

Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline.

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<https://creativecommons.org/licenses/by-nc/4.0/> This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org Guideline-directed management of COVID-19: Do's and Don'ts 57 4 15 4 2021 2100753 The European Respiratory Journal 10.1183/13993003.00753-2021 PMC7996221 33766949 "Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline." James D. Chalmers, Megan L. Crichton, Pieter C. Goeminne, et al . Eur Respir J 2021; 57: 2100048. 60 2 11 8 2022 2150048 The European Respiratory Journal 10.1183/13993003.50048-2021 PMC12435462 35948349 Introduction Hospitalised patients with coronavirus disease 2019 (COVID-19) as a result of SARS-CoV-2 infection have a high mortality rate and frequently require noninvasive respiratory support or invasive ventilation. Optimising and standardising management through evidence-based guidelines may improve quality of care and therefore patient outcomes.

A task force from the European Respiratory Society and endorsed by the Chinese Thoracic Society identified priority interventions (pharmacological and non-pharmacological) for the initial version of this "living guideline" using the PICO (population, intervention, comparator, outcome) format. The GRADE approach was used for assessing the quality of evidence and strength of recommendations. Systematic literature reviews were performed, and data pooled by meta-analysis where possible. Evidence tables were presented and evidence to decision frameworks were used to formulate recommendations.

Based on the available evidence at the time of guideline development (20 February, 2021), the panel makes a strong recommendation in favour of the use of systemic corticosteroids in patients requiring supplementary oxygen or ventilatory support, and for the use of anticoagulation in hospitalised patients. The panel makes a conditional recommendation for interleukin (IL)-6 receptor antagonist monoclonal antibody treatment and high-flow nasal oxygen or continuous positive airway pressure in patients with hypoxaemic respiratory failure. The panel make strong recommendations against the use of hydroxychloroquine and lopinavir–ritonavir. Conditional recommendations are made against the use of azithromycin, hydroxychloroquine combined with azithromycin, colchicine, and remdesivir, in the latter case specifically in patients requiring invasive mechanical ventilation. No recommendation was made for remdesivir in patients requiring supplemental oxygen. Further recommendations for research are made.

The evidence base for management of COVID-19 now supports strong recommendations in favour and against specific interventions. These guidelines will be regularly updated as further evidence becomes available.

The ERS guidelines for the management of COVID-19 makes recommendations in favour of corticosteroids, thromboprophylaxis, anti-IL-6 and noninvasive ventilatory support. These guidelines will be regularly updated as further evidence becomes available. <https://bit.ly/2OlpmiF>

COVID-19 (coronavirus disease 2019) is the disease resulting from infection by the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) virus. First identified in Wuhan, China in November 2019, the disease rapidly developed into a global pandemic with over 62.2 million infections and more than 1.4 million deaths recorded worldwide, as of the end of November 2020 [1 – 3] The onset of symptoms occurs around 3–5 days from initial infection, with fever, new continuous cough, dyspnoea, anosmia, ageusia and fatigue being amongst the most frequently experienced symptoms [3 – 5]. Pre-symptomatic transmission has been suggested as one of the features that promote the widespread transmission of the virus [1 , 6]. The spectrum of disease is remarkably broad, ranging from true asymptomatic or paucisymptomatic infection to fatal acute respiratory distress syndrome [4 , 7 – 9]. The case fatality rate of COVID-19 is debated but appears to be lower than Middle East respiratory syndrome (MERS) and severe acute respiratory

syndrome (SARS), with an estimated 5% of those experiencing symptoms requiring hospitalisation. The mortality rate in those requiring hospitalisation ranges from 5% to 25% [2 , 10 , 11]. Risk factors for hospitalisation and mortality have been defined [12 – 15]. In hospitalised patients, the ISARIC risk prediction tool incorporates increased age, male sex, number of comorbidities, increased respiratory rate, oxygen saturations, Glasgow coma scale, urea and C-reactive protein as risk factors for mortality [12]. Risk of hospitalisation and mortality is most strongly associated with age, and therefore SARS-CoV-2 infection rarely results in hospitalisation or mortality in children [16].

COVID-19 is often described as a biphasic illness with distinct stages [17]. The initial stage of infection with fever, cough and other symptoms is associated with the highest viral loads, which peak in the first 7 days of illness [18]. Live virus remains detectable in the respiratory tract for up to 9 days and, in the majority of individuals, symptoms start to improve after the first week of symptoms [18]. In a proportion of patients, however, a second phase, characterised by a dysfunctional host inflammatory response and the development of lung inflammation and lung injury, follows [19 – 23]. The inflammatory response in moderate and severe COVID-19 has been variously described as a pro-inflammatory cytokine storm or a manifestation of profound immunosuppression [22 – 24]. There is, nevertheless, clear evidence of increased systemic inflammatory markers, including interleukin (IL)-6, IL-8, IL-1 β , activation of coagulation pathways with increased markers such as D-dimer, neutrophil recruitment, activation and extracellular trap formation, deficient production in some patients of antiviral defence mediators such as interferon- α and - β , autoimmunity and T-cell activation, among multiple other mechanisms [4 , 19 , 25 – 28].

In view of the involvement of both the viral load and host inflammatory response in the disease, repurposing and development of new therapies in COVID-19 has focused primarily on antiviral, immunosuppressive and immunomodulatory treatments [18 , 29 – 32]. Randomised clinical trials have been conducted at an unprecedented rate to generate evidence for specific interventions [33]. During the early stages of the pandemic in particular, empirical use of antiviral and anti-inflammatory drugs, such as hydroxychloroquine, lopinavir–ritonavir, remdesivir and monoclonal antibodies, was widespread globally in the absence of formal guidelines or randomised trial evidence [34 – 37]. It is therefore important to have both recommendations in favour of successful interventions but also evidence to avoid certain therapies if their benefit–risk balance is unfavourable [34].

