



Position paper

Balancing evidence and frontline experience in the early phases of the COVID-19 pandemic: current position of the Italian Society of Anti-infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)

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ABSTRACT

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which has rapidly become epidemic in Italy and other European countries. The disease spectrum ranges from asymptomatic/mildly symptomatic presentations to acute respiratory failure. At the present time the absolute number of severe cases requiring ventilator support is reaching or even surpassing the intensive care unit bed capacity in the most affected regions and countries.

Objectives: To narratively summarize the available literature on the management of COVID-19 in order to combine current evidence and frontline opinions and to provide balanced answers to pressing clinical questions.

Sources: Inductive PubMed search for publications relevant to the topic.

Content: The available literature and the authors' frontline-based opinion are summarized in brief narrative answers to selected clinical questions, with a conclusive statement provided for each answer. **Implications:** Many off-label antiviral and anti-inflammatory drugs are currently being administered to patients with COVID-19. Physicians must be aware that, as they are not supported by high-level evidence, these treatments may often be ethically justifiable only in those worsening patients unlikely to improve only with supportive care, and who cannot be enrolled onto randomized clinical trials. Access to well-designed randomized controlled trials should be expanded as much as possible because it is the most

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which has rapidly become epidemic in Italy and other European countries [1–3]. The disease spectrum ranges from asymptomatic/mildly symptomatic presentations to acute respiratory failure, with the true proportion of severe cases still remaining partly unclear as a result of an incomplete denominator and a possible lack of adjustment for relevant confounding factors [4,5]. Nonetheless, of particular clinical concern at the present time is not the relative frequency of severe cases in patients requiring ventilation support, but rather their absolute number, which is reaching or even surpassing the intensive care unit (ICU) bed capacity in the most affected regions and countries [6].

From this perspective, in addition to the important prevention and restrictive measures implemented for reducing transmission [7], it remains crucial to optimize the therapeutic management of symptomatic patients requiring noninvasive oxygen therapy in order both to improve the absolute cure rates and to reduce and prevent the need for ICU admission. However, the lack of high-level evidence, inherent to the novelty and rapid spread of COVID-19, has led to the adoption of heterogeneous approaches worldwide, often without a clear distinction between the relative weight of available evidence and expert opinion in informing therapeutic choices.

In this narrative review, we sought to summarize the available evidence on important therapeutic questions we are continuously facing as clinicians caring for COVID-19 patients in Italy, trying to find a balance between current evidence, frontline experiences and expert opinions.

Methods

Members of a panel of 17 experts from the Italian Society of Anti-infective Therapy (SITA) and the Italian Society of Pulmonology (SIP) were selected; they developed a list of 8 practical therapeutic questions to be addressed. The members of the panel (which included infectious diseases specialists and pneumonologists) were divided into small groups and asked to summarize the available literature and their frontline-based opinion in brief (500 words maximum) narrative answers, plus a conclusive statement for each answer. All the answers and statements were ultimately reviewed and discussed by the entire panel until a consensus was reached. A brief summary of questions and conclusive statements is available in [Table 1](#). [Table 2](#) summarizes available or ongoing randomized controlled trial (RCT) information for off-label/compassionate-use drugs mostly used for the treatment of COVID-19 patients. Of note, we focused on pneumologic and anti-infective/anti-inflammatory treatments; the discussion of the therapeutic approach to COVID-19-related cardiovascular/coagulative disorders is outside the scope of this narrative review.

Question 1. how to use at best oxygen therapy and noninvasive mechanical ventilation for preventing intubation?

In moderate to severe cases, COVID-19 usually presents as a lung disease (mostly in the form of bilateral interstitial pneumonia)

causing hypoxic respiratory failure and requiring passive oxygen therapy. The prevalence of hypoxic respiratory failure in patients with COVID-19 may be as high as 19% [8]. In observational studies conducted in China, 4% to 13% of COVID-19 patients received noninvasive positive pressure ventilation, and 2.3% to 12% required invasive mechanical ventilation [8–10].

In general, oxygen treatment should be provided to patients with shortness of breath or hypoxaemia, or those in shock, which is aimed at maintaining an appropriate level of peripheral capillary oxygen saturation (SpO_2), avoiding values of SpO_2 lower than 90% (92–95% in pregnant women). During oxygen supplementation, SpO_2 should not surpass 96% [11].

An alternative to conventional oxygen supplementation is supplementation through high-flow nasal cannula (HFNC). HFNC is an oxygen supply system that provides a mixture of air and oxygen with a known concentration. HFNC provides high concentrations of humidified oxygen and low levels of positive end-expiratory pressure; it can also facilitate the elimination of carbon dioxide, thereby potentially reducing the need for intubation compared to standard oxygen supplementation [12–14]. However, it should also be considered that there are no standard evidence-based guidelines for the use of HFNC and that the experience in patients with COVID-19 is still limited (and without adjusted comparison to standard oxygen supplement) to provide universal recommendations, at least pending further data [9]. Other relevant things to be considered are: (a) HFNC should be used in settings with rapid availability of endotracheal intubation in the case of rapid deterioration [15]; and (b) the possible increased risk of contracting the infection for healthcare personnel as a result of aerosol generation should be appropriately managed (HFNC should be used in negative-pressure rooms) [16]. These two considerations also apply to continuous positive airway pressure (CPAP) with helmet (the most frequent system of noninvasive mechanical ventilation used in real life), which can be considered if the patient does not respond to standard or HFNC oxygen supplementation (i.e. if the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) has a decreasing trend) and there is no urgent indication for endotracheal intubation. As for HFNC, also in the case of CPAP with helmet, close monitoring and short interval assessment for worsening of respiratory failure are mandatory. In addition, it should be necessarily noted that although CPAP with helmet has become an established procedure for primary hypoxemic lung failure in the last few years, some experts do not support its use for COVID-19 [15], arguing that success rates in critically ill COVID-19 patients may be limited and there could be a risk of delayed intubation unfavourably influencing the outcome. However, considering the atypical physiopathology of acute lung injury in patients with COVID-19 [17], gentle ventilation with a positive end expiratory pressure (PEEP) not higher than 10 to 12 cm of water may represent a reasonable approach for avoiding excessive damage during CPAP with helmet and possibly also the need for intubation. Large studies, possibly RCT, are urgently needed to definitely clarify the precise role of CPAP with helmet in patients with COVID-19. Finally, borrowing from what is already known and used in intensive care, pronation, although certainly more difficult to implement during noninvasive than invasive mechanical ventilation, may allow

