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Editorial

Collaborative Response to COVID-19 Pandemic, and Development of Treatment Guidelines

Kyong Ran Peck [1,2]

[1]Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]The Korean Society of Infectious Diseases, Seoul, Korea

▸ See the article "Revised Korean Society of Infectious Diseases/National Evidence-based Healthcarea Collaborating Agency Guidelines on the Treatment of Patients with COVID-19" in volume 53 on page 166.

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Corresponding Author:
Kyong Ran Peck, MD, PhD
Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Tel: +82-2-3410-0329
Fax: +82-2-3410-0064
E-mail: krpeck@skku.edu

ORCID iDs
Kyong Ran Peck
https://orcid.org/0000-0002-7464-9780

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After the outbreak of pneumonia of unknown cause occurred in December 2019 in Wuhan, it rapidly spread worldwide, and the World Health Organization (WHO) declared it a pandemic within three months. The northern hemisphere experienced a winter pandemic larger than the initial one, and as of February 15, 2021, over 100,000,000 people have been infected and approximately 2,380,000 people have died [1]. In Korea, since the first confirmed case on January 20, 2020, a third epidemic crisis has occurred, and 1,527 people have died among 83,869 confirmed cases as of February 15, 2021. It took less than a year to discover that the causative pathogen of this pneumonia of unknown cause (Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV-2), perform whole genome sequencing, and develop vaccines accordingly. This is the result of collaborative efforts from medical scientists worldwide based on modern technologies which are under continuous development.

It is known that of patients with coronavirus disease 2019 (COVID-19; the infectious disease caused by SARS-CoV-2), 80% or more have mild symptoms, about 15% require hospitalization for medical care including oxygen therapy, and 4 - 5% progress to severe disease needing a ventilator or critical care [2]. Elderly patients or those with chronic diseases show a tendency to progress into severe conditions. Thus, there has been an urgent need to develop medications to prevent this aggravation, decrease mortality rate, and/or reduce viral spread from mild patients. Since no medication had been developed for coronavirus infection, a reassessment of medications used for other purposes was performed first regarding their effects on the disease. In addition, new drugs such as therapeutic antibodies have been developed as the pathophysiological characteristics of SARS-CoV-2 and COVID-19 were been explored. From published results of clinical research on various drugs undertaken since the early stage of the pandemic, "living guidelines" have been developed based on the periodic review of supplementary evidences. The Korean Society of Infectious Diseases (KSID) and related societies released national guidelines at the early response to COVID-19 by comprehensively evaluating data, which contributed to treatment standardization [3]. Although there was a need to revise these guidelines earlier, it was being for a period of six months due to practical overloads of clinical and infection control activities. Hence, this allowed for the possibility of this revision to be made based on accumulated higher-quality clinical research and more reliable scientific evidences [4].

Although a variety of drugs were reviewed in the revised guidelines, high-quality studies that demonstrated a treatment effect were scarce, and only remdesivir and dexamethasone showed significant treatment effects. Among the selected drugs based on their *in vitro* efficacy, drugs such as hydroxychloroquine or lopinavir/ritonavir were proven to have no effect through comparative clinical studies or meta-analyses and, accordingly, not recommended to be used for treatment. Despite the existence of a report revealing that hydroxychloroquine decreased fever duration if given at the very early stage [5], no significant effect was observed on reducing mortality rate in large-scale trials. Although many researchers employed convalescent plasma therapy [6], no effect was demonstrated by meta-analysis. However, considering the disease progression from the viral infection phase to the host inflammatory response phase, the stage of patients showing a response to each drug can be limited, raising the possibility that the participant groups were not be properly stratified according to the disease stage in previous clinical studies. In addition, there could be differences in results depending on which variables were considered as the criteria for the assessment of treatment effect. For instance, a large-scale study on remdesivir by WHO in patients with varying severities demonstrated no significant effect on reducing mortality rate [7], whereas a well-designed randomized clinical trial in homogeneous patients showed an enhancing effect on clinical recovery in those requiring oxygen therapy [8]. Even though convalescent plasma therapy showed no effect on reducing mortality rate in a study including patients with severe pneumonia [9], it showed a preventive effect on disease progression into severe conditions in a study including elderly early-stage patients with mild symptoms [10]. At this point, it is necessary to continue to perform studies in order to develop and discover new drugs due to very few effective ones. In particular, there is an urgent need to develop drugs that are easy to administer in patients with mild symptoms, and prevent the aggravation and spread of the disease in early stages. Since the stages of patients would be varying, in whom drugs show therapeutic efficacy according to its action mechanism and disease progression, it seems very important to obtain the homogeneity of patients in clinical research.

Unfortunately, there are only few national data on clinical studies that can support the development of national guidelines. Moreover, in the midst of scarcity of specialists, physicians also took charge of patient care and infection control and played the role of researchers to perform clinical studies. Therefore, human resources to conduct clinical studies during the surge period was inadequate due to the burden of patient treatment, and even after the surge period, there were limitations due to paucity of patients. The KSID tried to establish a system for society members to perform collaborative clinical research from the beginning of the pandemic. However, planned studies could not be conducted due to limitations in the rapid resolution of legal regulations (which were not ready to respond to the emergency situation), and a lack of institutional support. It is of utmost importance to discover answers through establishment of evidences from research, thereby galvanizing a significant response to an enigmatic disease (COVID-19). This process can be accomplished by the harmonious collaboration of basic scientists and clinical experts, and political and institutional support from the government and relevant regulatory institutions. In an unprecedented context of the pandemic, there were excessive passions but a lack of specialty, thereby leading to delayed and missed portions in the results. We look forward to institutional complementation and administrative support to continue further investigation in cases where proper therapy is not established yet.

This revised version of guidelines is of great significance in that it is a result of collaboration between the KSID and the National Evidence-based Healthcare Collaboration Agency

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(NECA). Since there were collaborations between experts and institutions in the response to COVID-19, the guidelines were revised based on recent evidences by searching and analyzing high-quality data retrieved from numerous newly published papers. Medicine is a science that evolves and develops together with novel research results. COVID-19 is a new research field with the most rapid accumulation of data among all other fields. This revised version of guidelines will be modified again and supplemented according to future published data. We look forward to constant collaborations with relevant institutions in order to continuously revise these guidelines and even involve guidelines on therapeutic antibodies, which could not be covered in this revision. Ultimately, like the advanced countries where a variety of main agents are collaborating to develop "living guidelines" in the health crisis requiring urgent responses, we hope the national establishment of infrastructure and institutional support to evaluate scientific evidences will help in the development of these guidelines.

SUPPLEMENTARY MATERIAL

Editorial Korean version.

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