The objective of these guidelines is to provide evidence-based recommendations, primarily related to the management of hospitalised adults with COVID-19. This guideline does not address in detail the management of COVID-19 in the community, as the majority of evidence obtained relates to hospitalised patients. In addition, management in children is not addressed. A guideline cannot address the full complexity of a disease; hence, all recommendations should be interpreted considering the clinical circumstances and patients' perceptions, values and preferences.

The evidence for the management of COVID-19 is accumulating at an unprecedented rate with new trials published every day. The formal literature review and evidence synthesis process of these guidelines, and the lagtime to publication, mean that all guidelines will be “out of date” at the point that they are published. Consequently, the present document represents the first European Respiratory Society (ERS) guideline on this topic and is therefore the starting point. It is intended to be continuously updated as a “living guideline” with rapid literature searches and updated grading and recommendations as new evidence emerges, published as rapid guideline updates on specific topics in the ERS journals (figure 1).

Process of guideline development. PICO: population, intervention, comparator, outcome.

The target audience for this guideline comprises all stakeholders involved in the care of patients with COVID-19 in hospital. This includes specialists in respiratory medicine, infectious diseases, general internal medicine and multiple other medical and surgical specialities in view of the high prevalence of COVID-19; allied health professionals, including but not limited to, pharmacists,

physiotherapists and nurses; regulatory authorities; pharmaceutical companies; policy makers; and patients and their families. Table 1 provides a framework to interpret the recommendations made in this document.

Framework for interpretation of recommendations

: strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the unique features of individual patients and clinical circumstances [38, 39].

This guideline was developed by a European Respiratory Society COVID-19 task force chaired by J.D. Chalmers (UK) and N. Roche (France) and utilised the GRADE methodology [38]. The task force recommendations have been endorsed by the Chinese Thoracic Society (CTS) and three members of CTS participated as full members of the task force panel.

Due to the COVID-19 pandemic, all panel meetings were held online via teleconference and email, with the initial meeting on 26 June 2020 to identify and prioritise the key topics with the most important associated endpoints. From this meeting, the steering group were divided into working groups to focus on specific topics, including antivirals, anti-inflammatories, anticoagulants and ventilation strategies. The patient representative was involved in all discussions with the guideline panel, providing input into the final recommendations and will be involved in developing a lay version of the guideline [40].

A total of 11 clinical questions were generated using the PICO format (Patients, Intervention, Comparison, Outcomes) and systematic reviews were conducted to answer these specific questions. The cut-off date for literature searches was 31 October 2020, with updates performed to identify key studies in November 2020 and again in February 2021. Further details of the literature review process are described below.

Committee members disclosed all potential conflicts of interest according to ERS policy. Conflicted members were asked to abstain from discussions and voting on recommendations in which they were considered to have potential conflicts. Compliance with the conflict of interest policy was monitored by the chairs. The methodologists were non-voting members of the panel.

Two experienced external librarians from KU Leuven libraries (Belgium) designed and ran search strategies using MeSH terms and keywords for each clinical question, in collaboration with the methodology working group (P.C. Goeminne, M.L. Crichton, J.D. Chalmers, T. Tonia). More details of the search strategy are provided in the supplementary material . The search focused on identifying studies that included hospitalised patients or outpatients with confirmed or highly suspected COVID-19, which included a treatment group and control group that could be used to establish the efficacy and safety of the intervention being studied. The search retrieved 14 851 articles; after removal of duplicates and exclusion of citations that did not meet the established inclusion criteria, a total of 44 references were included in the initial evidence summaries.

The ERS methodology approach allows for results of existing systematic review and meta-analyses, when conducted to a high methodological standard, to be used for evidence synthesis and grading. If existing systematic reviews are not identified, then randomised controlled trials were identified and data extracted as described in the supplementary material . Observational studies are only considered for inclusion in the evidence tables if randomised controlled trials were not available. The results of randomised trials and observational studies are not pooled together but are considered separately.

The panel selected outcomes of interest for each clinical question a priori , based on their relative importance to adult patients with COVID-19 and to clinical decision making (supplementary

material). The importance of outcomes was rated on a 9-point scale (ranging from “not important” to “critical”) and only outcomes rated as important or critical for clinical decision making were included in the evidence tables. We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations. The GRADE methodology was used to rate the body of evidence at the outcome level rather than the study level, with assessment of risk of bias at study level performed as described [41]. One recommendation (on ventilatory support) was addressed using a narrative format due to the lack of homogeneous literature.

Recommendations are reported as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation. The quality of evidence was rated on four levels (high, moderate, low or very low) based on the GRADE methodology [39]. The overall quality of evidence is then rated as the lowest of the critical outcomes, except where the evidence for all of the critical outcomes favours the same alternative and where the quality of evidence for outcomes that are considered key to clinical decision takes precedence [42]. Evidence summary of findings tables and evidence to decision frameworks were generated for each clinical question (supplementary material). Based on these formats, the panel formulated the clinical recommendations and decided on their strength by consensus, or, if required, by voting. Following the GRADE approach, strong recommendations are worded as “we recommend”, while conditional recommendations are worded as “we suggest” [43].

Table 2 summarises the 14 formal, graded recommendations made within the guideline. In each of the following sections we include a discussion of the underlying evidence and the rationale for the recommendations made. Further details are provided in the evidence tables and evidence to decision frameworks provided online.

Summary of recommendations in this guideline

In the document, high-flow nasal cannula oxygen therapy (HFNC) is integrated in the term “noninvasive ventilatory support”. IL: interleukin; COVID-19: coronavirus disease 2019; CPAP: continuous positive airway pressure.

