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

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an emerging zoonotic agent [1] is responsible of new severe acute syndrome called COVID-19 [2]. In Italy, the percentage of infected subjects was greater in the northern regions (particularly in Lombardy, Piedmont and Emilia-Romagna) [3] than in the southern regions and large islands, most probably reflecting the different entity in trade with China among different regions. Since the beginning of the epidemic, the treatment of the first cases relayed on drugs showing some efficacy on other viruses responsible for epidemics, i.e. flu, SARS, Ebola etc, but during the following months recommendations on treatment changed according with evidences from the literature. At present, only a few anti-COVID-19 medications have been approved for the treatment of COVID-19 by regulatory agencies on the basis of randomized controlled trials. Moreover, clinicians who at present are facing either the first or the beginning of the second epidemic wave are influenced in their everyday clinical practice not only by new published study, but also by press releases concerning randomized trials. Aim of present paper is, on the basis of the evidences present in the literature, to recommend as Italian Society of Infectious Disease (SIMIT) on which treatment should to be considered as standard of care of COVID19, with particular attention to severe cases.

Antivirals and hydroxychloroquine therapy

In the first weeks of SARS-CoV-2 pandemic no clinical trials on hydroxychloroquine were available. Regional guidelines of Lombardy, the most affected region in Italy, initially recommended the use of HIV protease inhibitors (lopinavir/ritonavir as first choice, darunavir (DRV)/cobicistat as second one) associated with chloroquine or hydroxychloroquine [4]. Afterwards, the effect of these anti-COVID-19 treatments were evaluated in randomized clinical trials. The first one was performed in China on

199 patients with laboratory-confirmed SARS-CoV-2 and demonstrated, even if underpowered, that no benefit was observed with lopinavir-ritonavir treatment beyond standard of care in hospitalized adult patients [5]. These data were confirmed by the larger RECOVERY trial (Randomised Evaluation of COVID-19 Therapy). A total of 1596 patients were randomized to receive lopinavir/ritonavir and on 25th June 2020 the Steering Committee concluded that there was no beneficial effect of lopinavir/ritonavir in patients hospitalized with COVID-19 and this arm of the study was closed [6]. As regards to DRV/cobicistat no clear clinical evidence supports the use of DRV (boosted with either ritonavir or cobicistat) in viral diseases other than HIV. DRV showed no antiviral activity against SARS-CoV-2 at clinically relevant concentrations (EC50 > 100 μM) in an *in vitro* study [7].

Remdesivir (GS-5734) is a nucleoside analogue prodrug displaying in vitro inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2 [8]. The first trial showed that Remdesivir was superior to placebo in shortening the time to recovery but did not show a significant difference in mortality [9]. 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 [10]. A randomized, open-label, phase 3 trial involving hospitalized patients with confirmed SARS-CoV-2 infection (ClinicalTrials.gov number, NCT04292899) did not show a significant difference between a 5-day course and a 10-day course of remdesivir. By day 14, 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, in patients who did not need mechanical ventilation [11]. Finally, a press release by Gilead, including a comparative analysis of the Phase 3 SIMPLE-Severe trial and a real-world retrospective cohort of patients with severe COVID-19 presented in July at the Virtual COVID-19 Conference as part of the 23rd International AIDS Conference (AIDS 2020: Virtual) stated very promising results of remdesivir in patients with earlier phases of pneumonia [12]. Despite the magnitude of benefit on mortality is still to be defined, FDA and EMA issued an emergency use authorization of the drug for COVID-19 treatment of hospitalized patient with COVID-19 pneumoniae requiring oxygen supplementation [13]. At present remdesivir has not been approved by the Italian Agency AIFA and it is available only for compassionate use.

Two other RNA-dependent polymerase inhibitors are favipiravir and ribavirin, but until today remdesivir showed better efficacy than them [14].

Hydroxychloroquine (HCQ) was one of the first drugs worldwide used to treat COVID-19. HCQ was found to decrease viral replication in a concentration-dependent manner *in vitro* inhibiting the entry step, as well as the post-entry stages of SARS-CoV-2 infection, by changing the glycosylation of the

ACE2 receptor and the spike protein [15]. (the US Company Moreover, HCQ is also known for its modulation of the immune response [16].

