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Review Article

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Empirical Treatment and Prevention of COVID-19

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ABSTRACT

The rapid spread of severe acute respiratory coronavirus syndrome 2 (SARS-CoV-2) in the population and throughout the cells within our body has been developing. Another major cycle of coronavirus disease 2019 (COVID-19), which is expected in the coming fall, could be even more severe than the current one. Therefore, effective countermeasures should be developed based on the already obtained clinical and research information about SARS-CoV-2. The aim of this review was to summarize the data on the empirical treatment of COVID-19 acquired during this SARS-CoV-2 infection cycle; this would aid the establishment of an appropriate healthcare policy to meet the challenges in the future. The infectious disease caused by SARS-CoV-2 is characterized by common cold along with hypersensitivity reaction. Thus, in addition to treating common cold, it is essential to minimize the exposure of cells to the virus and to mitigate the uncontrolled immune response. A proper combination of antiviral agents, immune modulators such as prednisolone, and anticoagulants such as heparin and anti-C5a antagonists could be employed to minimize lung damage and prevent systemic involvements. Finally, strategies to achieve population immunity against SARS-CoV-2 should be developed through understanding of the interaction between the immune system and the virus.

Keywords: COVID-19; SARS-CoV-2; Coronavirus; Treatment; Prevention

INTRODUCTION

Novel coronavirus (severe acute respiratory coronavirus syndrome 2, SARS-CoV-2) has been rapidly spreading in the population [1] as well as throughout the cells within their bodies [2, 3]. To date, it has been around 4 months that the whole world suffered from it. Another major cycle of the infection is expected in the coming fall from the northern hemisphere which would be even more severe than the first one [4]. Therefore, it is important to develop more effective countermeasures based on the scientific data obtained during the first round of coronavirus disease 2019 (COVID-19).

Our previous article defined the nature of the infectious diseases as the hypersensitivity reaction by the virus and presented the basic treatments based on the hypersensitivity pneumonitis (HP) [5, 6]. The diagnosis of COVID-19 can be empirically achieved by one or

more of the following: 1) clinical symptoms, 2) radiologic imaging studies such as chest computed tomography or magnetic resonance imaging of central nervous system, and 3) detection of virus by real-time reverse transcriptase polymerase chain reaction/serology.

The aim of this review is to present empirical treatment and preventive strategies for COVID-19 based on the accumulated experience in managing the disease, which may aid in clarifying the confusion associated with research results and would help shape the healthcare policies. However, researchers should consider the fact that the data published currently in scientific journals might be somewhat biased because of the turbulent environment due to the COVID-19 pandemic. Therefore, the proposed guidelines should be revised as soon as new and reliable research data are available.

MEDICATIONS FOR COMMON COLD

Though the COVID-19 showed pandemic spread and unexpected clinical manifestations characterized by various symptoms throughout the whole body, SARS-CoV-2 seems to be less virulent especially in children and adolescents, in whom the disease mimics common cold caused by seasonal coronaviruses [7]. Therefore, basic therapeutic approaches used for common cold would be effective in case of mild symptoms and further treatment is not required in the absence of any other clinical manifestations [8]. **Table 1** summarizes the treatments used for common cold including that caused by coronaviruses.

Non-steroidal anti-inflammatory drugs (NSAIDs) can be safely used for 2 - 3 days without affecting the pentose phosphate pathway. In contrast, acetaminophen can increase reactive oxygen species in the cell and induce cell death [9, 10]. However, use of NSAIDs can result in hypersensitivity [11] and acute thromboembolic events [12]. There were a few reports regarding concerns that NSAIDs can weaken the immune system if applied a week or longer [10, 13]. Prednisolone is safer and more efficacious, considering that it can overcome the overall inflammatory process in a cell by suppressing the diverse kind of cytokines including interleukins and tumor necrosis factor-α [14]. Hydrocortisone is considered the best medicine with fewer side effects.

Pseudoephedrine at dose of 10 - 20 mg is effective for the protection of epithelial cells by raising the intracellular cyclic guanosine monophosphate [15]. Antihistamine can help lessen the vascular permeability by blocking the platelet activating factor [16] and alleviate allergic symptoms [17]. Cimetidine can improve the heartburn symptom and elevate the immune

Table 1. Medications for common cold

Class/Symptoms	Drug
Analgesics for pain and fever	Prednisolone 10 mg PO
	Hydrocortisone 25 - 50 mg PO
	Ibuprofen, naproxen, and other NSAIDs: be cautious to hypersensitivity reactions and acute thromboembolic side effects.
	Aspirin can cause Reye's syndrome
Antihistamines for runny nose	Diphenhydramine, loratadine, fexofenadine, cetirizine, levocetirizine, etc.
Decongestants for stuffy nose	Pseudoephedrine: contraindicated for the patients with uncontrolled high blood pressure
Anti-tussives	Dextromethorphan, codeine.
Phosphodiesterase inhibitor, nonselective	Theophylline at low doses (100 - 200 mg PO twice per day)
Immune modulators with antibacterial effect	Azithromycin, clarithromycin

PO, per os.

