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Early View

Editorial

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Update March 2022: Management of Hospitalised Adults with Coronavirus Disease-19 (COVID-19) : A European Respiratory Society Living Guideline

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Introduction

Since the identification of SARS-CoV2 at the end of 2019, the COVID-19 pandemic has affected more than 410 million people worldwide and killed almost 6 million.[1,2] The predecessors of COVID-19 (i.e., SARS for severe acute respiratory syndrome and MERS for Middle-East respiratory syndrom) had been relatively self-limiting, preventing clinicians and researchers from establishing evidence-based specific therapeutic strategies.[3] Conversely, COVID-19 rapidly proved to be extremely fast spreading, which led stakeholders to encourage, guide, build or fund multidirectional therapeutic research strategies based on both repurposing and development of new agents.[4–8] In parallel, considerable efforts were directed at describing the disease and understanding the underlying mechanisms.[9–13] As a result, there has been a huge generation of evidence, as highlighted by the impressive number of COVID-19 publications (more than 200,000 since end 2019). As a consequence, it proved rapidly impossible for any clinician, researcher or decision-maker to gather and analyse all the corresponding literature to derive appropriate guidance.[14] The first step of such a process is to select the relevant high-quality research that can be used to answer the question(s) of interest.[15] Even if limiting the search to clinical trials, systematic reviews and meta-analyses, almost 4,000 papers appear in the PubMed database, as of mid-February, 2022. In June and July, 2020, the European Respiratory Society (ERS) and the American Thoracic Society (ATS) released early guidance on several aspects of COVID-19 management (i.e., rehabilitation, palliative care and acute management); at that time, direct specific evidence was sparse or absent.[16–18] Simultaneously, the ERS launched a living guideline on the management of COVID-19. The format was that of a "short" guideline, as per ERS standards[19,20], in that the purpose was to release the first iteration within 12 months. However, the number of PICO (Population Intervention Comparator Outcomes) questions to be addressed (n=12) already exceeded markedly what the ERS considers as being feasible during such a short timeframe (i.e., n=1-2), which was a direct consequence of the high number on unanswered issues in the field of acute COVID-19 management, all corresponding to outstanding clinical needs. The first version of these guidelines was released in March, 2021 and addressed the following potential therapeutic options: corticosteroids, IL-6 receptor antagonists, hydroxychloroquine, azithromycin and both combined, colchicine, lopinavir-ritonavir, remdesivir, interferon-β, anticoagulation and non-invasive ventilatory support.[21,22] An update of the mortality meta-analyses for corticosteroids, hydroxychloroquine, azithromycin, remdesivir, anti-IL-6 monoclonal antibodies, colchicine, lopinavir/ritonavir and interferon-β was published in December, 2021.[23]

The basic principle of a living guideline is that it should be updated as soon as new relevant evidence appears, following the World Health Organisation living systematic review guidance.[24]

Therefore, it was decided in August, 2021 to start preparing the second iteration of the guideline, which is published in this issue of the European Respiratory Journal. As for all ERS guidelines, the methodology relies on the GRADE (grading of recommendations, assessment, development and evaluations) system, with the aim of providing users with strictly evidence-based, explicit and transparent recommendations.[25] The panel was the same as for the initial version (see the authors' list).

Summary of the updating process

The first step was the selection of previous questions that needed to be updated, and new topics that warranted being addressed. Conditions for selection were the potential relevance of the considered treatment based on published research and clinical use, the existence of evidence and, for topics already addressed in the first version, the potential of new information or data for substantively changing the evidence base for the recommendation or the recommendation's credibility.[24] Two virtual panel meetings were held to conduct the selection process. The panel determined that no update was required for corticosteroids, hydroxychloroquine, lopinavir-ritonavir, remdesivir and interferon-beta. All other existing recommendations were suitable for an update, and four new PICO questions were generated for convalescent plasma, SARS-CoV-2 monoclonal antibodies, Interleukin-1 receptor mononclonal antibodies and JAK inhibitors.

Then, the GRADE methodology (i.e., literature searches, evidence tables and evidence to decision frameworks) was applied to questions that needed to be updated or addressed *de novo.* Altogether, the new guideline document addresses 16 PICO questions (5 unchanged since the first version, 7 updates, 4 new questions), resulting in 22 guideline recommendations formulated by the ERS panel and approved in February 2022. All details are provided in the dedicated manuscript. The previous version of the guideline remains as a supplement to allow transparency.

Summary of the guideline and rationale

Table 1 provides an overview of changes in and additions to the recommendations, while Figure 1 shows a summary of the whole new guideline.

Table 1: summary of the March, 2022 iteration of the ERS living guideline on the management of acute COVID-19. For items already addressed in the first version, the previous recommendation is mentioned.