The panel recommends offering treatment with corticosteroids to patients with COVID-19 requiring oxygen, noninvasive ventilation or invasive mechanical ventilation (strong recommendation, moderate quality of evidence).

The panel recommends NOT to offer corticosteroids to patients with COVID-19 requiring hospitalisation but not requiring supplementary oxygen or ventilatory support (strong recommendation, moderate quality of evidence).

It is clear that excessive inflammation and a dysregulated immune response play an important role in the progression of severe COVID-19, and therefore there is a strong scientific rationale for the use of anti-inflammatory treatments, particularly in patients with the most severe disease [20 , 21 , 44 , 45]. We reviewed data for six randomised trials and one existing meta-analysis [31 , 46 – 49]. The majority of evidence in support of the use of corticosteroids comes from the UK RECOVERY trial, which randomised 2104 patients to dexamethasone 6 mg daily and 4321 patients to standard care in a pragmatic, non-blinded controlled trial [47]. The results demonstrated a statistically significant reduction in mortality with corticosteroid treatment in patients receiving invasive mechanical ventilation at randomisation (41.4% versus 29.3% in standard care versus dexamethasone, respectively) and a lesser but still statistically significant mortality benefit in those requiring supplementary oxygen at randomisation (26.2% versus 23.3% in standard care and dexamethasone, respectively) [47]. There was no mortality benefit evident in patients that did not require supplementary oxygen (14.0% versus 17.8% in standard care and dexamethasone, respectively) [47]. The pooled odds ratio in the evidence table, which includes all patient

subgroups, for mortality was 0.70 (95% CI 0.48–1.01). A systematic review and meta-analysis of critically ill patients with COVID-19, which included data from seven trials, confirms the benefit of corticosteroids on mortality in this population and included data for hydrocortisone and methylprednisolone, suggesting a class effect of steroids (OR 0.70, 95% CI 0.48–1.01; $p=0.053$ in random effects meta-analysis) [48].

The review of the data identified limited evidence on adverse events, and in particular the RECOVERY trial did not report detailed information on safety of the intervention [47]. Data from four trials did not show a significant increase in adverse events, with OR 1.09 (95% CI 0.37–3.18) [31 , 46 , 49 , 50]. Nevertheless, the adverse event profile of corticosteroids is well known, and these trials have not identified major safety signals to date. Evidence was rated as moderate or high quality for all of the outcomes except for adverse events.

The overall risk versus benefit for corticosteroids is favourable. Corticosteroids have been shown to significantly reduce mortality in a large-scale randomised trial and the consistency of results from other trials is reassuring that these data are generalisable. Results were significantly different between subgroups based on the requirement for oxygen, or requirement for mechanical ventilation, with clear absence of benefit in patients not requiring oxygen, justifying different recommendations for different subgroups of patients.

Dexamethasone 6 mg daily for 10 days was the regimen selected for RECOVERY and is therefore the regimen that is used as standard [47]. Unanswered questions regarding corticosteroids include the optimal molecule, the optimal timing, dose and scheme as well as the optimal duration of treatment, long term side-effects and whether other subgroups of patients, such as those not requiring oxygen but with evidence of increased systemic inflammation or radiographic changes, would benefit.

The panel suggests offering IL-6 receptor antagonist monoclonal antibody therapy to hospitalised patients with COVID-19 requiring oxygen or ventilatory support (conditional recommendation, low quality of evidence).

The panel suggests NOT to offer IL-6 receptor antagonist monoclonal antibody therapy to patients not requiring supplementary oxygen (conditional recommendation, low quality of evidence).

Notes: 1) All patients eligible for IL-6 receptor antagonist monoclonal antibody treatment should have already received or should be receiving treatment with corticosteroids, unless contraindicated. 2) The patients most likely to benefit are: those in the first 24 h after receiving noninvasive or invasive ventilatory support; and those receiving supplementary oxygen and who are progressing despite corticosteroid treatment, or who are considered at high risk of future requirement for ventilatory support.

Observational studies in severe COVID-19 found elevated levels of IL-6 that were associated with increased mortality [20 , 25 , 51]. Several uncontrolled trials suggested benefit of treatment with anti-IL-6 receptor monoclonal antibodies with improvements in disease severity and recovery of inflammatory markers reported [52 – 54].

The panel assessed eight randomised, controlled studies comparing IL-6 receptor antagonist monoclonal antibody treatment (a total of 3309 patients), to usual care (3038 patients) [55 – 62]. The vast majority of studies utilised tocilizumab, but sarilumab was also studied [62]. Patient populations varied but the majority of subjects were either hospitalised with severe COVID-19 requiring oxygen treatment but not mechanical ventilation, with evidence for increased inflammatory markers, or were requiring ventilatory support.

Our meta-analysis identified no significant effect of anti-IL-6 receptor monoclonal antibody treatment on mortality (820/3309 (24.8%) with active treatment versus 893/3038 (29.4%) with usual

care; OR 0.90, 95% CI 0.73–1.12, from eight studies with only limited heterogeneity $I^2 = 28\%$) [55 – 62]. It was noted that the two largest studies, RECOVERY and REMAP-CAP both demonstrated significant reductions in mortality [61 , 62]. RECOVERY enrolled patients admitted to hospital with COVID-19 who required oxygen and had a C-reactive protein level in blood greater than or equal to 75 mg·L⁻¹ . REMAP-CAP enrolled patients within the first 24 h of requiring noninvasive or invasive ventilatory support. Mechanical ventilation was significantly reduced by 25% (280/2161 (13%) versus 322/2038 (15.8%); OR 0.75, 95% CI 0.63–0.90, from four studies). The combined endpoint of requirement for mechanical ventilation or death was also reduced OR 0.74 (95% CI 0.72–0.88, from six studies). Adverse events and serious adverse events were not increased.