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functions [18]. Theophylline at low doses (100 – 200 mg twice daily), the medicine applied to the treatment of asthma for a long time, can be administered safely. It can protect alveolar epithelium with the suppression of cytokine-inducible nitric oxide synthase (NOS) and raising intracellular cyclic adenosine monophosphate [19]. Macrolide antibiotics including azithromycin cause few side effects and their early application can support epithelial cells for some time [20]. Macrolides transform gut microbiome so that they protect against the respiratory virus and strengthen endothelial NOS pathway [20-22].

Human immunodeficiency virus (HIV) non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as rilpivirine described below can be used for the patients with common cold symptoms preemptively, instead of all medications mentioned above. That is what we experienced the effect of oseltamivir in the 2009 Influenza (H1N1) pandemic.

TREATMENT FOR PNEUMONIA

At the early stage of the epidemic, it had been recommended to apply the treatment regimen of middle east respiratory syndrome coronavirus (MERS-CoV) in the case of the patients with severe symptoms [23]. An interim guideline was suggested by the members of Korean Society of Infectious Diseases (KSID) in April, 2020 [24]. This treatment strategy is further proposed with taking into consideration of the KSID guideline. Pneumonia features observed in COVID-19 are similar to that of HP. Therefore, it is needed to follow the application of basic treatment strategy for HP [14], which is to prevent cell exposure to the virus and to abate the excessive immune reactions. In addition to this treatment strategy, it is needed to apply anticoagulants [25, 26]. It is required not to interrupt the initiation of adaptive immunity as augmenting the innate immune system. Another purpose of the treatment regimen in this review is to sustain lifeforce without the application of the mechanical ventilator and extracorporeal membrane oxygenation and thereby to result in the blockade of breakdown of healthcare system (**Table 2**).

The aim of the administration of antiviral agents is to lessen the exposure to antigen (virus). Ribonucleic acid (RNA) dependent RNA polymerization is considered as a crucial step in the RNA virus because SARS-CoV-2 is positive sense single-stranded (ss)RNA virus. Unfortunately, it appeared to be controversial to apply remdesivir that was developed for the negative sense ssRNA virus such as Ebola virus [27, 28]. Also, side effects of remdesivir were not well known, and its intravenous administration can cause another burden to the healthcare system. Safer medicine is the best for patients as an empirical regimen. Treatment with most nucleotide/nucleoside inhibitors is theoretically applicable [29, 30]. Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), which has been prescribed for HIV-infected or hepatitis B virus-infected patients for a long time can be used safely as a short-term medicine for COVID-19 patients. Despite the unfavorable result in a small case series study [31], TDF/FTC would serve a good candidate because of its high concentration in the epithelium and safety profile.

An *in vivo* study showed that an HIV NNRTI rilpivirine was very effective against positive sense ssRNA Zika virus [32]. There was a report on HIV NNRTIs to be effective with the molecular docking by computational simulation [33]. Furthermore, it was reported that rilpivirine had comparable efficacy to remdesivir *in vitro* [34]. Antiviral therapy has the best effect when administered for a minimum of 5 days and a maximum of 14 days to avoid unexpected side effects; earlier discontinuation should be considered if clinical progress is evident, including

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Table 2. Treatments for pneumonia