Table 1
Summary of questions and statements

Question	Statement
Question 1. How to use at best oxygen therapy and noninvasive mechanical ventilation for preventing intubation?	Supplementary oxygen should be administered to patients with hypoxic respiratory failure for avoiding values of SpO ₂ lower than 90% and it should be aimed at reaching values not higher than 96%. Although still without firm evidence, we currently support the use of CPAP helmet (with gentle ventilation and a PEEP of no more than 10–12 cm of water) if the patient does not respond to standard/HFNC oxygen supplementation and there is no urgent indication for endotracheal intubation (expert opinion). However, no clear indications/criteria can be provided pending further experience. Finally, it should be kept in mind that patients with COVID-19 can get worse in a few hours, so they should be carefully monitored for worsening respiratory function for rapidly prompting tracheal intubation and mechanical ventilation.
Question 2. Should antiviral agents be administered?	At the present time, evidence from the first published RCT does not support off-label treatment with LPV/RTV in COVID-19 patients. This result should also discourage the use of other protease inhibitors (e.g. darunavir), at least until results of dedicated RCT are available. Although promising in preclinical studies, remdesivir should be currently provided to COVID-19 patients only within RCT (preferentially) or compassionate-use/expanded-access programmes, owing to its investigational nature. Pending high-level supporting evidence, favipiravir and umifenovir should not be provided an outside RCT, at least in those countries where they are not approved for other indications. Oseltamivir or zanamivir should be provided only in the presence of suspected/proven concomitant influenza.
Question 3. Should chloroquine/hydroxychloroquine be administered?	Pending results of RCT, the use of hydroxychloroquine may be considered for treating worsening patients with COVID-19 only if no important drug interactions can be anticipated and with close monitoring of hepatic, renal function and QT prolongation. This is based on its activity <i>in vitro</i> against SARS-CoV-2 (although weak) and on the availability of low-level clinical evidence of anticipation of virus clearance from a small controlled, nonrandomized study. However, it should also be kept in mind that the study was highly susceptible to bias and there are still no data regarding hard clinical endpoints such as crude mortality. For these reasons, hydroxychloroquine should be preferentially administered within the framework of investigational studies. When this is unfeasible, off-label use may be considered according to local protocols and consent procedures. In view of the absence of evidence, we are currently unable to support the use of hydroxychloroquine in asymptomatic or mildly symptomatic nonhospitalized patients outside investigational studies. The same applies to prophylactic use.
Question 4. Should antibiotics be administered?	In our opinion, it might be prudent to consider empiric antibiotic treatment in critically ill patients with pneumonia due to COVID-19 in whom bacterial infection cannot be excluded. This suggestion is based on the fact that bacterial coinfection (a) is common in patients with viral pneumonia and (b) can be associated with a substantial risk of delaying appropriate treatment, thereby potentially increasing mortality. Because of the limited available data on both the microbiologic epidemiology (and the prevalence of antimicrobial resistance) of bacterial superinfections in COVID-19 patients, it is difficult to provide specific pathogen-oriented recommendations. Therefore, pending further studies, we suggest to empirically treat COVID-19 patients according to their clinical syndrome (e.g. community-acquired pneumonia, hospital-acquired pneumonia), choosing the best antimicrobial agent or agents on the basis of local guidelines and local antibiotic susceptibility patterns, with early de-escalation or discontinuation according to microbiology results, whenever available.
Question 5. Should steroids be administered?	So far, no definitive efficacy or effectiveness data are available on the benefit of corticosteroid administration in patients with SARS-CoV-2 infection. As the WHO underlines, there is an important need for efficacy data from RCT for supporting corticosteroid therapy in patients with SARS-Cov-2. However, considering that overwhelming inflammation and cytokine-related lung injury might be responsible for rapidly progressive pneumonia and clinical deterioration in COVID-19 patients, we suggest (expert opinion only) to consider administration of corticosteroids in critically ill COVID-19 patients with ARDS or with worsening of non-ARDS respiratory failure in the absence of bacterial/fungal superinfections (independent of ICU admission). Yet in the absence of convincing evidence, the following cannot currently be supported: (1) steroid administration stratified according to inflammatory markers; and (b) steroid administration in non-critically ill COVID-19 patients.
Question 6. Should other immunosuppressive and/or immunomodulatory therapies be administered?	Owing to the lack of high-level evidence, administration of tocilizumab to patients with COVID-19 should preferentially occur within the framework of RCT. Off-label use according to local protocols and consent procedures may be considered only in those COVID-19 patients excluded from RCT (or hospitalized where RCT are not available or still to be implemented) and who are worsening while receiving standard supportive care (in the absence of concomitant/superimposed infections). In our opinion, this could be a reasonable off-label use of tocilizumab in these early phases of the COVID-19 pandemic, although patients and physicians should be aware that currently there is only a non-peer-reviewed, noncomparative, observational experience (very low evidence from an unreviewed cases series) and that it only supports a potential favourable effect on inflammatory signs and symptoms, while there is no information on any possible effect on survival. In the absence of clinical studies, we suggest to preferentially administer also other immunosuppressive and/or immunomodulatory therapies (e.g. anakinra, Janus kinase family enzyme inhibitors) within RCT. This also applies to modifications of the immune response through high-dose intravenous immunoglobulins or plasma from convalescent patients, which, although promising in small case series, both deserve dedicated RCT investigation to clearly understand their role in impacting COVID-19 outcomes and their tolerability.
Question 7. What is the optimal timing of treatment initiation?	Supportive therapy (symptomatic therapy, rehydration and oxygen supplementation, if necessary), should be initiated as soon as the patient manifests respiratory or systemic symptoms, including severe asthenia, high fever, persistent cough and/or clinical or radiologic signs of lung involvement. Pending further evidence, in our opinion, antiviral treatments should not be provided to patients with SARS-CoV-2 infection outside RCT or compassionate-use programmes (with the exception of early oseltamivir initiation in patients with suspected concomitant influenza). Corticosteroids should be provided early in well-defined categories of patients (patients with ARDS or with worsening of non-ARDS respiratory failure in the absence of bacterial/fungal superinfections), while their role in other COVID-19 patients still remains uncertain. Although based on low-level evidence and pending RCT results, in our opinion, early hydroxychloroquine administration may be considered in COVID-19 patients manifesting

Table 1 (continued)

Question	Statement
Question 8. What is the optimal treatment duration?	<p>moderate to severe symptoms, whereas further data are needed to better delineate the true balance between possible favourable effects and toxicity of hydroxychloroquine in mildly symptomatic and asymptomatic patients.</p> <p>Chloroquine/hydroxychloroquine treatment should be continued for at least 5 days, and possibly up to 20 days, according to some expert opinions, although it should be noted that data regarding the relative safety of different lengths of administration in COVID-19 patients are currently unavailable. Early discontinuation should be considered in the presence of adverse effects (e.g. QT prolongation or hepatic/renal toxicity). If the administration of remdesivir is approved within compassionate-use/expanded-access programmes, treatment duration should follow compassionate or expanded access protocols (e.g. up to 10 days according to the most recent compassionate protocol at the time of this review). If corticosteroids are provided, we suggest a total treatment duration of 7–10 days, with progressive dose reduction. If the patient's condition deteriorates with worsening lung physiology after withdrawal of steroid treatment in the absence of bacterial or fungal superinfection, a second course of corticosteroid treatment may be considered, followed by slow tapering after improvement.</p>

ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; ICU, intensive care unit; LPV/RTV, lopinavir/ritonavir; PEEP, positive end expiratory pressure; RCT, randomized controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

improved gas exchange and decreased respiratory distress, and may also promote lung recruitment [18].

Question 1 statement

Supplementary oxygen should be administered to patients with hypoxic respiratory failure for avoiding values of SpO_2 lower than 90%, and it should be aimed at reaching values not higher than 96%. Although still without firm evidence, we currently support the use of CPAP helmet (with gentle ventilation and a PEEP of no more than 10–12 cm of water) if the patient does not respond to standard/HFNC oxygen supplementation and there is no urgent indication for endotracheal intubation (expert opinion). However, no clear indications/criteria can be provided pending further experience. Finally, it should be kept in mind that patients with COVID-19 can get worse in a few hours, so they should be closely monitored for worsening respiratory function so that tracheal intubation and mechanical ventilation can be quickly performed if needed.

Question 2. should antiviral agents be administered?

Several antiviral agents have demonstrated *in vitro* activity against SARS-CoV-2 or other coronaviruses, but currently there are no approved antiviral agents for coronavirus-related diseases, and there are still no favourable efficacy results from RCT available at the present time. Lopinavir, a protease inhibitor used for the treatment of HIV patients, administered in combination with ritonavir to improve its serum half-life. On the basis of its activity against SARS-CoV-1 and/or Middle East respiratory syndrome (MERS)-CoV observed in *in vitro* and animal studies [19–21], lopinavir/ritonavir (LPV/RTV) was compared to supportive care alone for the treatment of COVID-19 patients in an open-label RCT in China [22]. The primary time-to-event endpoint was clinical improvement from randomization (defined as a composite of discharge from the hospital or improvement of two points on a seven-category ordinal scale, ranging from no need of hospitalization to death). Overall, 199 patients were enrolled (99 and 100 in the LPV/RTV and supportive care arms, respectively). No differences were observed in the intent-to-treat population with regard to clinical improvement (hazard ratio 1.24 with standard of care as reference, 95% confidence interval (CI) 0.90 to 1.72). In addition, no associations were observed with regard to 28-day mortality, although a smaller number of deaths were registered in the LPV/RTV arm (19.2% vs. 25.0% in investigational and comparator arms, respectively; percentage difference –5.8%, 95% CI –17.3 to 5.7).

Although some important considerations preclude a definite judgement on the possible efficacy of LPV/RTV (e.g. some major limitations are the open-label nature of the trial and the fact that LPV/RTV was initiated late with respect to the onset of symptoms; see question 7), especially in the case of early therapy initiation, the results of this RCT provide evidence currently discouraging the use of LPV/RTV (or of other protease inhibitors such as darunavir) in COVID-19 patients (also considering the potential side effects; Table 3), unless favourable results from other ongoing RCT in specific subgroups of patients are available (Table 2). Furthermore, harmful drug interactions of antivirals with other drugs (such as hydroxychloroquine) cannot be excluded *a priori* because there are currently no large clinical data about the use of these combinations.