Anti-IL-6 receptor monoclonal antibody treatment reduces the risk of mechanical ventilation or death in hospitalised COVID-19 patients. No major safety concerns were identified. The panel considers that currently it is hard to identify the optimal patient population to benefit from this treatment, but RECOVERY found a benefit in addition to treatment with corticosteroids. As corticosteroids are also recommended for patients requiring oxygen and ventilatory support, anti-IL-6 monoclonal antibody treatment would be expected to be given to patients also receiving corticosteroids in nearly all cases. Anti-IL-6 receptor therapy is relatively expensive, but it is expected the benefits will outweigh the costs. Patient populations most likely to benefit include those meeting the inclusion criteria for REMAP-CAP (within 24 h of requirement for noninvasive or invasive ventilatory support) and hospitalised patients requiring oxygen who are considered at high risk of requiring mechanical ventilation or who have progressed despite treatment with corticosteroids, which is consistent with patients enrolled in RECOVERY and other trials included in our analysis.

Further research is needed to identify the optimal patient population for treatment with IL-6 receptor antagonist monoclonal antibody treatment, including whether biomarkers of inflammation are useful to identify responders.

The panel recommends NOT to offer hydroxychloroquine to patients with COVID-19, including hospitalised patients and outpatients.

Chloroquine and hydroxychloroquine are 4-aminoquinoline drugs primarily used for the treatment of malaria. These agents have immunomodulatory properties and also have in vitro activity against a variety of viruses, including SARS-CoV-2 [63]. Early observational studies of these repurposed medications (alone or in combination with azithromycin) have given divergent results in patients with mild to severe COVID-19 [34]. Despite the preliminary nature of these studies, the reported results have led to confusion about the usefulness of this treatment and widespread empirical use in some parts of the world [37]. Large randomised controlled studies have now been performed allowing robust analysis of key outcomes in groups of patients with COVID-19 of diverse severity. Our evidence review included 11 randomised studies [10 , 30 , 64 – 72]. The results were heavily influenced by the two largest studies performed by the UK RECOVERY group and World Health Organization (WHO) SOLIDARITY trial [10 , 30]. In RECOVERY, participants who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care [10]. This is in agreement with the interim results of the WHO SOLIDARITY trial, showing no apparent effect of hydroxychloroquine on mortality, irrespective of disease severity at study entry [30]. Our pooled estimate for mortality from nine trials was 1.08 (95% CI 0.97–1.19), which effectively excludes a meaningful beneficial effect. Besides the absence of a survival benefit, currently available evidence does not show significant positive trends in terms of clinical outcomes, including time to clinical improvements, clinical resolution, deterioration, hospitalisation, intensive care unit (ICU) admission, and noninvasive or invasive ventilation. Moreover, hydroxychloroquine did not substantially reduce symptom severity in outpatients with early COVID-19. Regarding safety, there is an increased risk of adverse events with hydroxychloroquine, such as gastro-intestinal, ocular, liver and cardiac toxicity. Our pooled estimate for adverse effects was OR 4.23 (95% CI 3.30–5.42), indicating a substantial increase in adverse effects in participants receiving hydroxychloroquine compared to those randomised to the control. Among Brazilian patients hospitalised with mild-to-moderate COVID-19, prolongation of the QT interval was more

frequent in patients receiving hydroxychloroquine (alone or with azithromycin), than in those who were not receiving these drugs [64]. In the RECOVERY study, there was a small absolute excess of cardiac mortality of 0.4 percentage points in the hydroxychloroquine group on the basis of very few events [10].

There is no evidence of significant clinical benefits associated with hydroxychloroquine, as compared to standard of care, while there is an increased risk of adverse events. Where there is no benefit and evidence of potential harm, a strong recommendation against the intervention is justified.

The panel considers that a sufficient number of studies have been performed to conclusively recommend not using hydroxychloroquine in COVID-19 patients. Several institutions, including WHO and the National Institutes of Health, have ceased trials of its use in hospitalised patients on the ground of lack of efficacy. The US Food and Drug Administration has revoked the early use authorisation for chloroquine and hydroxychloroquine. Future studies on this repurposed agent should not be encouraged. The committee recommends studying other antiviral options in well-designed studies of repurposed or SARS-CoV-2 specific medications.

The panel suggests NOT to offer azithromycin to hospitalised patients with COVID-19 in the absence of bacterial infection (conditional recommendation, very low quality of evidence).

Azithromycin is a macrolide antibiotic with reported antiviral and immunomodulatory activities, and also a well-documented effect on exacerbation rate in patients with chronic lung diseases, including asthma and bronchiectasis [73 , 74]. It is one of the most popular antibiotics used in inpatients and outpatients with acute respiratory infections worldwide [75]. Azithromycin is widely available and has a well-established safety profile.

The literature search identified three randomised studies which investigated azithromycin. One study, from Brazil (COALITION 1), examined azithromycin plus hydroxychloroquine versus hydroxychloroquine alone [64]. Since hydroxychloroquine has been shown to have no beneficial effect and was regarded as standard of care in many parts of the world during the early part of the pandemic, the panel judged that this data could be used to infer the efficacy of azithromycin. Two studies were identified that examined the effect of azithromycin alone in hospitalised patients, COALITION 2, also performed in Brazil [76] and an open label trial performed by S ekhavati et al . [77].

These individual trials, and the pooled data from these three trials, demonstrate no difference in mortality (OR 1.02, 95% CI 0.69–1.49), length of hospital stay, clinical status or deterioration.