The first observational French study (that was subsequently retracted by the Lancet) reported enthusiastic results with HCQ associated to azithromycin for the treatment of COVID-19 [17]. Since then, no clear evidence of the efficacy of this drug against SARS-CoV-2 has been published. At time, we know that HCQ does not substantially reduce symptom severity in outpatients with early, mild COVID-19 [18] and to date there is a dearth of evidence to support the efficacy of HCQ in preventing COVID-19 [19]. Data about efficacy in hospitalized patients are also conflicting leading to rapid change of indications. On June 15, The Food and Drug Administration (FDA) revoked the emergency use authorization that permitted the use of chloroquine and hydroxychloroquine donated to the Strategic National Stockpile to treat certain patients with COVID-19. This decision was made after the publication of a multinational, observational, real-world study of patients with COVID-19 using a regimen containing HCQ or chloroquine that showed not only the absence of benefit, but instead an increase in the risk of ventricular arrhythmias. This study was retracted by the authors (the US Company Surgisphere) since they could not provide the dataset to the journal [20]. A randomized Brazilian study conducted in patients with mild to moderate COVID-19 pneumonia showed no impact on 15-day clinical improvement of HCQ both alone or in combination with azithromycin [21]. Moreover, a press release from RECOVERY trial declared that HCQ showed no difference in 28-day mortality and other clinical endpoints including hospital stay duration compared to standard of care (26% among 1542 patients treated with HCQ vs 24% among those receiving standard of care) [22]. Finally, WHO discontinued both arms, lopinavir/ritonavir and HCQ in the SOLIDARITY trial after an interim analysis showing no benefits of these 2 drugs over standard of care [23].

International guidelines as NIH and IDSA COVID-19 Treatment Guidelines actually recommends against the use of chloroquine or HCQ for the treatment of COVID-19 [24,25].

Anticoagulant therapy

The COVID-19 has been associated with vascular inflammation, endothelial dysfunction and hypercoagulable state that may predispose to hemostatic abnormalities such as disseminated intravascular coagulation (DIC) or thromboembolic disease [26]. This condition has been associated with poor outcomes especially in those patients with severe disease [27]. Anticoagulant therapy may potentially reduce the risk of thrombotic complications and improve clinical outcomes [28]. This has fueled interest in anticoagulant therapy for patients with COVID-19. Moreover, interest in the use of heparin has increased for its anticoagulant and anti-inflammatory activity.

Data from a retrospective study in China showed that anticoagulant therapy with heparin [with low molecular weight heparin (LMWH)] seems to be associated to better outcome reducing 28-day mortality by 20 % in patients with COVID19 and Sepsis-Induced Coagulopathy (SIC) score $\geq$ 4 or D-dimer > 6-fold of upper limit of normal [29]. Moreover, results from a large US Cohort of COVID-19 hospitalized patients suggest that systemic anticoagulant treatment could be associated with improved outcomes, even if this study shows important limitations [30]. These results were confirmed also in a more recently published study which analyzed 4,389 patients hospitalized with COVID-19. The authors found approximately 50% reduced hazard of in-hospital mortality and 30% reduced hazard of intubation compared to patients without anticoagulant therapy. In a sub analysis, comparing to prophylactic dosage, therapeutic anticoagulant treatment was associated with lower in- hospital mortality, although not statistically significant [31].

At present, several randomized controlled trials are ongoing in order to assess doses, risk and benefits of anticoagulant therapy (ClinicalTrials.gov). In the meantime, many scientific societies have released interim guidance for the management of thromboembolism and anticoagulation therapy [32-35]. This is a summary of current recommendations:

1. Deep venous thrombosis (DVT) prophylaxis should be prescribed for all hospitalized non-pregnant 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 or unfractionated heparin may be preferred over oral anticoagulant therapy in hospitalized patients with critical disease because of their shorter half-lives, best route of administration (intravenously or subcutaneously), less drug-drug interactions.
2. For non-critically hospitalized patients a standard dose of LMWH is recommended.
3. For severe-critical patients, an Intermediate-dose LMWH (i.e., enoxaparin 40 mg subcutaneous twice daily, enoxaparin 0.5 mg/kg subcutaneous twice daily, heparin 7500 units subcutaneous 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., BMI > 30, previous DVT, active cancer, large increase in D-dimers, severe inflammation, signs of imminent respiratory failure etc.)
4. Therapeutic dosage of LMWH is not supported by evidence outside of proven DVT
5. The treatment duration recommended is until hospital discharge and at least 7-14 days
6. Standard risk for bleeding should be considered before starting anticoagulant therapy assessing individual potential advantages.

Anti-inflammatory drugs

SARS-CoV-2 infection may cause a host hyper immune response that is associated with the most severe clinical pictures as ARDS or coagulopathy [36]. In particular, patients may develop a so-called "cytokine storm", characterized by the increase of many cytokines, mainly IL-1, IL-6, similar to that developing after chimeric antigen receptor T-cell treatment (CAR-T) [37]. Cytokine blocking agents are effective treatments in post- CAR-T cytokine storm and this constituted the rational for the use of these drugs in severe COVID-19 patients [38].

Tocilizumab is a recombinant humanized monoclonal antibody, of the IgG1 class, directed against both the soluble and the membrane bound IL-6 receptor [39]. Several observational studies have shown promising results [40-45]. In particular, a large retrospective cohort study has been conducted on 544 patients with severe SARS-CoV-2 pneumonia on patients treated with 2 doses both intravenous and subcutaneous formulations. Criteria used to prescribe tocilizumab were: oxygen saturation <92% in room air and a PaO2/FiO2 <250 mmHg or a decrease in PaO2/FiO2 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 SOFA score (aHR=0.61, 95% CI:0.40-0.92; p=0.02). The impact on 14-day mortality was greater with 73 (20%) patients in the standard care group dying, compared with 13 (7%; p<0.001) patients treated with tocilizumab [42]. Moreover, promising results were also obtained in another two Italian cohort of COVID-19 hospitalized patients from Milan and among critical patients admitted to intensive care unit [43-45]. These results were obtained in patients with severe pneumonia, while the scenario could be completely different in those with a less severe disease. Indeed, a press release from the Italian Medicine Agency (AIFA) on a randomized multicenter study (early discontinued) comparing tocilizumab to standard of care claimed that there was no difference between the 2 arms, but mortality was only 3 % in the standard of care arm [46]. A systematic review and meta-analysis conducted by Zhao at al. including all studies demonstrated the efficacy of tocilizumab treatment in severely ill COVID-19 patients, despite the limitations due to the retrospective design of the studies examined [47]. Recently, ROCHE press release stated that their phase III double-blind randomized trial on safety and efficacy of tocilizumab in patients with severe pneumonia did not meet neither the primary endpoint of clinical improvement nor the secondary on mortality (19.7% vs 19.4 % with placebo), but sub-analyses are ongoing [48]. Results from other randomized trials will be available soon.

A recent press release from Sanofi stated that sarilumab, another IL-6 antagonist failed the primary endpoint in a randomized trial [49].

Another therapeutic target could be IL-1. Anakinra is an interleukin (IL)-1 receptor antagonist that blocks activity of the proinflammatory cytokines IL-1α and IL-1β and is used to treat auto-

inflammatory disorders at a daily dose of 100 mg subcutaneously in adult patients [50]. At present, data from randomized controlled trials are not available, nevertheless small clinical studies have been published showing an advantage of high doses of anakinra [51-53].

Concerning possible side-effects of immunomodulatory drugs, Tocilizumab was associated with an increased risk of infectious complications when compared to standard of care. In particular, 24 (13%) of 179 patients treated with tocilizumab were diagnosed with new other infections, versus 14 (4%) of 365 patients treated with standard of care alone ($p<0.001$) [42]. The most worrisome infection was herpes simplex re-activation determining a fulminant hepatitis [54]. This finding is in contrast with those among patients undergoing CAR-T patients who did not show an increase risk of infections [55]. The few patients treated with anakinra were evaluated only for the risk of developing bacteremia and there was no difference when compared to patients receiving standard treatment [51].