Therapy	**Updated evidence?**	**Previous recommendation**	**Updated recommendation**
Corticosteroids	No	Strong recommendation for the intervention	Strong recommendation for the intervention
IL-6 receptor antagonist monoclonal antibody	Yes	Conditional recommendation for the intervention	Strong recommendation for the intervention
Hydroxychloroquine	No	Strong recommendation against the intervention	Strong recommendation against the intervention
Azithromycin	Yes	Conditional recommendation against the intervention	Strong recommendation against the intervention
Azithromycin and Hydroxychloroquine	Yes	Conditional recommendation against the intervention	Strong recommendation against the intervention
Colchicine	Yes	Conditional recommendation against the intervention	Strong recommendation against the intervention
Lopinavir-ritonavir	No	Strong recommendation against the intervention	Strong recommendation

			against the intervention
Remdesivir	No	No recommendation	No recommendation
Interferon beta	No	Conditional recommendation against the intervention	Conditional recommendation against the intervention
Anticoagulation	Yes	Strong recommendation for the intervention	Strong recommendation for the intervention
Continuous positive airway pressure (CPAP)	Yes	Conditional recommendation for the intervention	Conditional recommendation for the intervention
High Flow Nasal Oxygen (HFNO)	Yes	Conditional recommendation for the intervention	Conditional recommendation for the intervention
Convalescent plasma	Yes	New recommendation	Strong recommendation against the intervention
Specific anti-SARS-CoV-2 monoclonal antibodies	Yes	New recommendation	Conditional recommendation for the intervention
IL-1 receptor antagonist monoclonal antibody	Yes	New recommendation	Conditional recommendation against the intervention

JAK inhibitors	Yes	New recommendation	Strong recommendation for the intervention

For patients with severe COVID-19, systematic corticosteroids remain standard of care and the strong recommendation to use these in patients with requirement for oxygen therapy or ventilatory support remains unchanged.[14,23,26,27] Interleukin-6 receptor antagonist monoclonal antibodies were given a conditional recommendation in the previous version of the guideline on the basis of 8 randomized controlled trials, some of which were only available as preprints at the time of the previous guideline publication.[23,28,29] In the updated guideline 12 randomized trials were available with a total of 5,188 patients data. The larger dataset makes the beneficial effects of IL-6 receptor antagonists on mortality and requirement for ventilatory support more clear, resulting in a strong recommendation in favour of these therapies.[22]

In the previous version of the guideline conditional recommendations were made against the use of azithromycin, azithromycin and hydroxychloroquine in combination, and colchicine.[4,23,30–32] For each of these drugs further randomized trials have been published confirming the lack of beneficial effects in hospitalized patients and therefore these treatments now received a strong recommendation against their use.

The previous version of the guideline made a strong recommendation to use a form of anticoagulation in hospitalized patients with COVID-19, but was unable to determine whether prophylactic or treatment dose was superior due to a lack of data. In this update 5 randomized controlled trials are included for analysis.[33–37] No mortality benefit is evident but a reduction in major thrombotic events is balanced by an increase in major bleeding. The panel therefore concluded that anticoagulation should continue to be standard care for hospitalized COVID-19 patients but that the evidence currently does not conclusively favour either prophylactic or therapeutic dose and so both may be appropriate in different patients based on their risk of bleeding vs embolic complications.

The ventilation section of the guideline has been updated to reflect the newly published RECOVERY-RS trial which compared CPAP, high flow nasal oxygen and conventional oxygen therapy.[38] This trial showed that CPAP reduced the requirement for mechanical ventilation but HFNO did not. In the

original guideline it was recommended to use CPAP or HFNO in patients without an immediate requirement for mechanical ventilation based on observational studies.[7,39,40] The updated version of the guideline suggests to use CPAP first line and makes a conditional recommendation for HFNO in patients who cannot tolerate or are not suitable for CPAP.[38]

Of the new therapies, a large number of randomized trials were available to address the questions related to convalescent plasma, interleukin-1 beta receptor monoclonal antibodies, SARS-CoV-2 specific antibody treatments and JAK inhibitors. Our literature review identified no evidence of benefit for convalescent plasma resulting in a strong recommendation against treatment. Importantly, this recommendation does not exclude the possibility of this treatment being effective in highly selected patient subgroups that were not included in the trials (e.g., highly immunosuppressed patients with prolonged disease and viral excretion). However, to date there is no firm demonstration supporting this possibility. IL-1 beta receptor therapy has shown mixed results in trials, and its place in therapy is unclear resulting in a conditional recommendation against use while awaiting further data. Monoclonal antibody treatment with casirivimab and imdevimab was tested in the RECOVERY trial where it was associated with reduced mortality in seronegative individuals.[41] The utility of this therapy has been questioned because of reduced activity against the omicron variant which is now spreading rapidly around the world.[42] In view of this, a recommendation is made to limit use of this therapy to patients who are seronegative and are known to have, or are likely to have, infection with a susceptible variant. Finally, JAK inhibitors, particularly baricitinib have shown improvements in mortality and other clinical outcomes in our systematic review.[43–45] Following completion of our systematic review the RECOVERY trial published data on a further 8156 patients randomized to baricitinib or usual care, demonstrating a significant reduction in mortality age-adjusted rate ratio of 0.87 95%CI 0.77-0.98.[46] A meta-analysis incorporating these data supported a 20% reduction in mortality. Importantly, 95-96% of patients were receiving corticosteroids and 23% were receiving tocilizumab in RECOVERY and the efficacy and safety of baricitinib was not affected by co-administration with tocilizumab.[46] This therapy therefore receives a strong recommendation and noting that it may be administered as an alternative to anti-IL6 therapy, or in combination with anti-IL6 therapy in patients at the highest risk.