Remdesivir is an investigational nucleotide analogue undergoing clinical development for Ebola and showing *in vitro* activity against coronaviruses (SARS-CoV-2, SARS-CoV-1 and MERS-CoV) and favourable effects in animal MERS models [23–26]. Following these promising preclinical findings, RCT in COVID-19 patients have been initiated (Table 2). However, pending their results, and considering the investigational nature of the drug, access to remdesivir outside RCT is currently provided only within strictly regulated and limited compassionate-use/expanded-access frameworks.

Oseltamivir and zanamivir are neuraminidase inhibitors used for treating influenza which are also being tested in RCT for treating COVID-19 patients (Table 2). However, no apparent activity of oseltamivir and zanamivir has previously been observed against SARS-CoV-1 *in vitro* [27], and the fact that up to 76% of the first critically ill patients with COVID-19 received oseltamivir may also be related to the suspicion of infection (or coinfection) with influenza [28]. Overall, this information is currently insufficient for supporting the use of these agents in COVID-19 patients unless in the presence of suspected/proven concomitant influenza.

Other antiviral agents currently being investigated in RCT for the treatment of COVID-19 patients are favipiravir, an RNA-dependent RNA polymerase inhibitor with anti-influenza activity, and umifenovir, and anti-influenza membrane fusion inhibitor [29]. Even though these two agents attracted important media attention in the last few months, and even though there were some favourable preliminary results, especially for favipiravir, released as preprints, we advocate caution in using these agents outside investigational studies until completion of the standard peer-review processes of the first released trials. For example, in a recent RCT comparing 120

Table 2
Available and ongoing RCT on anti-infective and anti-inflammatory drugs most provided as off-label/compassionate treatments in the first phase of the COVID-19 pandemic

Drug	Class/mechanism	Published RCT	Ongoing RCT for treatment/prevention of COVID-19 (recruiting or not yet recruiting) registered at ClinicalTrials.gov
Lopinavir/ritonavir	Lopinavir is an HIV type 1 protease inhibitor. Ritonavir is a CYP3A4 inhibitor that boosts lopinavir concentrations	<ul style="list-style-type: none"> Open-label RCT comparing lopinavir/ritonavir (99 patients) vs. standard of care (100) in patients with COVID-19 in China. Lopinavir/ritonavir was administered at the dosage of 400/100 mg for 14 days. The primary time-to-event endpoint was clinical improvement from randomization. In the primary study population (ITT), no statistically significant differences were observed with regard to the primary endpoint of clinical improvement (HR 1.24 with standard of care as reference, 95% CI 0.90 to 1.72) and the secondary endpoint of 28-day mortality (19.2% vs. 25.0% in investigational and comparator arms, respectively; percentage difference –5.8%, 95% CI –17.3 to 5.7). In the mITT population, lopinavir/ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care. Median time between symptoms onset and randomization was 13 days (IQR 11–16) [22] 	<ul style="list-style-type: none"> Comparison of lopinavir/ritonavir vs. hydroxychloroquine in patients with mild COVID-19. Open-label RCT (NCT04307693, recruiting). Primary endpoint: virus load at day 3, 5, 7, 10, 14 and 18. Comparison of ASC09/ritonavir vs. lopinavir/ritonavir in patients with confirmed COVID-19 pneumoniae. Open-label RCT (NCT04261907, not yet recruiting). Primary endpoint: adverse outcome at day 14 (composite of $SpO_2 \leq 93\%$ without oxygen supplementation, $PaO_2/FiO_2 \leq 300$ mm Hg or respiratory rate ≥ 30 breaths per minute). Comparison of lopinavir/ritonavir vs. lopinavir/ritonavir plus umifenovir in patients with COVID-19. Open-label RCT (NCT04252885, recruiting). Primary endpoint: rate of virus inhibition at day 0, 2, 4, 7, 10, 14 and 21. Comparison of lopinavir/ritonavir vs. lopinavir/ritonavir plus ribavirin plus interferon beta 1b in patients with COVID-19. Open-label RCT (NCT04276688, recruiting). Primary endpoint: time to negative nasopharyngeal swab RT-PCR (follow-up 30 days). Comparison of only supportive treatment vs. lopinavir/ritonavir vs. oseltamivir vs. umifenovir in patients with confirmed COVID-19 pneumonia. Open-label RCT (NCT04255017, recruiting). Primary endpoints: (a) rate of disease remission (mild disease: fever, cough and other symptoms relieved with improved lung CT; severe disease: fever, cough and other symptoms relieved with improved lung CT, $SpO_2 > 93\%$ or $PaO_2/FiO_2 > 300$ mm Hg); (b) time to lung recovery. Comparison of chemoprophylaxis with lopinavir/ritonavir vs. placebo in healthcare workers exposed to COVID-19. Double-blind RCT (NCT04328285, not yet recruiting). Primary endpoint: occurrence of a symptomatic or asymptomatic COVID-19 (follow-up 2.5 months). Comparison of carrimycin vs. lopinavir/ritonavir or umifenovir or chloroquine in patients with COVID-19 pneumonia. Open-label RCT (NCT04286503, not yet recruiting). Primary endpoints: (a) fever to normal time (follow-up 30 days); (b) pulmonary inflammation resolution time (follow-up 30 days); (c) negative conversion of throat swab RT-PCR at EOT. Comparison of lopinavir/ritonavir vs. lopinavir/ritonavir plus xiyanning (injectable component derived from a plant used in traditional Chinese medicine) in patients with COVID-19. Open-label RCT (NCT04295551, not yet recruiting). Primary endpoint: clinical recovery time (follow-up 28 days). Comparison of lopinavir/ritonavir plus inhaled interferon alfa vs. lopinavir/ritonavir plus inhaled interferon alfa plus xiyanning injection in patients with COVID-19. Open-label RCT (NCT04275388, not yet recruiting). Primary endpoint: clinical recovery time (follow-up 14 days). Comparison of lopinavir/ritonavir plus inhaled interferon alfa vs. lopinavir/ritonavir plus inhaled interferon alfa plus traditional Chinese medicines in patients with COVID-19. Open-label RCT (NCT04251871, recruiting). Primary endpoint: time to complete remission of symptoms (follow-up 28 days). Comparison of lopinavir/ritonavir plus hydroxychloroquine vs. lopinavir/ritonavir plus hydroxychloroquine plus levamisole pill plus budesonide plus formoterol inhaler in patients with nonsevere COVID-19 pneumonia. Partly blinded RCT (NCT04331470, not yet recruiting). Primary endpoint: (a) clear CT scan at 3–7 days; (b) negative RT-PCR at 3–7 days. Comparison of lopinavir/ritonavir vs. hydroxychloroquine vs. losartan vs. placebo in patients with COVID-19. Double-blind, adaptive RCT (NCT04328012, not yet recruiting). Primary endpoint:

Table 2 (continued)