Janus kinase (JAK) 1/2 inhibitors have been also proposed as attractive candidates to treat COVID-19 due to their properties as anti-inflammatory agents and their hypothesized off-target antiviral effect against SARS-Cov-2 [56-57]. The most interesting drug of this group is baricitinib, and preliminary experience demonstrated a high rate of recovery in COVID-19 patients receiving this drug [58]. Randomized clinical trials on the use of baricitinib for patients with COVID-19 are ongoing. Other immunomodulators are currently studied as interferon Beta and Bruton's tyrosine kinase inhibitors [59, 60].

Concerning immunomodulatory drugs, all international guidelines agree to recommend their use only in the contest of clinical trials [24,25].

Finally, an important role among anti-inflammatory drugs should be played by glucocorticoids. Indeed, these molecules act as a wider immune modulator than the single cytokine blockers [61, 62]. At beginning of the epidemic, the use of these drugs was somehow discouraged. Indeed, until August 2020, WHO recommended against the routine use of corticosteroids in patients with COVID-19 for treatment of viral pneumonia or ARDS unless indicated for another reason [63]. A recent publication of the randomized RECOVERY Trial conducted in UK forced a review of this position [6]. The RECOVERY trial showed that Dexamethasone at the dose of 6 mg given once daily for up to ten days compared to standard of care reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; $p<0.001$), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; $p=0.002$), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; $p=0.14$) [64]. To date, on the basis of these results and reviewed evidence from other preliminary data from seven RCTs evaluating systemic corticosteroids versus usual care in COVID-19, all international guidelines strong 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 recommend not to use corticosteroid therapy in patients with non- severe COVID-19 not receiving respiratory support [65-66].

Convalescent plasma

Another potential therapeutic strategy for patients with SARS-Cov-2 infection is passive transfer of neutralizing antibodies using plasma from recovered patients with COVID-19. There is evidence that over 99% of patients with laboratory-confirmed SARS-Cov-2 infection develop a detectable antibody response, and the 88% of them present neutralizing antibodies [67]. Safety and tolerability of the administration of convalescent plasma seem to be reassuring, indeed a large observational study on more than 5000 patients receiving convalescent plasma showed an incidence of serious adverse events in the first 4 hours of infusion below 1% [68]. Concerning efficacy, the observational study conducted on 138 patients from China showed that 70% of patients with severe respiratory impairment improved and removed oxygen supports within 7 days from infusion. The beneficial effect was significantly higher among patients who received the convalescent plasma within 7 weeks from the onset of symptoms [69]. Promising results were reported also from a single-arm Italian study showing a beneficial effect of convalescent plasma on 7-day hospital mortality compared to expected mortality from the National Statistics in Italy [70]. More recently, results from an underpowered randomized trial did not show a significant shortening in time to clinical improvement [71]. Finally, a pre-print not peer-reviewed large observational study on 35322 hospitalized patients with COVID-19 found that the early infusion of convalescent plasma was associated with improved 7- and 30-day mortality [72]. Even if the study is not yet published, on the basis of these results FDA approved the use of convalescent plasma against SARS-CoV-2 [73].

Antibiotic therapy in patients with SARS-Cov-2 pneumonia

It is very important to assess the relationship between SARS-CoV-2 and the effective risk of bacterial coinfections and superinfections. This allows to better define the appropriate role of antibiotic therapy (such as macrolides or fluoroquinolones or anti-staphylococcal beta-lactams) in patients with SARS-CoV-2 pneumonia. Undoubtedly, many national and international guidelines on COVID-19 management and treatment recommended to consider empirical antibiotic treatment in all critically ill patients with COVID-19 pneumonia due to the fear of co-existing undiagnosed bacterial infections