Bacterial co-infection is reported infrequently in COVID-19 patients, with a systematic review suggesting <10% of patients isolate a bacterial pathogen [78], but there may still be a role for antibiotics in selected patients with proven or strongly suspected bacterial co-infection. The authors therefore recommend against routine use specifically for COVID-19, but acknowledge use for other indications is outside the scope of this guideline. Although adverse events were not increased in COVID-19 patients in these three trials, long term concerns, such as antimicrobial resistance that may result from widespread use of azithromycin, should be considered [75].

The panel is aware at the time of writing that results of the azithromycin treatment arm of RECOVERY have been announced indicating no benefit of azithromycin in COVID-19 [79]. These were not included in our meta-analysis but support our recommendation.

The panel recommends studies into the frequency of bacterial co-infection in COVID-19 patients utilising molecular techniques and/or biomarkers in view of the outstanding question over the use of antibiotics in this disease.

The panel recommends NOT to offer hydroxychloroquine and azithromycin in combination for hospitalised patients with COVID-19 (conditional recommendation, moderate quality of evidence).

The potential antiviral and anti-inflammatory effects of azithromycin and hydroxychloroquine are discussed in separate sections above. The use of azithromycin in combination with hydroxychloroquine has been tested in a Brazilian multicentre, randomised, open label, controlled trial, involving hospitalised patients who were receiving a maximum of 4 L per minute of supplemental oxygen [64]. The use of hydroxychloroquine with azithromycin in this population did not improve clinical status at 15 days, as compared with standard care. There was an increased number of adverse events in patients receiving hydroxychloroquine plus azithromycin (39.3%) or hydroxychloroquine alone (33.7%) than in those receiving none of the trial drugs (22.6%) [64].

No clinical benefits were noted in a single randomised, open label study where azithromycin was combined with hydroxychloroquine. The panel notes that azithromycin has a well-established safety profile, but that antibiotic use promotes antibiotic resistance. Despite the limited data, the absence of any clinically relevant benefits of hydroxychloroquine or azithromycin alone argues against any benefit of the combination treatment.

Despite limited data for the combination therapy, the lack of benefit of hydroxychloroquine alone suggests no further trials of a combination treatment containing hydroxychloroquine are justified, particularly in light of potential serious cardiac adverse events and other side-effects [80]. The committee recommends studying other antiviral options in well-designed studies of repurposed or SARS-CoV-2 specific medications.

The panel suggests NOT to offer colchicine to patients hospitalised with COVID-19 (conditional recommendation, very low quality of evidence).

The intense inflammatory response following a SARS-CoV-2 infection prompted the investigation of other possible anti-inflammatory therapies which do not show similar adverse effects as seen with corticosteroid or other non-steroidal anti-inflammatory treatments. Colchicine is considered to have anti-inflammatory properties through targeting IL-1 and IL-6 in hyperinflammatory syndromes and blocking the inflammasome as well as having in vitro evidence for blocking the coagulation pathway and thrombosis [81 – 83]. One case–control analysis in COVID-19 suggested survival benefit in patients treated with colchicine as compared to standard of care (84.2% versus 63.6%) [84]. Two randomised controlled trials in COVID-19 were identified in the literature search. In one small randomised trial with 38 patients, Lopez et al . [85] found a better evolution in terms of need for supplemental oxygen in the colchicine group (median: 7 versus 3; $p=0.02$) while also demonstrating a significant reduction in length of hospital stay versus standard of care (median: 8.5 versus 6.0; $p=0.03$). This was in contrast with an earlier analysis on 100 randomised patients, where no difference in hospitalisation length was seen (median: 12 versus 13; $p=0.91$) [86]. Deftereos et al . [86] did however show a significant improvement in time to clinical deterioration in participants receiving colchicine (cumulative event-free 10-day survival of 83% in the control versus 93% in the colchicine group; $p=0.03$). The confidence intervals of these effects estimates are wide due to the low number of patients studied to date.

The benefit of colchicine is uncertain as both trials had a small sample size. There is no consistency in the reported effect on length of hospital stay. The effect of colchicine in the GRECCO-19 trial on a lower risk of deterioration was also based on a small number of events and is therefore uncertain in nature. Other important endpoints, such as ICU admission (OR 1.06, 95% CI 0.06–18.45) and mortality (OR 0.21, 95% CI 0.02–1.97) were not significantly reduced with therapy, and the studies were underpowered to address these endpoints. Moreover, a significant increase in adverse events (mainly diarrhea) was noted with the administration of colchicine (OR 3.96, 95% CI 1.72–9.12), which may be expected based longstanding experience with this drug.

The lack of clear benefits with an increase in adverse events results in a recommendation against use while awaiting further data.

Colchicine should be evaluated in large randomised controlled trials and at the time of writing it has been tested in the large pragmatic RECOVERY trial.

The panel recommends NOT to offer lopinavir–ritonavir to hospitalised patients with COVID-19 (strong recommendation, low quality of evidence).

Lopinavir is a HIV type 1 aspartate protease inhibitor, which is usually combined with ritonavir to increase its plasma half-life through inhibition of cytochrome P450 [87]. These drugs are widely available as a drug in clinical use for HIV. The combination was shown to reduce the risk of adverse clinical outcomes and viral load among patients with SARS as compared to historical controls [88]. Our evidence review included three randomised trials, including the previously mentioned RECOVERY [89] and SOLIDARITY [30] platform trials, plus a Chinese trial by C ao et al. [90]. No effect on mortality was observed (OR 1.02, 95% CI 0.90–1.15). No other clinical benefits were evident on endpoints including time to clinical improvement, viral load, viral clearance, discharge from hospital within 28 days and invasive mechanical ventilation. Adverse events and serious adverse events were not increased.

