anti-inflammatory agents and their hypothesized off-target antiviral effect against SARS-CoV-2 [50]. The most interesting drug of this group is baricitinib, and preliminary experience has demonstrated a high rate of recovery in COVID-19 patients receiving this drug [51,52]. Baricitinib has been recently approved by the FDA for the treatment of COVID-19 in combination with remdesivir on the basis of the ACTT2 trial which showed a better outcome than remdesivir alone in patients with high-flow oxygen and non-invasive mechanical ventilation [53,54]. RCTs on the use of baricitinib for patients with COVID-19 are ongoing. Other immunomodulators currently being studied are interferon beta and Bruton tyrosine kinase inhibitors [55,56].

Concerning immunomodulatory drugs, all international guidelines recommend their use only in the context of a RCT, but it is not easy to randomize a study during the pandemic's peak, and not all centres have access to trials [19,20].

Finally, an important role among anti-inflammatory drugs should be played by glucocorticoids. Glucocorticosteroids act as a wider immune modulator than the single cytokine blockers [57,58]. At beginning of the epidemic, the use of these drugs was somehow discouraged, and the WHO recommended against the routine use of corticosteroids in patients with COVID-19 unless indicated for another reason [59]. The RECOVERY trial showed that dexamethasone at a dosage of 6 mg provided once daily for up to 10 days compared to standard of care reduced deaths by one third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%; relative risk 0.65 (95% CI 0.51–0.82);  $p < 0.001$ ) and by one fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%; relative risk 0.80 (95% CI 0.70–0.92);  $p < 0.002$ ), but it did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%; relative risk 1.22 (95% CI 0.93–1.61);  $p < 0.14$ ) [60]. To date, all international guidelines strongly suggest the use of systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19 while conditionally recommending that corticosteroid therapy be withheld from patients with nonsevere COVID-19 not receiving respiratory support [61,62].

#### *Convalescent plasma*

Another potential therapeutic strategy for patients with SARS-CoV-2 infection is passive transfer of neutralizing antibodies using plasma from patients who recovered from COVID-19. There is evidence that over 99% of patients with laboratory-confirmed SARS-CoV-2 infection develop a detectable antibody response, and 88% of them present neutralizing antibodies [63]. The safety and tolerability of the administration of convalescent plasma (CP) have been evaluated in an observational study on more than 5000 patients and showed an incidence of serious adverse events in the first 4 hours of infusion of  $< 1\%$  [64]. Concerning efficacy, an observational study conducted on 138 patients from China showed that 70% of patients with severe respiratory impairment improved and did not need oxygen support within 7 days from infusion [65]. Promising results were also reported from a single-arm Italian study showing a beneficial effect of CP on 7-day hospital mortality compared to expected mortality from the National Statistics in Italy [66], and a preprint (not peer reviewed) large observational study of 35 322 hospitalized COVID-19 patients found that the early infusion of CP was associated with improved 7- and 30-day mortality [67].

However, results from an underpowered RCT from China did not show a significant shortening in time to clinical improvement [68]. More recently, data from an open-label multicentre RCT from India have been published. The main outcome measure was a composite endpoint of progression to severe disease or all-cause mortality at 28 days post-enrolment. The administration of CP was not associated with improved outcomes [69]. The major drawback of this study is that the presence and levels of neutralizing antibodies were not measured a priori, and a low titre (less than 1:160) of neutralizing antibodies may be associated with reduced efficacy of CP. A further RCT, the PLACID study, did not detect significant difference between the CP and the placebo group in the distribution of clinical outcomes, and the overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of  $-0.46$  percentage points (95% CI,  $-7.8$  to  $6.8$ ) [70]. Instead, a

recently published RCT found that early administration (within 72 hours after the onset of COVID-19 symptoms) was effective in reducing the risk of progression to severe diseases in a population of elderly patients with COVID-19 [71]. The TSUNAMI trial (NCT04393727) is currently investigating the efficacy and safety of CP units with a titre of  $\geq 1:160$  for the treatment of patients with moderately severe disease, but data are not yet available. The use of CP is approved by the FDA for the treatment of COVID-19 [72].