(24,25,74). Indeed, differential diagnosis is complicated since inflammation signs and symptoms, often related to the cytokine storm rather than to a bacterial co-infection, could lead to overestimate the superinfections [75]. Finally, the lack of efficacious licensed therapies to treat COVID-19 has led physicians to consider and use drugs based on modulating the immune response, such as anti-inflammatories, as IL-1 and IL-6 which might impact on the risk of superinfections [76]. As a consequence, several studies reported that 80-100% of COVID-19 patients received at least one antibiotic course during hospital stay [77]. These rates were confirmed also in a recently published European survey collecting data on antibiotic use in patients with COVID-19 among 166 participants from 23 countries and 82 different hospitals. Local guidelines for antibiotic use in COVID-19 patients were reported by 61.8% of participants and for 82.9% they did not differ from local community-acquired pneumonia guidelines [78]. The authors reported a median duration of antibiotic therapy in COVID-19 patients of 5 days in the UK and North America, and even more, 8 days in Italy [76]. A review of the medical literature was conducted in order to explore commonly reported bacterial/fungal co-infections in patients admitted to hospital with coronavirus, not only SARS_CoV-2, lower respiratory tract infections. The study showed a prevalence of bacterial co-infections ranging from 5 to 27%, thus not supporting the large use of antibiotics [79]. Moreover, a recent systematic review shows that rates of bacterial co-infections reported in patients with COVID-19 appear to be 7%, increasing to 14% in studies that include only ICU patients [80]. These data suggest a significant lower frequency in COVID-19 co-infections compared to severe cases of 2009 influenza A H1N1 but similar rates comparing patients with MERS-CoV and SARS-CoV disease [81]. Of interest, differently from influenza, *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* [80]. These data should be interpreted with caution since the prevalence of selected bacteria may be influenced by the microbiology technique adopted in the single hospital and the peculiar epidemiology of a geographic area [82]. A recent study from UK showed that the incidence of early confirmed bacterial coinfections (0-5 days post-admission) is lower than that superinfections detected during the hospital course [83]. Most super-infections diagnosed in this study were caused by Gram negative bacilli (GNB) including *Enterobacter* spp, *Pseudomonas* spp. and *Serratia* spp [80]. Moreover, data on the prevalence of MDROs among COVID-19 patients are scarce. Future studies will be crucial to produce robust data about attributable mortality in COVID-19 patients with bacterial co-infections, in order to solve the dilemma about the best timing for starting antibiotic therapy in these patients. It 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 [84].

Indeed, a position paper of the ESCMID Study Group for Antimicrobial Stewardship (ESGAP), warning against non-critical use of antibiotics in COVID-19 patients suggests some practical recommendations inviting to strengthen the basic principles of the antimicrobial stewardship [85].

Interpretation of the data

In the recent months, treatment guidelines for COVID-19 based of published papers and press releases were similar to a rollercoaster. Indeed, randomized clinical trials and observational studies gave often contradicting results changing at a sudden the prescribing attitude of clinicians and of regulatory agencies. A major problem is represented by the fact that important randomized trials as the COVACTA, have not been published, so far, thus results are difficult to be interpreted. Indeed, each one of us has experienced how hard it is to select patients to enroll in randomized trials vs placebo or standard of care during the epidemic waves and some differences among studies could be due to the characteristics of the selected patients. In the meantime, while waiting for more definitive data on the best treatment for COVID-19, clinicians usually continue to treat patients affected by a new disease at first on the basis of their personal experience. Moreover, it is to be underlined that, since severe COVID-19 has shown a mortality of around 20% at our latitude, 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, since remdesivir, tocilizumab and sarilumab did not meet the mortality endpoint despite large sample size and dexamethasone showed to be effective either in ventilated or non-ventilated patients but the best performing arm of this RECOVERY trial showed a mortality of 21.5%. Indeed, , what it is really needed is the exact timing, doses of the drugs and the characteristics of the population who could benefit the most of each therapeutic intervention and the sub-analyses of large randomized trials could help in filling some of these gaps.