Lopinavir–ritonavir has a known adverse event profile and significant drug–drug interactions which present potential for patient harm [91 , 92]. Therefore, clear evidence of efficacy would be required to recommend its use. The literature review found no evidence of benefit across three randomised controlled trials. As the drug is not effective and may theoretically be harmful, this justifies a strong recommendation against its use, even considering the low quality of available evidence.

As two very large trials show no benefit, no further trials of lopinavir–ritonavir in this population are justified.

The panel makes no recommendation regarding the use of remdesivir in patients hospitalised with COVID-19 and not requiring invasive mechanical ventilation (no recommendation, moderate quality of evidence).

The panel suggests NOT to offer remdesivir to patients hospitalised with COVID-19 who require invasive mechanical ventilation (conditional recommendation, moderate quality of evidence).

Remdesivir is an inhibitor of the viral RNA-dependent RNA polymerase. It has proven effective in vitro against SARS-CoV-1, MERS-CoV and SARS-CoV-2 [93 , 94]. A reduction in time to recovery and length of hospital stay was demonstrated for remdesivir in one trial (ACTT1) [95]. This trial randomised 1062 patients (541 to remdesivir and 521 to placebo) [95]. The primary outcome of recovery time was reduced from 15 days to 10 days (rate ratio for recovery 1.29, 95% CI 1.12–1.48; $p < 0.001$). Length of hospital stay was also reduced from a median of 17 days to 12 days, and other secondary endpoints showed positive benefits [95]. In contrast, no clinical benefits were demonstrated in the other trials, including the large SOLIDARITY trial, which found no evidence of a mortality benefit. The SOLIDARITY analysis of remdesivir included 2743 receiving active treatment and 2708 controls. Mortality was not impacted, with a rate ratio of 0.95 (95% CI 0.81–1.11; $p = 0.50$) [30]. The SOLIDARITY group also included an updated meta-analysis of existing trials including ACTT1, SOLIDARITY and additional trials that randomised patients 2:1, and concluded there was no mortality benefit of remdesivir (RR 0.91, 95% CI 0.79–1.05) [30]. Our review identified very similar results with an odds ratio for mortality of 0.92 (95% CI 0.79–1.07) with no increase in adverse events (OR 1.05, 95% CI 0.71–1.55) from three studies.

In ACTT1, no benefit on the primary outcome of clinical recovery (recovery rate ratio 0.98, 95% CI 0.70–1.36) was observed in patients who started remdesivir when they were already on mechanical ventilation or extracorporeal membrane oxygenation [95]. If treatment is given it should be given

for 5 days based on evidence that this is at least as effective as 10 days administration [96]. Liver function tests should be checked prior to administration of remdesivir and checked while patients are on treatment, remdesivir should not be prescribed in patients with severe renal dysfunction (GFR <30 mL·min⁻¹).

The panel considers that time to recovery and length of hospital stay are relevant clinical endpoints in the absence of a mortality benefit of remdesivir. Nevertheless, these benefits have been demonstrated in only one randomised trial. The reported benefits are regarded by the panel as modest. The lack of significant adverse effects means that the balance of benefit versus risk was considered marginally in favour of the intervention by some members of the panel but not by others. The panel discussed this topic extensively, and voted on the final recommendation resulting in no majority favouring a recommendation for or a recommendation against remdesivir use. The panel therefore makes no recommendation regarding remdesivir in patients not requiring invasive mechanical ventilation. In GRADE methodology this is referred to as a condition recommendation for the intervention OR the alternative. This recommendation does not indicate that clinicians should use remdesivir routinely or that clinicians should avoid use of remdesivir in all cases. Rather it indicates that the balance of risks and benefits is uncertain and its use by patients should ideally be in the context of a randomised clinical study, or where patients have been fully informed of the risks and benefits.

Subgroup effects were observed with no benefit on the primary outcome evident in patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation. As this outcome is the main benefit supporting any use of remdesivir, the panel considers it appropriate to make a subgroup recommendation against remdesivir use in these patients where clear absence of benefit has been demonstrated. Availability and cost are important considerations for some healthcare systems.

As the benefit is unclear, further large studies including endpoints such as clinical improvement, clinical deterioration and length of stay should be performed to confirm the results of ACTT1. Identifying subgroups of patients who benefit is a priority, based on timing of administration and requirement for oxygen. The benefit of remdesivir on top of systemic corticosteroids, which are now regarded as standard of care for COVID-19, is to be established. There are strong theoretical reasons to believe antiviral treatments will be more effective when given earlier in the disease course and future studies should consider whether earlier administration would be beneficial. At the time of writing the guideline, the panel is aware of recently published data suggesting that the Janus kinase inhibitor baricitinib in combination with remdesivir decreases time to recovery in hospitalised patients in another study (ACTT2) [97]. Further data on remdesivir, with or without additional therapies, against standard of care will be required to conclusively demonstrate clinical benefit.

The panel suggests NOT to offer interferon-β to hospitalised patients with COVID-19 (conditional recommendation, very low quality of evidence).

Interferons are signalling proteins released by host cells as a component of innate immune system in response to viral infections [7 , 98]. Type 1 interferons have in vitro activity against coronaviruses [99], and in vivo promoted improved symptoms and viral clearance as part of a triple therapy regimen also containing lopinavir–ritonavir and ribavirin compared to lopinavir–ritonavir alone [100]. There is evidence that SARS-CoV-2 suppresses innate interferon release and the extent of this is linked to disease severity [98]. All of this provides a sound rationale for evaluating interferon as a therapy for COVID-19.

Our literature review identified three trials [30 , 101 , 102]. Two small proof of concept trials showed large benefits including reduced mortality [101 , 102] but a much larger trial (the WHO SOLIDARITY trial) suggests no evidence of benefit and potential harm (rate ratio 1.16, 95% CI 0.96–1.39; p=0.11). Our pooled estimate of these three trials showed no statistically significant mortality benefit or benefit on clinical deterioration. The quality of evidence was rated as very low.