Drug	Class/mechanism	Published RCT	Ongoing RCT for treatment/prevention of COVID-19 (recruiting or not yet recruiting) registered at ClinicalTrials.gov
Remdesivir	Adenosine analogue. It binds to RNA-dependent RNA polymerase and acts as an RNA-chain terminator	<ul style="list-style-type: none"> • Not available 	<p>NIAID COVID-19 ordinal severity scale (follow-up 60 days).</p> <ul style="list-style-type: none"> • Comparison of lopinavir/ritonavir vs. hydroxychloroquine vs. lopinavir/ritonavir plus interferon beta 1a vs. remdesivir vs. standard of care in patients with COVID-19. Double-blind, adaptive RCT (NCT04315948, recruiting). Primary endpoint: severity rating on a 7-point ordinal scale at day 15. • Comparison of lopinavir/ritonavir or umifenovir or chloroquine or hydroxychloroquine or oseltamivir (with or without azithromycin) vs. natural honey plus lopinavir/ritonavir or umifenovir or chloroquine or hydroxychloroquine or oseltamivir (with or without azithromycin) in patients with COVID-19. Single-blind RCT (NCT04323345, not yet recruiting). Primary endpoints: (a) positive to negative swabs at day 14; (b) fever to normal temperature in days (follow-up 14 days); (c) resolution of lung inflammation in CT or X-ray (follow-up 30 days). • Comparison of colchicine (with or without lopinavir/ritonavir) vs. local standard of care in patients with moderate to severe COVID-19. Open-label RCT (NCT04328480, not yet recruiting). Primary endpoint: all-cause mortality (follow-up 30 days). • Comparison of oseltamivir plus chloroquine vs. oseltamivir plus lopinavir/ritonavir in patients with mild COVID-19 and of lopinavir/ritonavir plus oseltamivir vs. darunavir/ritonavir plus oseltamivir vs. favipiravir plus lopinavir/ritonavir vs. darunavir/ritonavir plus oseltamivir plus chloroquine vs. darunavir/ritonavir plus favipiravir plus oseltamivir in patients with moderate to severe COVID-19. Open-label RCT (NCT04303299, not yet recruiting). Primary endpoint: SARS-CoV-2 eradication time (follow-up 24 weeks). • Comparison of remdesivir vs. placebo in patients with severe COVID-19. Double-blind RCT (NCT04257656, recruiting). Primary endpoint: clinical status, assessed by an ordinal scale at days 7, 14, 21 and 28. • Comparison of remdesivir vs. placebo in patients with mild to moderate COVID-19. Double-blind RCT (NCT04252664, recruiting). Primary endpoint: time to clinical recovery in hours (follow-up 28 days). • Comparison of remdesivir vs. local standard of care in patients with severe COVID-19. Open-label RCT (NCT04252664, recruiting). Primary endpoint: composite of fever normalization and oxygen saturation normalization (follow-up 14 days). • Comparison of remdesivir vs. local standard of care in patients with moderate COVID-19. Open-label RCT (NCT04292730, recruiting). Primary endpoint: discharged status at day 14. • Comparison of remdesivir vs. placebo in patients with COVID-19. Double-blind RCT (NCT04280705, recruiting). Primary endpoint: severity rating on a 8-point ordinal scale at day 15. • Comparison of remdesivir vs. hydroxychloroquine vs. remdesivir plus hydroxychloroquine in patients with COVID-19. Open-label adaptive RCT (NCT04321616, not yet recruiting). Primary endpoint: all-cause in-hospital mortality (follow-up 3 weeks). • Comparison of lopinavir/ritonavir vs. hydroxychloroquine vs. lopinavir/ritonavir plus interferon beta 1a vs. remdesivir vs. standard of care in patients with COVID-19. Double-blind, adaptive RCT (NCT04315948, recruiting). Primary endpoint: severity rating on a 7-point ordinal scale at day 15. • Comparison of darunavir/cobicistat vs. standard of care in patients with COVID-19 pneumonia. Open-label RCT (NCT04252274, recruiting). Primary endpoint: virologic clearance rate of throat swabs, sputum or lower respiratory tract secretions at day 7.
Darunavir/cobicistat	Darunavir is an HIV type 1 protease inhibitor. Cobicistat is a CYP3A4 inhibitor that boosts darunavir concentrations	<ul style="list-style-type: none"> • Not available 	<ul style="list-style-type: none"> • Comparison of darunavir/cobicistat vs. standard of care in patients with COVID-19 pneumonia. Open-label RCT (NCT04252274, recruiting). Primary endpoint: virologic clearance rate of throat swabs, sputum or lower respiratory tract secretions at day 7.

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Table 2 (continued)

Drug	Class/mechanism	Published RCT	Ongoing RCT for treatment/prevention of COVID-19 (recruiting or not yet recruiting) registered at ClinicalTrials.gov
Favipiravir	Anti-influenza RNA-dependent RNA polymerase inhibitor	<ul style="list-style-type: none"> In a recent RCT published on a preprint server and comparing 120 COVID-19 patients treated with favipiravir vs. 120 COVID-19 patients receiving umifenovir, higher rates of clinical recovery were observed in patients receiving favipiravir. The manuscript is publicly available but still to be peer reviewed [30] 	<ul style="list-style-type: none"> Comparison of favipiravir vs. tocilizumab vs. favipiravir plus tocilizumab in patients with COVID-19. Open-label RCT (NCT04310228, recruiting). Primary endpoint: clinical cure (follow-up 3 months). Comparison of oseltamivir plus chloroquine vs. oseltamivir plus lopinavir/ritonavir in patients with mild COVID-19 and of lopinavir/ritonavir plus oseltamivir vs. darunavir/ritonavir plus oseltamivir vs. favipiravir plus lopinavir/ritonavir vs. darunavir/ritonavir plus oseltamivir plus chloroquine vs. darunavir/ritonavir plus favipiravir plus oseltamivir in patients with moderate to severe COVID-19. Open-label RCT (NCT04303299, not yet recruiting). Primary endpoint: SARS-CoV-2 eradication time (follow-up 24 weeks). Comparison of hydroxychloroquine plus darunavir/cobicistat vs. standard of care in patients with COVID-19. Open-label RCT (NCT04304053, recruiting). Primary endpoint: incidence of secondary cases among contacts of a case and contacts of contacts (follow-up 14 days). Comparison of chloroquine plus favipiravir vs. favipiravir vs. placebo in patients with COVID-19. Double-blind RCT (NCT04319900, recruiting). Primary endpoints: (a) time to improvement/recovery and frequency of improvement/recovery (follow-up 10 days); (b) time to negative swab/sputum RT-PCR (follow-up 10 days). Comparison of favipiravir vs. standard of care in patients with COVID-19. Open-label RCT (NCT04333589, not yet recruiting). Primary endpoint: viral nucleic acid test negative conversion rate in nasopharyngeal swabs (follow-up 5 months). Comparison of oseltamivir plus chloroquine vs. oseltamivir plus lopinavir/ritonavir in patients with mild COVID-19 and of lopinavir/ritonavir plus oseltamivir vs. darunavir/ritonavir plus oseltamivir vs. favipiravir plus lopinavir/ritonavir vs. darunavir/ritonavir plus oseltamivir plus chloroquine vs. darunavir/ritonavir plus favipiravir plus oseltamivir in patients with moderate to severe COVID-19. Open-label RCT (NCT04303299, not yet recruiting). Primary endpoint: SARS-CoV-2 eradication time (follow-up 24 weeks).
Umifenovir	Anti-influenza membrane fusion inhibitor	<ul style="list-style-type: none"> In a recent RCT published on a preprint server and comparing 120 COVID-19 patients treated with favipiravir vs. 120 COVID-19 patients receiving umifenovir, higher rates of clinical recovery were observed in patients receiving favipiravir. The manuscript is publicly available but still to be peer reviewed [30] 	<ul style="list-style-type: none"> Comparison of umifenovir vs. standard of care in patients with COVID-19 pneumonia. Open-label RCT (NCT04260594, not yet recruiting). Primary endpoint: virus negative conversion rate (follow-up 7 days).
Chloroquine, hydroxychloroquine	Some proposed mechanisms are the following: increase in the endosomal Ph necessary for the virus/host cell fusion; interference with the glycosylation of cell receptors; immunomodulatory activity	<ul style="list-style-type: none"> Not available 	<ul style="list-style-type: none"> Comparison of different hydroxychloroquine dosages vs. placebo in three cohorts (outpatients, inpatients, healthcare workers a risk). Double-blind RCT for outpatients and healthcare workers and open-label RCT for inpatients (NCT04329923, not yet recruiting). Primary endpoints: (a) release from quarantine (outpatients, follow-up 14 days); (b) discharge (inpatients, follow-up 14 days); (c) development of COVID-19 (healthcare workers, follow-up 2 months). Comparison of hydroxychloroquine vs. ascorbic acid in contacts of COVID-19 patients. Double-blind RCT (NCT04328961, not yet recruiting). Primary endpoint: laboratory-confirmed COVID-19 (follow-up 14 days). Comparison of tocilizumab plus hydroxychloroquine plus azithromycin vs. tocilizumab plus hydroxychloroquine in patients with COVID-19. Open-label RCT (NCT04332094, not yet recruiting). Primary endpoints: (a) in-hospital mortality (follow-up 2 weeks); (b) need for mechanical ventilation in the ICU (follow-up 2 weeks). Comparison of ciclesonide plus hydroxychloroquine vs. ciclesonide in patients with COVID-19. Open-label RCT (NCT04330586, not yet recruiting). Primary endpoint: SARS-CoV-2 eradication (based on virus load) at day 14.