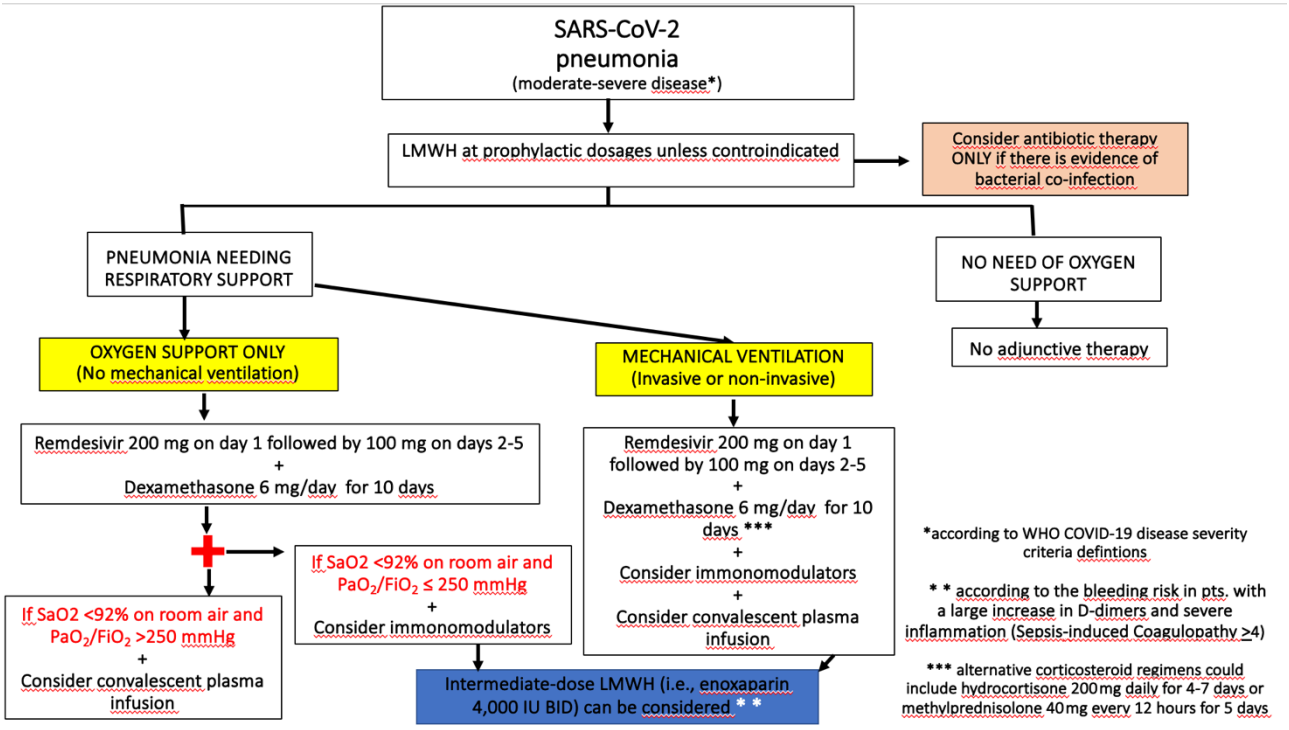
Conclusions

On the basis of all these evidences, press release of pharmaceutical companies concerning randomized clinical trials and on our everyday clinical experiences that may differ from trial results it will be difficult to decide which could be the standard of care of patients with COVID-19 severe pneumonia. In general, we do not recommend the use of protease inhibitors and hydroxychloroquine in patients with severe COVID-19 pneumonia, Moreover, the available evidence does not support the

systematic prescription of broad-spectrum empirical antimicrobials, and underlines the need to develop antimicrobial policies and appropriate stewardship interventions specifically designed for the COVID-19 pandemic.

The SIMIT recommendations are a stepwise approach in order to distinguish standard of care on the basis of respiratory impairment. We recommend remdesivir for 5 days (if rapidly available for a large number of patients) and prophylactic dosage LMWH in all hospitalized patients. In case of oxygen support steroids should be started and eventually convalescent plasma should be considered when available. In the absence of clinical and respiratory response (stabilization or increase in PaO2/FiO2 on day 2 or continuous deterioration) tocilizumab or other immune-modulatory agents should be prescribed. A description of the recommended therapeutic approach is presented in Figure 1.

FIGURE A.



Suggested Flow Chart for the treatment of severe cases of COVID-19. The use of remdesivir will depend on AIFA approval.

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