### Antibiotic therapy in patients with SARS-CoV-2 pneumonia

During the first phase of the coronavirus pandemic, many national and international guidelines on COVID-19 management recommended that empirical antibiotic treatment be considered in all critically ill patients with COVID-19 pneumonia, according to previous data from severe influenza A infection [19,20]. As a consequence, a recently published international survey collecting data on antibiotic use in patients with COVID-19 among 166 participants from 23 countries and 82 different hospitals showed that antibiotic therapy was prescribed in the majority of cases (61.8%). The authors reported a median duration of antibiotic therapy in COVID-19 patients of 5 days in the United Kingdom and North America, and 8 days in Italy [73]. However, the prevalence of bacterial coinfections in COVID-19 seems to be low [74]. A recent systematic review showed that rates of bacterial coinfections reported in patients with COVID-19 appear to be 7%, increasing to 14% in studies that include only ICU patients [75]. These data suggest a significantly lower frequency of COVID-19 coinfections compared to severe cases of 2009's influenza A H1N1 but similar rates to patients with Middle East respiratory syndrome-CoV and SARS-CoV disease [76]. Of interest, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes* appear to be uncommon in patients with COVID-19, while the most common isolated bacteria are *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa* and *Haemophilus influenzae* [77]. A recent study from the United Kingdom showed that the incidence of early confirmed bacterial coinfections (0–5 days after admission) is lower than that superinfections detected during the hospital course [78]. Most superinfections diagnosed in this study were caused by Gram-negative bacilli, including *Enterobacter* spp., *Pseudomonas* spp. and *Serratia* spp [75]. Moreover, data on the prevalence of multidrug-resistant organisms among COVID-19 patients are scarce. Future studies will be crucial to produce robust data about attributable mortality in COVID-19 patients with bacterial coinfections in order to solve the dilemma about the best timing for starting antibiotic therapy in these patients. It is important to underline that without a strong rationale, the indiscriminate use of antibiotics in patients with COVID-19 increases the risk of side effects, drug interactions and selection of multidrug-resistant organisms [79,80].

### Interpretation of data

Recent months have seen a rollercoaster of treatment guidelines for COVID-19 based on published papers and press releases. Indeed, randomized clinical trials and observational studies often gave contradicting results, resulting in sudden changes in the prescribing habits of clinicians and regulatory agencies. A major problem is that the results of important randomized trials have not yet been published, so results are difficult to interpret. Indeed, each one of us has experienced the difficulty of selecting patients to enroll onto randomized trials vs. placebo or standard of care during epidemic waves, and some differences among studies could be due to the characteristics of the selected patients or to the different time points within an epidemic wave.

Because severe COVID-19 has resulted in a mortality of around 20% among hospitalized patients in European countries, it is important to understand which drugs could actually decrease this level of mortality. At present no drug has reached this goal in randomized clinical trials because remdesivir, tocilizumab and sarilumab did not meet the mortality endpoint despite large sample sizes, and the effect on mortality of dexamethasone varied widely according to the level of respiratory support at randomization. For example, patients allocated to dexamethasone receiving oxygen without invasive mechanical ventilation had a mortality rate of 21.5% compared to 25% in the control arm. What it is really needed is information about the exact timing and dose of drug delivery as well as knowledge of the characteristics of the population that could most benefit from each therapeutic intervention. Subanalyses of large randomized trials could help fill some of these gaps.

### Conclusions

On the bases of the evidence, press releases from pharmaceutical companies concerning randomized clinical trials and our everyday clinical experiences (which may differ from trial results), it is difficult to decide what the standard of care should be for patients with COVID-19 severe pneumonia, particularly because of differing inclusion criteria and differing time points within the pandemic. In general we do not suggest the use of protease inhibitors and HCQ in patients with COVID-19 pneumonia. Moreover, the available evidence does not support the systematic prescription of broad-spectrum empirical antimicrobials, which emphasizes the need to develop antimicrobial policies and appropriate stewardship interventions specifically designed for the COVID-19 pandemic.

Concerning the other treatments, because there are conflicting results from clinical trials (such as with tocilizumab and remdesivir), we think that a therapeutic strategy based on a specific sequencing and/or combination of different treatments should be prioritized in future clinical trials. The SIMIT recommendations are a stepwise approach that permits distinguishing standard of care on the basis of respiratory impairment. We suggest that LMWH be provided at a prophylactic dosage in all hospitalized patients with COVID-19. In case of oxygen supplementation, glucocorticoids (preferably dexamethasone) should be started. The use of remdesivir for 5 days and the addition of CP (the latter particularly in patients with mild to moderate illness and  $\text{PaO}_2/\text{FiO}_2$  ratio of 200–350) should be considered with caution and according to the recommendations of regulatory agencies because data suggesting benefit from these strategies are limited, and conclusive RCTs are ongoing. In the absence of clinical and respiratory response (stabilization or increase in  $\text{PaO}_2/\text{FiO}_2$  on day 2 or continuous deterioration) tocilizumab or other immunomodulatory agents such as baricitinib could be taken into consideration. A description of the suggested therapeutic approach is presented in Fig. 1. Finally, as a result of the incomplete evidence in treatment approach of COVID-19, we suggest that all these drugs be considered for use in clinical trials.

### Transparency declaration

The authors declare that they have no conflicts of interest.

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