Executive Summary

Developing the evidence-based Korean clinical practice guideline for treating patients : Applying living guideline methodology

Miyoung Choi[1], Joonsup Yeom[2], Dong Ah Park[1], Suyeon Yu[1], Lee Hyeon-Jeong[1], Jimin Kim[1], Yan Jin[1], Jungeun Park[1], Seungeun Ryoo[1], Sunbean Kim[3], Kyungmin Huh[4], Jungyeon Heo[5], Eunjeong Joo[6], Youngkyung Yoon[3], Younjeong Kim[7], Sujin Jeong[2], Yubin Seo[8], Wonsuk Choi[9], Yaejean Kim[10], Kyongran Peck[4]

[1] National Evidence-based Healthcare Collaborating Agency

[2] Department of infectious diseases, Sevrance Hospital, Yonsei University College of Medicine

[3] Department of infectious diseases, Anam Hospital, Korea University College of Medicine

[4] Department of infectious diseases, Samsung Medical Center

[5] Department of infectious diseases, Ajou University Hospital

[6] Department of infectious diseases, Kangbuk Samsung Hospital

[7] Department of infectious diseases, Incheon ST.Mary's Hospital, Catholic University College of Medicine

[8] Department of infectious diseases, Hallym University Medical Center

[9] Department of infectious diseases, Ansan Hospital, Korea University College of Medicine

[10]Department of pediatrics, Samsung Medical Center

▢ Background

Despite the preventive efforts being made globally against coronavirus disease 2019, the most widely spread infectious disease in the world as of 2020, no definitive cure has been developed and the vaccine is in the early stages of development. While South Korea has been successful in protecting

its citizens from large-scale COVID-19 breakouts, healthcare providers at the coalface are demanding rapid and evidence-based clinical practice guidelines for treating inpatients with pneumonia and infections of other organs. Currently, there are many ongoing clinical studies aiming to develop vaccines and cures around the world. Compared to the early phase of the COVID-19 pandemic, many studies on clinical results are being published on a daily basis now. Therefore, it is necessary to develop an evidence-based methodology as well as continuously check for additional evidence and update recommendations. Since no standard antiviral treatment method other than supportive care has been established, we aim to provide guidelines on helpful antiviral and other drug treatments based on the latest evidence on COVID-19 in light of its clinical manifestations and fatality rates.

▢ Objective

This study aimed to review evidence on the latest treatments for COVID-19 and outline evidence-based clinical practice guidelines for healthcare professionals; it also aimed to devise a guideline development methodology that can be applied quickly in different settings

▢ Methods

Regarding the guideline development methodology, we used the adaptation method wherein the latest guidelines from major countries and organizations are reviewed in a short period of time. In addition, we applied the living guidelines development methodology that is consistently being updated using the latest evidence. The guideline development process is described in the following sections.

○ Search practice guidelines

With the help of literature search specialists, we selected the database, devised a search strategy, and developed the process of literature search. We decided to include practice guidelines from papers published after June, 2020 or regularly updated living guidelines.

○ Search database

We searched international literature databases such as PubMed and EMBASE as well as major practice guideline databases and websites. We also searched the official websites of major government organizations, institutions, and conferences because the data on these resources are updated in real time.

○ Search strategy

We applied filters including disease and cure search words and practice guidelines to the PubMed and EMBASE databases. The search words were combinations of specific and informal words based on treatment

terminologies from each clinical question : “coronavirus”, “novel coronavirus”, “novel coronavirus 2019”, “2019 nCoV”, “COVID-19”, “Wuhan coronavirus”, “Wuhan pneumonia”, “SARS-CoV-2”, “severe acute respiratory syndrome”, “treatment”, “therapy”, and “antiviral.”

○ Criteria for selection of guidelines

Since the studies released after June 2020 contain qualitatively and quantitatively reliable information on the COVID-19 treatment experience, we decided to select the latest practice guidelines with high methodological quality. We targeted guidelines developed by major countries and organizations that included recommendations for the selected clinical questions and are frequently updated.

○ Quality appraisal of guidelines

The quality of the practice guidelines was evaluated by three researchers using the AGREE (The Appraisal of Guidelines for Research and Evaluation) 2 tool. To reduce the variation between the evaluators, the K-AGREE evaluation form developed by the Korean Medical Association was used. During the AGREE evaluation, to ensure the reproducibility and clarity of the result, the evaluators were asked to describe the reason for awarding a score in the comment section, share evaluation results, and, if necessary, correct errors or mistakes via a review. After quality evaluation of the practice guidelines, we decided to use the guidelines that received more than 70 points in the three areas of AGREE.

○ Searching and selection of the latest evidence

The references selected from the reference tables of existing practice guidelines were reviewed before being included. For additional literature search, we used one international database (PubMed and one domestic database (KMBASE) for rapid development. Considering the rapid publication of literature on COVID-19-related evidence, we initially decided to use two

preprint databases, MedRxiv and bioRxiv. However, we decided to exclude them later because there was sufficient amount of literature from our primary search. For the search words, a search strategy was devised by selecting separate search words for each treatment.

As the literature on COVID-19 treatment is constantly being updated, the search will be updated on a monthly basis to check the main evidence and reflect the revisions of the recommendations. For constantly updating evidence, a semi-automated software for systematic review, Covidence, was purchased and used in the process of literature selection.