Table 2 (continued)

Drug	Class/mechanism	Published RCT	Ongoing RCT for treatment/prevention of COVID-19 (recruiting or not yet recruiting) registered at ClinicalTrials.gov
Methylprednisolone	A subgroup of patients with severe COVID-19 might develop a cytokine storm syndrome which causes rapidly progressive pneumonia, ARDS and clinical deterioration and corticosteroids administration may halt the dysregulated cytokine release	<ul style="list-style-type: none"> • Not available 	<ul style="list-style-type: none"> • Comparison of hydroxychloroquine vs. placebo in patients with COVID-19 and under biological treatment and/or JAK inhibitors. Double-blind RCT (NCT04330495, not yet recruiting). Primary endpoints: (a) incidence rate of COVID-19 (follow-up 27 weeks); (b) prevalence of COVID-19 (follow-up 27 weeks); (c) case fatality rate (follow-up 27 weeks); (d) ICU admission rate (follow-up 27 weeks). • Comparison of hydroxychloroquine vs. placebo for the prevention of COVID-19 in healthcare workers at risk. Double-blind RCT (NCT04328467, not yet recruiting). Primary endpoint: prevalence of COVID-19 (follow-up 12 weeks). • Comparison of chemoprophylaxis with lopinavir/ritonavir vs. placebo in healthcare workers exposed to COVID-19. Double-blind RCT (NCT04328285, not yet recruiting). Primary endpoint: Occurrence of a symptomatic or asymptomatic SARS-CoV-2 infection (follow-up 2.5 months). • Comparison of hydroxychloroquine vs. placebo in symptomatic COVID-19 patients or exposed healthcare workers/households. Double-blind RCT (NCT04308668, recruiting). Primary endpoints: (a) incidence of symptomatic COVID-19 among asymptomatic participants; (b) severity rating on a 3-point ordinal scale at day 14. • Comparison of remdesivir vs. hydroxychloroquine vs. remdesivir plus hydroxychloroquine in patients with COVID-19. Open-label adaptive RCT (NCT04321616, not yet recruiting). Primary endpoint: all-cause in-hospital mortality (follow-up 3 weeks). • Comparison of lopinavir/ritonavir vs. hydroxychloroquine vs. losartan vs. placebos in patients with COVID-19. Double-blind, adaptive RCT (NCT04328012, not yet recruiting). Primary endpoint: NIAID COVID-19 Ordinal Severity Scale (follow-up 60 days). • Comparison of convalescent plasma plus hydroxychloroquine plus azithromycin vs. hydroxychloroquine plus azithromycin in hospitalized patients with COVID-19. Open-label RCT (NCT04332835, not yet recruiting). Primary endpoints: (a) change in virus load at days 0, 4, 7, 14 and 28; (b) change in IgM COVID-19 titers at days 0, 4, 7, 14 and 28; (c) change in IgG at days 0, 4, 7, 14 and 28. • Comparison of lopinavir/ritonavir vs. hydroxychloroquine vs. lopinavir/ritonavir plus interferon beta-1a vs. remdesivir vs. standard of care in patients with COVID-19. Double-blind, adaptive RCT (NCT04315948, recruiting). Primary endpoint: severity rating on a 7-point ordinal scale at day 15. • Comparison of methylprednisolone vs. standard of care in patients with severe COVID-19. Open-label RCT (NCT04244591, recruiting). Primary endpoint: lower Murray lung injury score at days 7 and 14. • Comparison of methylprednisolone vs. standard of care in patients with COVID-19. Open-label RCT (NCT04273321, recruiting). Primary endpoint: treatment failure (follow-up 14 days). • Comparison of inhaled alpha interferon plus methylprednisolone plus umifenovir vs. thalidomide plus inhaled alpha interferon plus methylprednisolone plus umifenovir in patients with severe COVID-19. Double-blind RCT (NCT04273581, not yet recruiting). Primary endpoint: time to clinical improvement (follow-up 28 days). • Comparison of different dosages of methylprednisolone in patients with COVID-19. Open-label RCT (NCT04263402, recruiting). Primary endpoints: (a) disease readmission at day 7; (b) critical stage at day 7. • Comparison of siltuximab (anti-IL-6 monoclonal antibody) vs. methylprednisolone in patients with COVID-19. Open-label RCT (NCT04329650, not yet

(continued on next page)

Table 2 (continued)

Drug	Class/mechanism	Published RCT	Ongoing RCT for treatment/prevention of COVID-19 (recruiting or not yet recruiting) registered at ClinicalTrials.gov
Tocilizumab	Humanized monoclonal IgG1 antibody, tocilizumab inhibits both membrane-bound and soluble IL-6 receptors. IL-6, is one of the main drivers of immunologic response and symptoms in patients with dysregulated cytokine release that has been observed in severe COVID-19	<ul style="list-style-type: none"> • Not available 	<p>recruiting). Primary endpoint: ICU admission (follow-up 29 days)</p> <ul style="list-style-type: none"> • Comparison of tocilizumab vs. standard of care in patients with COVID-19. Open-label RCT (NCT04331808, not yet recruiting). Primary endpoint: WHO progression scale at day 7 and 14 (severity rating on a 10-point ordinal scale). • Comparison of favipiravir vs. tocilizumab vs. favipiravir plus tocilizumab in patients with COVID-19. Open-label RCT (NCT04310228, recruiting). Primary endpoint: clinical cure (follow-up 3 months). • Comparison of tocilizumab vs. placebo in hospitalized patients with COVID-19. Double-blind RCT (NCT04320615, not yet recruiting). Primary endpoint: severity rating on a 7-point ordinal scale at day 28. • Comparison of tocilizumab plus hydroxychloroquine plus azithromycin vs. tocilizumab plus hydroxychloroquine in patients with COVID-19. Open-label RCT (NCT04332094, not yet recruiting). Primary endpoints: (a) in-hospital mortality (follow-up 2 weeks); (b) need for mechanical ventilation in the ICU (follow-up 2 weeks). • Comparison of chloroquine analog (GNS651) vs. tocilizumab vs. nivolumab vs. standard of care in patients with advanced or metastatic cancer and COVID-19. Open-label RCT (NCT04333914, not yet recruiting). Primary endpoint: 28-day survival. • Comparison of tocilizumab intravenously vs. tocilizumab subcutaneously vs. sarilumab (anti-interleukin 6 receptor α monoclonal antibody) subcutaneously vs. standard of care in patients with COVID-19. Open-label RCT (NCT04322773, not yet recruiting). Primary endpoint: time to independence from supplementary oxygen therapy (follow-up 28 days). • Comparison of tocilizumab vs. anakinra (recombinant IL-1 receptor antagonist) vs. siltuximab vs. anakinra plus siltuximab vs. anakinra plus tocilizumab vs. standard of care in patients with COVID-19. Open-label RCT (NCT04330638, not yet recruiting). Primary endpoint: time to clinical improvement (follow-up 15 days). • Comparison of carrimycin vs. lopinavir/ritonavir or umifenovir or chloroquine in patients with COVID-19 pneumonia. Open-label RCT (NCT04286503, not yet recruiting). Primary endpoints: (a) fever to normal time (follow-up 30 days); (b) pulmonary inflammation resolution time (follow-up 30 days); (c) negative conversion of throat swab RT-PCR at EOT.
Anakinra	Antagonist of IL-1 receptor. IL-1 is one of the main drivers of immunologic response and symptoms in patients with cytokine-release syndrome.	<ul style="list-style-type: none"> • Not available 	<ul style="list-style-type: none"> • Comparison of anakinra vs. emapalumab (anti-interferon γ monoclonal antibody) vs. standard of care in patients with COVID-19. Open-label RCT (NCT04324021, not yet recruiting). Primary endpoint: treatment success at day 15. • Comparison of tocilizumab vs. anakinra (recombinant IL-1 receptor antagonist) vs. siltuximab vs. anakinra plus siltuximab vs. anakinra plus tocilizumab vs. standard of care in patients with COVID-19. Open-label RCT (NCT04330638, not yet recruiting). Primary endpoint: time to clinical improvement (follow-up 15 days).

Off-label drugs mostly provided in Italy during the first phase of the COVID-19 pandemic according to the authors' direct experience. Of note, there are also registered RCT for other drugs to be investigated in patients with COVID-19 (e.g. the Janus kinase family inhibitors ruxolitinib, baricitinib and tofacitinib).

ARDS = acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography; EOT, end of treatment; HR, hazard ratio; Ig, immunoglobulin; IL-1, interleukin 1; IQR, interquartile range; ITT, intent to treat; mITT, modified intent to treat; P_{aO_2}/F_{iO_2} , of arterial oxygen partial pressure to fractional inspired oxygen; RCT, randomized controlled trial; RT-PCR, real-time PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

COVID-19 patients treated with favipiravir versus 120 COVID-19 patients receiving umifenovir, higher rates of clinical recovery were observed in patients receiving favipiravir, but it is of note that the all-cause mortality was 0 in the entire study population, making it uncertain whether, if confirmed, these favourable results may be extrapolated to relevant survival endpoints in critically ill COVID-19 patients [30]. Finally, antiviral activity against SARS-CoV-2 *in vitro* has been recently reported for ivermectin, but clinical data are still lacking [31].