Clinical benefit has not been clearly demonstrated for systemic interferon treatment. The largest trial on this drug showed no effect on mortality and a trend towards an increase in mortality. Safety data is incompletely reported across all trials. In the absence of clear benefit or safety, a recommendation for use cannot be made. The conditional recommendation is based on very low quality of evidence.

A recent trial published after the systematic review was completed demonstrated a significant benefit of inhaled interferon- β -1a in 101 patients conducted in the UK [103]. While the results of small trials should be treated with caution, this suggests the possibility that inhaled delivery has a different effect to systemic delivery of interferon. Further studies to investigate the efficacy of inhaled interferon- β are justified.

The panel recommends offering a form of anticoagulation for hospitalised patients with COVID-19 (strong recommendation, very low quality of evidence).

Notes accompanying this recommendation: the panel are unable to make a recommendation regarding the dose of anticoagulation (prophylactic, high-dose prophylactic or therapeutic) or the preferred type of anticoagulant medication.

SARS-CoV-2 infection has been associated with an increased risk of venous thromboembolism (VTE) attributed to features of coagulopathy [4 , 104]. The incidence of VTE is highly variable, ranging from 0% to 85% in reported studies. This variability likely relates to differences in population characteristics (especially regarding severity, age, comorbidities and setting) and diagnostic procedures. Pooled estimates of incidence recently reported in a systematic review of 48 studies were 17.0% for VTE, 7.1% for pulmonary embolism and 12.1% for deep vein thrombosis [105]. This high incidence is associated with a pro-thrombotic state characterised by increased D-dimer levels, associated with the hyperinflammatory state triggered by the host's immune response against SARS-CoV-2 [106].

To date, no results from randomised controlled trials have been published, although several such studies are ongoing based on registrations in clinicaltrials.gov and similar registries. Therefore, available evidence is restricted to data from observational studies [107]. Altogether, 19 studies were analysed, 16 retrospective cohorts and three prospective cohorts, eight of which were considered of good or fair quality following risk of bias assessment. Anticoagulants used were low molecular weight heparin, unfractionated heparin and direct oral anticoagulants. In five studies, the adjusted mortality rate ratio was 0.56 (95% CI 0.36–0.92; $p=0.0218$) comparing patients with and without receipt of anticoagulation [107]. This result remained stable after elimination of outliers and restriction to studies of good and fair quality. Risk reduction was significant with both prophylactic and therapeutic anticoagulation therapy, but these options could be compared in only three studies providing adjusted estimates, which significantly favoured therapeutic doses but needs to be weighed against potential harm (i.e. bleeding events) [107].

The panel notes that the high frequency of pulmonary embolism in patients hospitalised with COVID-19 justifies a low threshold for investigation, e.g . with computed tomography pulmonary angiogram, in severe patients or those that experience a deterioration in oxygenation [105], as a diagnosis of VTE will impact on the indicated dose and length of anticoagulation.

Although the quality of evidence is very low, prophylactic anticoagulation is routine practice for hospitalised patients at risk of thromboembolic complications in many countries, and the existing evidence and existing practice makes this an intervention that can be strongly advocated. The panel are unable to determine whether the benefit–risk balance is superior for prophylactic versus therapeutic dose anticoagulation, nor to identify subgroups with different benefit–risk ratios, and therefore rather than recommending one or the other, the panel makes clear that this is a matter for clinical judgement while awaiting randomised clinical trials.

The panel considers that randomised controlled trials comparing various modalities of prophylactic, prophylactic-high and therapeutic anticoagulation are needed. In addition to the dosing issue, questions to address include the duration and type of agent. It is crucial to consider subgroups based on severity and biomarkers of inflammation and/or coagulation.

We suggest high-flow nasal cannula oxygen (HFNC) or noninvasive continuous positive airway pressure (CPAP) delivered through either a helmet or a facemask for patients with COVID-19 and hypoxaemic acute respiratory failure (hARF) in the absence of immediate indications for invasive mechanical ventilation (conditional recommendation, very low quality of evidence).

Notes accompanying this recommendation: 1) HFNC and noninvasive CPAP are classified as aerosol generating and should therefore be delivered in a safe environment with staff wearing appropriate personal protective equipment; 2) HFNC and noninvasive CPAP should not delay mechanical ventilation in patients who are not responding to treatment; 3) prone positioning may improve oxygenation in non-intubated patients with hARF and is widely used for mechanically ventilated patients with COVID-19.

This question was addressed in a narrative format due to the identification of heterogeneous observational studies that could not be pooled for meta-analysis.

HFNC therapy and noninvasive CPAP have been used in patients with hARF due to COVID-19 pneumonia [108 – 111]. HFNC delivers a high flow of humidified heated gas at 30–60 L·min⁻¹ with a controlled oxygen concentration, via a nasal interface. Compared to standard oxygen therapy, HFNC therapy reduced 90-day mortality and increased the number of ventilator free days, in hARF due to non-COVID-19 causes [112]. Small case series suggest HFNC may decrease the need for intubation in COVID-19 patients more effectively than standard oxygen therapy, and large uncontrolled case series of application outside the ICU suggests HFNC and CPAP have similar efficacy, but these results are unconfirmed and patient groups may not be comparable [108 , 109 , 113 , 114].