As with the guideline selection criteria, we decided to include studies on COVID-19 treatment that were published after June, 2020 and addressed the clinical questions on human subjects receiving interventions. For the study design, we decided to include randomized clinical trials or observational studies with comparative design after checking the amount of evidence for each clinical question.

○ Assessment of the risk of bias in the selected primary literature

The risk of bias of the references in the reference table of existing practice guidelines was reviewed to determine if they met the quality criteria. For the quality evaluation of the additionally searched evidence, an appropriate tool was selected according to the research design. Two researchers evaluated each paper independently. If they did not reach an agreement, an additional researcher's input was used to help them arrive at a consensus.

○ Managing Conflicts of Interests

We set-up the policy of managing conflicts of interest (COI) and developed a format of COI disclosure including financial, intellectual and other potential conflicts. All members of guideline committee declared there were no potential COI related on interventions during the guideline development period.

▢ Results

○ Selection and evaluation of practice guidelines

Seven out of eleven practice guidelines found on manual search were subjected to the AGREE evaluation. As one of the five additionally searched practice guidelines overlapped with one of the guidelines found from the manual search, four more AGREE evaluations were performed. Finally, we selected four practice guidelines that are most up to date with a score of 70 or more in three major areas of the AGREE evaluation. A table of recommendations of 11 evaluated practice guidelines was prepared for comparison with the recommendation trends in other countries.

○ Preparation of evidence table and review of up-to-dateness

An evidence table of each clinical questions with the selected literature was prepared according to the selection and exclusion criteria for the practice guidelines. The results of quality evaluation of the existing guidelines were reviewed and reevaluated, if necessary. The studies retrieved on November 9 and December 9 were reviewed and added to the evidence table.

○ Recommendations and external review

The committee in charge of clinical questions reviewed the summary of evidence and recommendations; prepared the first draft of recommendations; and decided on the final recommendations, level of evidence, and recommendation level at a general meeting. Then, external reviews from advisory and review committees were received in writing. The final draft of recommendations was completed after another discussion.

- Summary of recommendations

  Recommendations for a total of 10 clinical questions are summarized as follows:

Clinical Questions	Recommendation	Level of evidence	Level of Recommendation
CQ1. Remdesivir	1-1. We suggest remdesivir for COVID-19 patients who needs oxygen treatment without ventilator or ECMO.	Moderate	B
	1-2. Remdesivir administration for patients who do not fall under 1, we are unable to make direction and strength of recommendation.	Moderate	I
CQ2. HCQ +/- azithromycin	Hydroxychloroquine alone or combination of hydroxychloroquine and azithromycin treatment is not recommended.	High	C
CQ3. LPV/r	Administration of lopinavir/ritonavir for COVID-19 patients is not recommended.	High	C
CQ4. Other antiviral drugs	Administration of other drugs known to have antiviral effects such as favipiravir, ribavirin, umifenovir, and baloxavir marboxil is not recommended except for clinical trials.	Low	C
CQ5. Steroids	5-1. For severe or critical COVID-19 patients, administration of steroids is recommended.	Moderate	A
	Clinical consideration: for the dosage of steroid, 6mg dexamethasone is administered for 7-10 days. Steroids of the same potency can be substituted (hydrocortisone 150-200mg, prednisone 40mg, and methylprednisolone 32mg)		
	5-2. For non-severe COVID-19 patients, administration of steroids is not recommended.	Moderate	C
CQ6. IL-6 inhibitors	6-1. We suggest interleukin-6(IL-6) inhibitors for severe COVID-19 patients in the purpose of clinical trials.	Moderate	B
	6-2. For mild COVID-19 patients, administration of interleukin-6 inhibitor is not recommended.	Moderate	C
CQ7. IL-1 inhibitors	We are unable to make direction and strength of recommendation for interleukin-1(IL-1) inhibitor administration in COVID-19 patients due to insufficient data at the level of evidence.	Low	I
CQ8. Interferon	We suggest interferon for COVID-19 patients in the purpose of clinical trials.	Low	B
CQ9. Convalescent plasma	We are unable to make direction and strength of recommendation due to insufficient evidence supporting the benefit of plasma treatment during recovery in COVID-19 patients.	Low	I
CQ10. Conventional IVIG	Conventional intravenous immunoglobulin(IVIG) treatment is not recommended except for the indication of complication treatment.	Low	C

▢ Conclusions

We reviewed the latest evidence and international recommendations for drugs that are considered preferentially in the treatment of COVID-19 inpatients and applied an evidence-based methodology to derive recommendations.

As a limitation, to quickly develop recommendations in a short period of time while taking into consideration the emergency situation of the COVID-19 pandemic, we could only apply limited stringency measures to certain methodological aspects, e.g., multidisciplinary structure or searching through all possible databases. In the future, by applying the living guideline methodology developed in this study and expanding the range of clinical questions with the help of various professional societies under the Korean Medical Association, we hope to derive additional recommendations for treatment methods and non-pharmaceutical interventions based on the latest evidence, as this could not be done in the current study due to time constraints.

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Key words

Covid-19, Pharmacotherapy, Clinical Practice Guideline