Anti-viral agents			
Drug		Duration	Remark
Nucleotide/nucleoside analogues	Remdesivir, tenofovir/emtricitabine	5 - 14 days	Acyclovir, famciclovir, and ganciclovir need to be studied
HIV NNRTIs	Rilpivirine, efavirenz, etravirine	5 - 14 days	Doravirine may be efficacious.
HIV protease inhibitors	Lopinavir/ritonavir, darunavir/ritonavir or cobicistat, atazanavir	5 - 14 days	
Antimalarials	Chloroquine, hydroxychloroquine, mefloquine	3 days	Mefloquine should be administered up to 5 tablets.
Corticosteroids			
Severity of pneumonia	Treatment	Duration	Remark
Mild pneumonia	Steroid inhaler or prednisolone 10 - 20 mg PO	Preemptive: 5 - 7 days Therapeutic: 5 - 21 days	Prednisolone is safer than methylprednisolone. Hydrocortisone 300 mg/day can be used for patients with unexpected side effects.
Moderate pneumonia	Prednisolone 30 mg PO	Not recommended after 3 weeks of illness, except for cases with proliferative inflammation on biopsy.	
Severe/critical pneumonia	Prednisolone 40 mg once or twice daily PO, or methylprednisolone 1mg/kg/day IV	Rapid tapering is required.	
Antibiotics for other coinfections/superinfections			
Severity of pneumonia, or coinfection	Treatment	Duration	Remark
Mild pneumonia	Ceftriaxone or macrolide (azithromycin/clarithromycin)	Around 3 days	Macrolide, cephalosporin, and glycopeptide antimicrobial increases the innate immunity
Moderate pneumonia	Ceftriaxone + macrolide ± teicoplanin/vancomycin	Around 7 days	
Severe/critical pneumonia	Vancomycin + macrolide ± meropenem	7 - 14 days	Consider the epidemiologic patterns of microbes
Influenza	Oseltamivir	5 days	Consider false negative result of the rapid diagnostic test

Anticoagulants: Recommended for patients with anyone of followings; 1) patients of ≥65 years 2) dyspnea and hypoxia requiring 3L/min oxygen to correct hypoxemia, 3) respiratory rate >24/min, 4) decreased consciousness, 5) unstable vital signs, 6) patients requiring mechanical ventilation, hemodialysis, CRRT, or ECMO. Preemptive use is preferable to decrease lung sequelae, if available.

Drug	Administration route/dose
Heparin	IV, SQ, inhalation; heparin has a thrombolytic effect. IV unfractionated heparin sulfate; initial dose: 80 units/kg bolus (maximum = 10,000 units), initial infusion rate: 18 units/kg/h (maximum = 23,000 units/h), then adjust the target aPTT range (60 - 85) Nebulized unfractionated heparin sulfate 10,000 - 25,000U every 4h (height ≥165 cm) or every 6 hours (height <165 cm)
Anti-C5a antagonist	IV; inhalation/nebulization may be possible.
Camostat mesylate/nafamostat mesylate	IV; the efficacy could be limited due to suppression of C3b and C5b facilitation.
Warfarin	PO; preemptive and prophylactic use is considered for high-risk patients. Drug interactions are common.

Interferon: 1) Interferon-β 1b, mainly by Inhalation. Consider the combination of SQ + inhalation. 2) Patients of the age ≥70 years are indicated. Consider the administration of interferon for the high-risk patients of ≥40 years. The maximum effect of interferon will be achieved within 3 days of the onset of COVID-19. 3) Duration: 7 days for patients of ≥70 years, 14 days for the patients of ≥80 years and high-risk patients

Antipyretics: Hydrocortisone 25 – 50 mg PO/IV, or prednisolone 10 mg PO

Phosphodiesterase type-5 inhibitors (sildenafil): rescue therapy (50 mg PO every 8 h) for patients with impending respiratory failure

Epinephrine: nebulization/endotracheal/IV; emergency use for patients showing acute hypersensitivity reactions with shock

HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; PO, per os; IV, intravenously; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; SQ, subcutaneously; aPTT, activated partial thromboplastin time.
All medications should be administered with caution as they might cause unexpected hypersensitivity reactions and serious side effects. Older medications are desirable but may have minor side effects that are easy to control. All medications can be used preemptively for patients with symptoms of pneumonia or systemic involvement and can be adjusted based on the ideal body weight, but should be prescribed for children at recommended doses.

clearance of symptoms, improved immune response, resolution of pneumonia as revealed by chest radiography. However, patients aged 65 years and older [35] or those with the impaired immune status due to diabetes mellitus, hypertension, and other conditions could receive the drugs beforehand and for a longer time.

Lopinavir/ritonavir does not appear to be a promising treatment for COVID-19 [36], although it was reported to have good efficacy for the treatment of SARS [37]. It may be effective to apply the kind of antimalarial drugs such as chloroquine, hydroxychloroquine, and

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mefloquine [10, 29, 38], however, side effects are concerned due to higher doses than those generally used for the treatment of malaria. It may be better not to exceed the treatment doses and period for malaria. The mechanism of azithromycin seems to be efficacious by strengthening the innate immunity [20] rather than antiviral efficacy against SARS-CoV-2 [38]. Serine protease inhibitors [39] such as camostat mesylate/nafamostat mesylate are limited options as they suppress the facilitation of C3b and C5b [40].