Future directions

At the time of writing the pandemic situation appears to be improving in many European countries but new outbreaks unfortunately remain possible. In addition, new variants could change the picture and, indeed, the Omicron variant already challenges some of the existing treatment options.[47]In

parallel, research is actively ongoing. Therefore, the ERS COVID-19 living guideline taskforce remains watchful and prepared to initiate the next update with the goal to provide all stakeholders with timely evidence-based recommendations developed following the highest quality standards.

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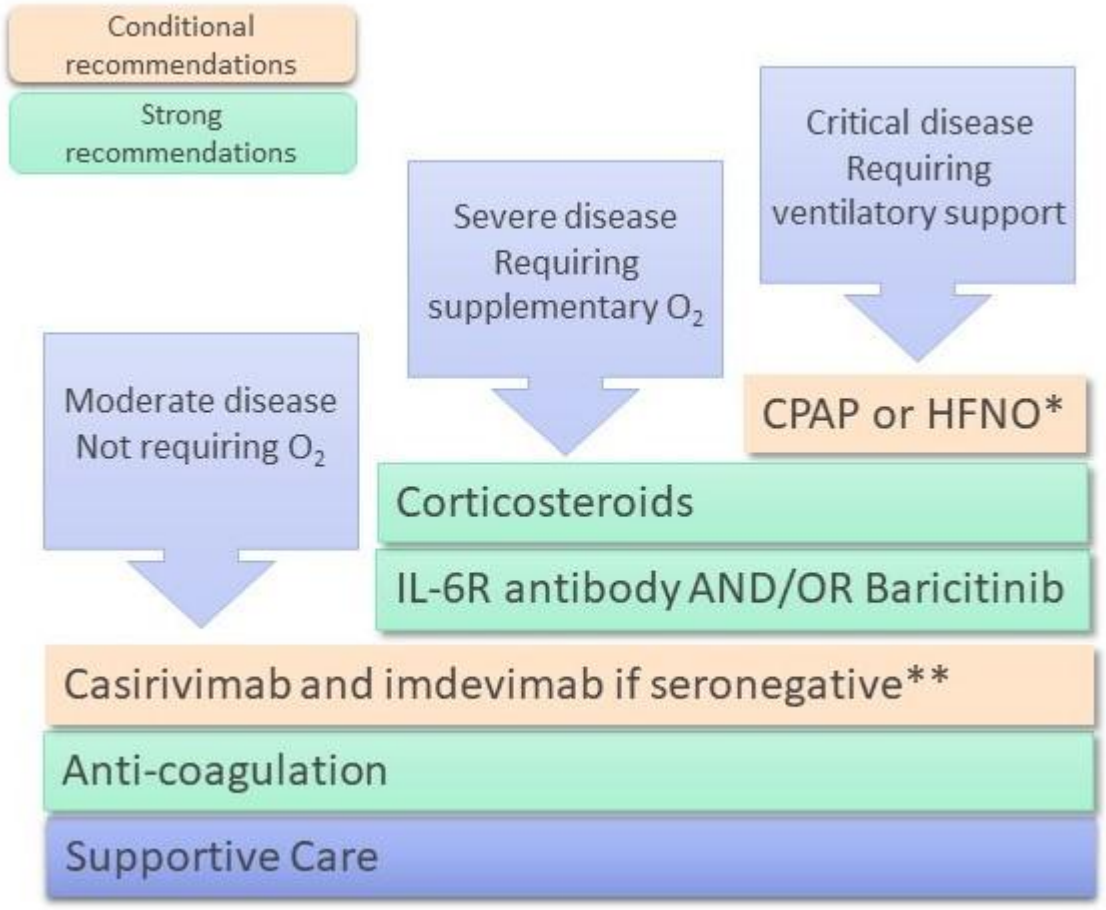

Figure 1. Summary of the ERS guideline for management of hospitalised patients with COVID-19. Abbreviations CPAP= continuous positive airway pressure. *HFNO is recommended where CPAP is contraindicated or not tolerated

**in addition, this therapy is only recommended where a susceptible variant is dominant or rapid testing is available to confirm a susceptible variant.