Question 2 statement

At the present time, evidence from the first published RCT does not support off-label treatment with LPV/RTV in COVID-19 patients. This result should also discourage the use of other protease inhibitors (e.g. darunavir), at least until results of dedicated RCT are available. Although promising in preclinical studies, remdesivir should be currently provided for treating COVID-19 patients only within RCT (preferentially) or compassionate-use/expanded-access programmes, owing to its investigational nature. Pending high-

level supporting evidence, favipiravir and umifenovir should not be provided outside RCT, at least in those countries where they are not approved for other indications. Oseltamivir or zanamivir should be provided only in the presence of suspected/proven concomitant influenza.

Question 3. should chloroquine/hydroxychloroquine be administered?

The rationale of using chloroquine for treating COVID-19 patients is based on two potential and non-mutually exclusive mechanisms: antiviral activity and immunomodulatory effects. With regard to antiviral activity, chloroquine has been shown to inhibit various viruses in cell cultures, including SARS-CoV-1 and SARS-CoV-2, possibly via pH-dependent inhibition of virus-endosome fusion and/or posttranslational modifications of CoV proteins, although other mechanisms may also contribute [32–35]. With regard to the immunomodulatory effects, the attenuated production of tumor necrosis factor alpha, interleukin (IL)-6 and interferons that follows the administration of chloroquine might help counteract an exaggerated proinflammatory response, which is thought to contribute to the organ damage observed in SARS-CoV-2-infected patients [36,37]. However, some authors have pointed out that an unfavourable immunomodulatory effect cannot be excluded, based on a reduced T helper 2 differentiation [38]. In our opinion, hydroxychloroquine should be preferred over chloroquine because of its less toxic profile (reduced ocular toxicity and fewer drug interactions) and its more potent *in vitro* activity against SARS-CoV-2 [39].

Recently, Cortegiani et al. [40] reviewed the available information on ongoing case series, comparative observational studies and RCT evaluating the use of chloroquine or hydroxychloroquine in patients with COVID-19 and registered in Chinese or US registries. They found 23 studies, all being conducted in China. However, in the few weeks after the paper was made available online (10 March 2020), the number of registered studies being conducted in countries other than China has multiplied (Table 2). In particular, results of registered RCT are necessary to guide (or discourage) the use of chloroquine/hydroxychloroquine in two different settings: prophylaxis of exposed individuals and treatment of proven cases, stratified for the severity of clinical presentation/progression.

In the meantime, a small controlled nonrandomized study of COVID-19 patients treated with hydroxychloroquine has been recently published [41]. In this study, Gautret et al. enrolled 26 COVID-19 patients to receive 200 mg of hydroxychloroquine every 8 hours for 10 days, whereas a total of 16 patients who denied consent as well as untreated patients from another centre were included as controls. Of note, six patients treated with hydroxychloroquine also received azithromycin. The primary endpoint was virologic clearance (based on results of real-time PCR on nasopharyngeal specimens) at day 6 after inclusion. At day 6, 70% (14/20) of hydroxychloroquine-treated patients were virologically cured versus 12.5% (2/16) in the control group (p 0.001), although it cannot be excluded that selection bias and baseline virus load played a role in influencing results, thereby biasing results towards observing a favourable effect of hydroxychloroquine administration [42]. Furthermore, the opposite results (apparent absence of reduction of virus clearance) were recently described by another French group (albeit in a tiny sample size of 11 patients receiving hydroxychloroquine plus azithromycin) [43]. Uncertainty also surrounds the more marked positive effect observed in patients receiving azithromycin in addition to hydroxychloroquine in the study by Gautret et al., especially because of the very small number of patients in the combined treatment subgroup and the possible

increased risk of QT prolongation by combining the two drugs (Table 3).

Question 3 statement

Pending results of RCT, the use of hydroxychloroquine may be considered for treating worsening patients with COVID-19 only if no important drug interactions can be anticipated and with close monitoring of hepatic function, renal function and QT prolongation. This is based on its activity *in vitro* against SARS-CoV-2 (although weak) and on the availability of low-level clinical evidence of anticipation of virus clearance from a small controlled nonrandomized study. However, it should also be kept in mind that the study was highly susceptible to bias and there are still no data regarding hard clinical endpoints such as crude mortality. For these reasons, hydroxychloroquine should be preferentially administered within the framework of investigational studies. When this is unfeasible, off-label use may be considered according to local protocols and consent procedures. In view of the absence of evidence, we are currently unable to support the use of hydroxychloroquine in asymptomatic or mildly symptomatic nonhospitalized patients outside investigational studies. The same applies to prophylactic use.

Question 4. should antibiotics be administered?

Bacterial infections can present simultaneously with COVID-19 or occur later during the course of the disease, worsening clinical conditions of patients who were recovering from primary viral pneumonia. Information regarding the prevalence of bacterial coinfection or superinfection is scant [28,44,45]. According to the available reports, prevalence of bacterial infections in patients with COVID-19 ranges between 1% and 10% [28,44,46]. In these reports, bacterial infections were due to Gram-negative bacteria including *Enterobacteriales* and nonfermenting rods [28,44]. It is of note that up to 98% of COVID-19 patients in available experiences received intravenous broad-spectrum empirical antibiotics [28,44,45,47], probably reflecting the frequent inability to exclude the presence of bacterial coinfection at the onset of severe clinical presentations of COVID-19. This could have possibly lowered the overall prevalence of bacterial superinfections.

Extrapolating data from experiences on bacterial superinfection in pneumonia due to other viruses in a retrospective case series of critically ill patients with MERS in Saudi Arabia, bacterial infection was registered in 18% of patients [48]. With similar prevalence, bacterial pneumonia occurred in about 20% of patients hospitalized for primary influenza virus infection [49,50]. In these studies, mortality related to influenza was mostly due to secondary bacterial pneumonia [49,50]. Common bacteria implicated were *Staphylococcus aureus*, including methicillin-resistant strains [51], *Streptococcus pneumoniae*, *Haemophilus influenzae* and group A streptococci [49,52,53].

There are currently no large data regarding any possible favourable effects in COVID-19 patients related to possible anti-inflammatory or antiviral effect of azithromycin. Furthermore, the small experiences of the administration of azithromycin in COVID-19 patients have provided conflicting results.

Question 4 statement

In our opinion, it might be prudent to consider empiric antibiotic treatment in critically ill patients with pneumonia due to COVID-19 in whom bacterial infection cannot be excluded. This suggestion is based on the facts that bacterial coinfection is common in patients with viral pneumonia and that it can be associated with a substantial risk of delaying appropriate treatment, thereby potentially increasing mortality. Because of the limited available

data on both the microbiologic epidemiology (and the prevalence of antimicrobial resistance) of bacterial superinfections in COVID-19 patients, it is difficult to provide specific pathogen-oriented recommendations. Therefore, pending further studies, we suggest to empirically treat COVID-19 patients according to their clinical syndrome (e.g. community-acquired pneumonia, hospital-acquired pneumonia), choosing the best antimicrobial agent or agents on the basis of local guidelines and local antibiotic susceptibility patterns, with early de-escalation or discontinuation according to microbiology results, whenever available.

Question 5. should steroids be administered?

So far, no RCT has been performed on corticosteroids administration in patients with COVID-19, and there are controversial opinions regarding the extrapolation of inference from previous studies in SARS-CoV-1 and MERS-CoV patients [15,54,55].

In an observational study conducted in 84 COVID-19 patients with acute respiratory distress syndrome (ARDS) in China, administration of methylprednisolone was associated with reduced progression to death (hazard ratio 0.38, 95% confidence interval 0.20–0.72, p 0.003), although the unadjusted analysis and the relatively small sample size preclude firm generalization and call for further investigation [47]. Indirect data on the possible efficacy (RCT) or effectiveness (observational comparative studies) of corticosteroid therapy come from studies performed in patients with MERS-CoV, SARS-CoV-1 or other viral infections.

With regard to patients with mild clinical presentation, a RCT including 16 not critically ill patients with SARS-CoV-1 did not report a beneficial effect of hydrocortisone administration. Of note, higher viraemia was observed in the second and third weeks after infection in the hydrocortisone group compared to the control group [56]. Moreover, as reported in a systematic review and meta-analysis of observational studies on corticosteroids provided to patients with SARS-CoV-1, only four studies provided conclusive data, reporting no survival benefit and possible harms including avascular necrosis, psychosis, diabetes and delayed virus clearance [57].