The role of CPAP, mainly delivered through either helmet or facemask, has been explored in more than 1100 patients with acute respiratory failure/acute respiratory distress syndrome (ARDS) due to COVID-19 pneumonia, also outside of the ICU [108 , 109 , 111 , 115 – 122]. The majority of studies were either case series or retrospective, single centre observational studies. Only three studies were prospectively designed and only two were multicentre [109 , 123 , 124]. A large heterogeneity can be identified in terms of number of patients enrolled (median 31, interquartile range 17–71) patient selection (ratio of arterial oxygen tension to inspired oxygen fraction (F IO 2) ranging from less than 100 to 211), CPAP generators, interface used, initial positive end-expiratory pressure and F IO 2 values. Some papers also evaluated prone positioning as an additional intervention [121 , 123 , 125 , 126]. The intubation rate for those undergoing CPAP ranged from 4% to 51% (median 22%, interquartile range 20–38%) and a death rate from 0% to 52% (median 20%, interquartile range 5%–34%).

Prone positioning of non-intubated patients with hARF due to COVID-19 pneumonia has been recently tested across different settings including emergency departments, hospital wards, or in ICUs as an adjunct to conventional oxygen therapies [118 , 120 – 123 , 125 – 131]. A large heterogeneity across these experiences can be recognised. They differ in terms of patient selection, type of oxygen therapy support used, setting, timing and duration of the intervention and therefore provide variable results. Despite this heterogeneity, reports document a significant improvement in oxygenation and respiratory rate upon prone positioning, and the majority were able to tolerate the procedure.

COVID-19-induced ARDS is a heterogeneous condition and the presence of specific phenotypes defined by physiological and biochemical markers is debated [7 , 132 – 135]. There is no randomised controlled trial on timing of intubation in COVID-19-induced ARDS. A review of the

evidence around invasive ventilatory strategies is beyond the scope of the present guideline. Low tidal volume ventilation, unless contraindicated, prone positioning and corticosteroid therapy as described elsewhere reduces mortality in patients receiving invasive ventilation [49 , 136 , 137].

Venous–venous extracorporeal membrane oxygenation (ECMO) is used in patients with refractory hypoxaemia despite optimal conventional ventilation and adjunctive interventions [138]. Case series show encouraging results but there has been no randomised controlled trial. ECMO is both staffing and resource intensive.

There are no randomised controlled trials completed yet comparing either HFNC or CPAP or noninvasive ventilation with standard oxygen therapy, or the three interventions in COVID-19 patients with hARF. However, reducing the need for invasive ventilation and pressure on ICU healthcare resources would be highly advantageous.

The application of CPAP and HFNC should not delay intubation and mechanical ventilation in patients who fail to respond to a noninvasive approach. CPAP and HFNC therapy are classified as aerosol generating procedures and should be used with healthcare professionals in full personal protective equipment [113 , 139]. The nature of aerosol generation or dispersion when using CPAP and HFNC has been explored using a range of imaging, particle sizing and virus sampling studies, producing mixed results [110 , 140 – 142]. Benefits of CPAP and HFNC should be balanced against risks.

Randomised studies addressing the optimal mode of ventilation in patients with hARF and COVID-19 are required. The Recovery–RS randomised controlled trial (ISRCTN16912075), comparing standard oxygen therapy with CPAP and HFNC in COVID-19 patients, is currently recruiting. This trial includes patients who fail to achieve arterial oxygen saturation of 94% and above on an F IO 2 40% or above and the trial has a composite primary endpoint of intubation or death at 30 days.

The guideline recommendations are summarised in figure 2 . The overall aim of management of hospitalised patients with COVID-19 is to reduce mortality and prevent complications, including requirement for ICU admission and prolonged length of hospital stay. This guideline indicates that with the exception of corticosteroids and IL-6 receptor antagonists there is limited evidence to support that any other antiviral or anti-inflammatory treatment achieves these objectives with a high level of confidence. This confirms the need for further research. The majority of repurposed therapies have failed to reduce mortality or improve other clinical outcomes which emphasises the need to develop specific therapies directly targeting SARS-CoV-2 and the associated inflammatory response.

Summary of the European Respiratory Society guideline for management of hospitalised patients with coronavirus disease 2019. NIV: noninvasive ventilation; HFNC: high-flow nasal cannula oxygen; CPAP: continuous positive airway pressure; IL: interleukin.

The recommendations in this guideline are derived from a systematic literature review and standardised GRADE methodology. This is distinct from a recent American Thoracic Society (ATS)/ERS consensus document which utilised the CORE process which requires 70% agreement on a topic among survey respondents without a systematic literature review [143]. There are similarities between the recommendations of that previous document and the current guideline, particularly the recommendation to use corticosteroids. There are, however, large differences in that the ATS-led document recommended remdesivir use in patients requiring supplemental oxygen, where the present guideline now does not recommend routine remdesivir use, and the previous document recommended remdesivir in mechanically ventilated patients where this document now suggests against its use in this group [143]. A previous version of the ATS-led document also suggested the use of hydroxychloroquine. This illustrates how differences in guideline methodology can lead to different conclusions as well as the need to continuously update

recommendations based on emerging data.

Nevertheless, demonstrating that many drugs should not be used in clinical practice is also important for patient care, particularly in the context of COVID-19 where clinicians worldwide have used many unproven therapies particularly in the early stages of the pandemic. The purpose of guidelines is to improve the quality of care that patients receive and to standardise care across different healthcare settings and systems. This guideline should be used as a starting point for treatment algorithms which have to be modified as additional data accumulates.

This is a living guideline with the panel continuously reviewing new evidence as it arises. Recommendations for additional therapies not addressed in this guideline such as convalescent plasma, monoclonal antibodies directed against SARS-CoV-2 and other therapies will be added in future versions, along with updates on the therapies already reviewed once new data are available.

Please note: supplementary material is not edited by the Editorial Office, and is uploaded as it has been supplied by the author.

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This one-page PDF can be shared freely online.

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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