In critically ill patients, corticosteroids may be provided to decrease the inflammation–coagulation–fibroproliferation observed during acute respiratory distress syndrome (ARDS) [58–61]. A meta-analysis on corticosteroid use in ARDS including eight controlled studies reported a significant reduction in markers of systemic inflammation, pulmonary and extrapulmonary organ dysfunction scores, duration of mechanical ventilation and ICU length of stay [62]. A recent multicentre RCT included 277 patients with ARDS to assess the effects of dexamethasone treatment. Patients in the study arm received dexamethasone 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. This study reported a significant reduction in duration of mechanical ventilation in the dexamethasone group than in the control group (between-group difference 4.8 days, p < 0.0001) and a significant reduction in mortality at 60 days (between-group difference –15.3%, p 0.0047). The proportion of adverse events did not differ significantly between the dexamethasone group and the control group [63].

Data on the use of corticosteroids in critically ill patients with SARS-CoV-1 and MERS-CoV infection are available, albeit with conflicting results. In a retrospective observational study of 152 SARS-CoV-1–infected, critically ill patients, corticosteroid therapy was found to reduce mortality and shorten the length of hospital stay (odds ratio 0.08, 95% confidence intervals 0.01–0.97, p 0.046). The study did not report increased secondary infections or other complications with corticosteroid administration [64]. Conversely, in a retrospective observational study on 309 critically ill patients

with MERS-CoV, the administration of a median hydrocortisone equivalent dose of 300 mg per day was not associated with a difference in 90-day mortality. In addition, corticosteroid administration was associated with delayed clearance of MERS-CoV RNA from the patients' respiratory tract [65].

With regard to other viral infections, it is worth noting that a recent meta-analysis on patients with influenza pneumonia (including ten observational studies with a total of 6548 included patients) reported increased mortality (risk ratio: 1.75, 95% CI 1.3–2.4; p 0.0002), increased length of ICU stay (mean difference: 2.1, 95% CI 1.2–3.1; p < 0.0001) and increased rate of secondary bacterial or fungal infection (risk ratio: 2.0, 95% CI 1.0–3.8; p 0.04) in patients who received corticosteroids [66].

Question 5 statement

So far, no definitive efficacy or effectiveness data are available on the benefit of corticosteroid administration in patients with SARS-CoV-2 infection. As the World Health Organization underlines, there is an important need for efficacy data from RCT for supporting corticosteroids therapy in patients with SARS-CoV-2. However, considering that overwhelming inflammation and cytokine-related lung injury might be responsible for the rapidly progressive pneumonia and clinical deterioration in COVID-19 patients [44,58,67], we suggest (expert opinion only) to consider administration of corticosteroids in critically ill COVID-19 patients with ARDS or with worsening of non-ARDS respiratory failure in the absence of bacterial/fungal superinfections (independent of ICU admission). However, in the absence of convincing evidence, the following cannot currently be supported: steroid administration stratified according to inflammatory markers and steroid administration in non–critically ill COVID-19 patients.

Question 6. should other immunosuppressive and/or immunomodulatory therapies be administered?

According to some recent evidence, some patients with COVID-19 may develop secondary haemophagocytic lymphohistiocytosis, an underrecognized hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinaemia, with development of ARDS and multiorgan failure [46,47,67]. Consequently, immunosuppressive and/or immunomodulatory therapies have been proposed to contrast COVID-19–associated hyperinflammation.

Tocilizumab is a recombinant humanized monoclonal antibody inhibiting membrane-bound and soluble IL-6 receptors [68] and is currently approved for the treatment of patients with rheumatoid arthritis, giant-cell arteritis, juvenile idiopathic arthritis and patients with chimeric antigen receptor T-cell–induced severe or life-threatening cytokine release syndrome [68,69]. In this regard, tocilizumab may help mitigate the cytokine release syndrome by decreasing cytokine concentrations and acute-phase reactant production [70]. In a recent preprint paper, Xu et al. [71] reported their experience of treating 21 COVID-19 patients with tocilizumab. In their still-to-be-peer-reviewed case series, the following were observed after tocilizumab administration: (a) reduction in body temperature (21/21, 100%); (b) improved blood oxygenation (15/21, 71.4%); (c) normalization of lymphocyte count (10/17, 58.8%); (d) normalization of C-reactive protein (16/19, 82.4%); and (e) resolution of abnormalities on computed tomography (19/21, 90.5%). Interestingly, no adverse reactions were observed after tocilizumab administration, but long-term follow-up was not available. Tocilizumab has been deemed by Chinese National Health Commission to be a possible treatment option for patients with severe COVID-19 with elevated IL-6 [72]. The recommended dose is 4 to 8 mg/kg or 400 mg standard dose provided intravenously once, with the option to repeat a dose after 8 to 12 hours (not to exceed a total dose of

Table 3

Known adverse events of marketed anti-infective and anti-inflammatory drugs mostly provided as off-label treatments in the first phase of the COVID-19 pandemic

Drug	Adverse events
Lopinavir/ritonavir	<ul style="list-style-type: none"> • Hypercholesterolaemia and increased serum triglycerides (3–39%) • Increased γ-glutamyl transferase (10–29%) • Diarrhoea (7–28%; greater with once-daily dosing) • Increased serum ALT (grade 3/4: 1–11%) • Nausea (5–16%) • Upper respiratory tract infection (14%) • Abdominal pain (1–11%) • Vomiting (2–7%) • Fatigue (8%) • Increased serum amylase and/or lipase (3–8%) • Headache (2–6%) • Skin rash (\leq5%) • Neutropenia (grade 3/4: 1–5%) • Anxiety (4%) • Insomnia (\leq4%)
Chloroquine/hydroxychloroquine	<ul style="list-style-type: none"> • Retinopathy (4% of treated patients)^a • Other adverse effects with unknown frequency included Stevens-Johnson syndrome, abdominal pain, diarrhoea, nausea, vomiting, agranulocytosis, leukopenia, thrombocytopenia, abnormal hepatic function tests, acute hepatic failure, myopathy, bronchospasm
Tocilizumab	<ul style="list-style-type: none"> • Risk of prolonged QT interval, further increased when administered with fluoroquinolones or azithromycin • Increased serum ALT (\leq36%) and AST (\leq22%) • Increased LDL cholesterol (9–10%) • Injection site reaction (4–10%) • Neutropenia (grade 3: 2–7% of all adult patients) • Headache (1–7%) • Hypertension (1–6%) • Dizziness (3%) • Hypothyroidism ($<$2%) • Abdominal pain (2%) • Oral mucosa or gastric ulcers (2%) • Infections due to <i>Pneumocystis</i>, <i>Mycobacterium tuberculosis</i> and varicella zoster have been reported after tocilizumab, but their prevalence has not been clearly established
Anakinra	<ul style="list-style-type: none"> • Injection site reaction^b (24–71%) • Antibody development (up to 50% of the patients but no correlation of antibody development and adverse effects) • Headache and vomiting (12–14%) • Arthralgia (10–12%) • Fever (10–12%) • Haematologic disorder including eosinophilia, leukopenia and change in platelet count (2–9%) • Nausea and diarrhoea (7–8%) • Serious infection^c (2–3%)

Off-label drugs mostly provided in Italy during the first phase of the COVID-19 pandemic according to the authors' direct experience.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; LDL, low-density lipoprotein.

^a Serum concentration dependent adverse effect; early changes are generally reversible but may progress despite discontinuation if advanced.

^b Injection site reactions were considered serious in 2–3% of cases.

^c Serious infections included cellulitis, pneumonia, and bone and joint infections.

800 mg). However, it should be noted that the optimal time for administering tocilizumab has not yet been fully elucidated; nor is there a clear IL-6 threshold associated with progression to severe disease. At the time of writing, there are at least eight ongoing RCT evaluating the efficacy and safety of tocilizumab in COVID-19 patients (Table 2).

Other immune-modulatory drugs including anakinra (interleukin 1 receptor antagonist) or Janus kinase family enzyme inhibitors have been proposed for the management of SARS-CoV-2-infected patients. Notably, there is currently no supporting clinical evidence, and RCT are ongoing (Table 2) [67,73].

Finally, modifications of the immune response through administration of high-dose intravenous immunoglobulin or convalescent plasma have also been proposed or used in small case series, and they merit further investigation in dedicated RCT [74–78].

Question 6 statement

Owing to the lack of high-level evidence, administration of tocilizumab in patients with COVID-19 should preferentially occur within the framework of RCT. Off-label use according to local

protocols and consent procedures may be considered only in those COVID-19 patients excluded from RCT (or hospitalized where RCT are not available or still to be implemented) and who are worsening while receiving standard supportive care (in the absence of concomitant/superimposed infections). In our opinion, this could be a reasonable off-label use of tocilizumab in these early phases of the COVID-19 pandemic, although patients and physicians should be fully aware that currently there is only a non-peer-reviewed, noncomparative, observational experience (very low evidence from an unreviewed cases series), and that it only supports a potential favourable effect on inflammatory signs and symptoms, while there is no information on any possible effect on survival.

In the absence of clinical studies, we suggest that also other immunosuppressive and/or immunomodulatory therapies (e.g. anakinra, Janus kinase family enzyme inhibitors) should be preferentially administered within RCT. This also applies to modifications of the immune response through high-dose intravenous immunoglobulins or plasma from convalescent patients, which, although promising in very small case series, both deserve dedicated RCT investigation to clearly understand

their tolerability as well as the role they play in affecting COVID-19 outcomes.

Question 7. what is the optimal timing of treatment initiation?

Most clinical data on the timing of antiviral therapy initiation are derived from studies on viruses other than SARS-CoV-2, and it remains unclear whether these data can be extrapolated to SARS-CoV-2. Previous studies in SARS-CoV-1 and influenza showed a possible favourable impact on mortality of early initiation of antiviral treatment after symptoms onset [79–82]. With regard to SARS-CoV-2, although the results of the previously cited RCT comparing LPV/RTV versus standard of care eventually does not support the use of LPV/RTV in patients with COVID-19, it is also of note that the median time between symptom onset and randomization was 13 days (interquartile range, 11–16 days), so in most cases, the drug was initiated late during the course of the disease [22]. Consequently, we cannot exclude the possibility that an earlier initiation of LPV/RTV may be associated with improved prognosis. In this regard, we think the results of this RCT may be hypothesis generating and may help guide the design of further RCT evaluating the efficacy of LPV/RTV (and/or other antivirals) in an earlier phase of the disease. However, until such RCT will be available, we think the currently available clinical evidence is insufficient to support the use of LPV/RTV and/or other antivirals for treating COVID-19 outside the framework of RCT or compassionate-use programmes.

The optimal time of chloroquine/hydroxychloroquine and corticosteroids initiation still remains unknown. Although based on low-level evidence, the positive effect of virus clearance observed by Gautret et al. [41] was observed in a mixed group of non-ICU patients with upper respiratory tract symptoms, non-ICU patients with lower respiratory tract symptoms and asymptomatic subjects, which overall may support a positive effect of early hydroxychloroquine initiation in non-ICU settings (although information on the exact time of treatment initiation with respect to symptoms onset was not provided). With regard to steroid treatment, there is currently no evidence of a positive impact of early initiation in non-critically ill, non-ARDS patients. Although lack of evidence is not a synonym of lack of effect, in our opinion, steroid treatment, considering also its potential detrimental effects, should currently be limited to ARDS patients or non-ARDS patients with worsening conditions (see question 5).

Question 7 statement

Supportive therapy (symptomatic therapy, rehydration and oxygen supplementation, if necessary) should be provided as soon as the patient presents with respiratory or systemic symptoms including severe asthenia, high fever, persistent cough and/or clinical or radiologic signs of lung involvement. Pending further evidence, in our opinion, antiviral treatments should not be initiated in patients with SARS-CoV-2 infection outside RCT or compassionate-use programmes (with the exception of early oseltamivir initiation in patients with suspected concomitant influenza). Corticosteroids should be initiated early in well-defined categories of patients (patients with ARDS or with worsening of non-ARDS respiratory failure in the absence of bacterial/fungal superinfections), while their role in other COVID-19 patients still remains uncertain. Although based on low-level evidence and pending RCT results, in our opinion, early hydroxychloroquine administration may be considered in COVID-19 patients who have moderate to severe symptoms, whereas further data are needed to better delineate the true balance between possible favourable effects and toxicity of hydroxychloroquine in mildly symptomatic and asymptomatic patients.

Question 8. what is the optimal treatment duration?

In the absence of proven effective treatment, treatment duration also remains unclear; it is currently based on expert opinion which is based on treatment durations in other approved indications for the drugs provided and aimed at a balance between potential activity and risk of undesired side effects. Nonetheless, suggested durations vary markedly. For example, a wide range of chloroquine/hydroxychloroquine treatment durations (from 5 to 20 days) have been recommended/provided in different centres/studies, making it impossible to provide an univocal recommendation in the absence of direct comparisons of different lengths of treatment with regard to relevant clinical endpoints (e.g. mortality, ICU admission) and safety [33,40,41,83–85]. There is no standard steroid treatment duration, with different consensus/study groups suggesting steroid administration for no longer than 7 to 10 days [54,85].

Question 8 statement

Chloroquine/hydroxychloroquine treatment should be continued for at least 5 days and possibly prolonged up to 20 days according to some expert opinions, although it should be noted that data regarding the relative safety of different lengths of administration in COVID-19 patients are currently unavailable. Early discontinuation should be considered in the presence of adverse effects (e.g. QT prolongation or hepatic/renal toxicity; Table 3). If the administration of remdesivir is approved within compassionate-use/expanded-access programmes, treatment duration should follow compassionate or expanded access protocols (e.g. up to 10 days according to the most recent compassionate protocol at the time of this review). If corticosteroids are administered, we suggest a total treatment duration of 7 to 10 days, with progressive dose reduction. If the patient deteriorates with worsening lung physiology after removal of steroid treatment in the absence of bacterial or fungal superinfection, a second course of corticosteroid treatment may be considered, followed by slow tapering after improvement.

Future perspectives

In these first phases of the COVID-19 pandemic, where there are no clearly supported and approved treatments, there are two apparently mutually exclusive forces driving therapeutic choices supported only by preclinical and/or low-level clinical evidence: the willingness to administer potentially active therapies to COVID-19 patients; and the willingness not to harm by administering potentially inactive therapies that may unfavourably influence the outcome because of either expected or unexpected toxicity. Finding the right balance between these two forces is certainly not simple, but it remains more necessary than ever if we want to rapidly find effective and safe treatment. For this reason, RCT should always be the first option to be proposed to patients because RCT are the only way to provide high-level efficacy and safety information for optimizing the treatment of future patients. However, even when rapidly implemented during evolving pandemics, RCT are usually not immediately available (e.g. even if accelerated, local approval still and correctly requires time to guarantee ethical standards), and also many patients are usually excluded from RCT because of strict selection criteria [86,87]. For some of these patients, off-label uses (for drugs approved for other indications) and compassionate-use/expanded-access programmes (for investigational drugs) may represent an ethically justifiable option in the case of worsening conditions and unlikely survival with only supportive care.

Against this background, the role of the attending physician is crucial, by favouring and not discouraging RCT participation (in

favour of off-label administration) whenever the former is possible. Otherwise, scientific data will still be produced, but most information will be burdened by only partially adjustable selection biases and confounding factors, with consequent risks of inconclusive results and low-level supporting evidence for the various treatment options. If participation in RCT is maximized, high-level evidence will be available for guiding treatment, with lower-level evidence from off-label uses still remaining useful for hypothesis-generating purposes in order to better design further RCT (and not for directly guiding treatment choices). Notably, this is what, in our opinion, happened with LPV/RTV: (a) preclinical data supported activity against coronaviruses; (b) patients were enrolled onto RCT whenever possible, and otherwise they were offered off-label administration when not spontaneously improving; (c) because many patients were rapidly enrolled onto the first RCT, evidence rapidly become available that in our opinion discouraged a universal off-label provision of LPV/RTV in COVID-19 patients.

Conclusions

Many off-label antiviral and anti-inflammatory drugs are being administered in this first phase of the COVID-19 pandemic. While we do not discourage their use, physicians must be aware that because of the lack of high-level evidence, they may be ethically justifiable only in those worsening patients unlikely to improve with only supportive care and who cannot be enrolled onto RCT. Implementation of well-designed RCT should be expanded as much as possible, as RCTs are the most secure way to change for the better our approach to COVID-19 patients, including our frontline opinions.

Transparency Declaration

All authors report no conflicts of interest relevant to this article.

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