Antiviral agents should be prescribed at the earlier stage of pneumonia to stop the progression to acute respiratory distress syndrome. If the supply of medicine is not enough, it can also be started around 5 - 7 days after the infection. Even so, antiviral treatment should be given to the patients with older age or risk factors such as diabetes mellitus, hypertension, or immunosuppressive disorders immediately.

As for the COVID-19, the application of steroids can be the basis for the treatment since the main symptom might be developed due to hypersensitivity reaction [14]. Although the various steroid inhaler could be effective, oral administration of prednisolone up to 0.5 mg/kg per day can treat a moderate degree of pneumonia. The nebulization with hydrocortisone would be safer among steroid inhalers. Prednisolone 40 mg per 12 hours PO is recommended to the patients with severe pneumonia [41]. In the case of patients requiring intensive care, the equivalent dose of methylprednisolone/hydrocortisone can be administered intravenously [42]. The short term treatment for 5 - 7 days for moderate pneumonia may be preferable [41]. The duration of administration for the severe cases can be extended to 10 - 21 days after the onset of infection until the immune function is optimal. If the clinical improvement of COVID-19 becomes obvious, rapid tapering is needed for optimal immune function. Although hyperinflammation by elevated cytokines such as IL-1, IL-6, or TNF-α can contribute to the lung damage, certain anti-cytokine strategy would be not good enough to suppress the whole inflammatory process [43].

In the case of severe/critical pneumonia, anticoagulants have to be applied as a basic treatment regimen [40] to help avoiding the use of mechanical ventilation or extracorporeal membrane oxygenation. It is required to make an adequate choice according to the symptom of the patients among warfarin, heparin [44], or camostat mesylate/nafamostat mesylate. Warfarin can be administered to high-risk groups from the beginning of infection as an oral medication. Because anti-C5a antagonist is not easily accessible and very expensive, inhalation of heparin [45] is more suitable in the case of lung involvement. Furthermore, injection of heparin is required for thrombin lysis if a patient shows symptoms of thromboembolism. Rapid alleviation of symptoms can be expected with intravenous administration of heparin and an anti-C5a antagonist in combination, especially in cases when the virus invades the central nervous system; therefore, camostat mesylate/nafamostat mesylate are not recommended as they suppress the formation of C3b and C5b [40].

Interferon (INF)β-1b is the most effective among various INFs [23] and is recommended in combination with other antiviral agents. INF treatment should initiate within three days of infection [23] and the duration of the treatment should depend on the age and immune status. A one- and two-week treatment regimen is recommended for people in their 70s and 80s, respectively, and longer treatment is recommended for those with weakened innate immunity [35].

Antibiotics can be used empirically for the treatment of superimposed/combined bacterial pneumonia. Vancomycin [46], teicoplanin [46, 47], and azithromycin [20, 38], which are

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expected to show efficacy against SARS-CoV-2, can be administered. If secondary infections emerge in intensive care units, the epidemiology profile of multidrug-resistant bacteria at the hospital should be taken into account, and an empirical combination of vancomycin/teicoplanin, meropenem, and macrolides can be used. Country-specific influenza trends should also be considered, and if a rapid diagnostic test is positive, oseltamivir is the treatment of choice; it should also be employed if false negative results are obtained for patients with typical flu symptoms, patients who are elderly (65 years and older), or those on immunosuppressants.

Phosphodiesterase type-5 inhibitors may relieve acute exudative damage in the lungs via the downregulation of proinflammatory and profibrotic cytokines induced in response to reactive oxygen species, thereby representing a rescue therapeutic modality [48]. Epinephrine should be also used in patients with acute hypersensitivity reactions with shock.

It should be always kept in mind that overtreatment may trigger and/or worsen efferocytosis or cause side effects; therefore, the clinical status of the patients should be closely monitored and even small changes should be considered for treatment adjustments.

PREVENTION OF RAPID SPREAD AND DISEASE PROGRESSION OF SARS-CoV-2

At present, it is not likely that effective strategies to block the spread of SARS-CoV-2 have already been developed in the present crisis and we can expect nothing more than the initiation of appropriate immune responses to lower the exposure to the virus. Changes in virus characteristics during the HIV epidemic provide a glimpse of how SARS-CoV-2 could evolve depending on the immune response. We can assume that the faster transmissibility (and/or higher pathogenicity) appears as the virus circulates in the elderly who have weaker innate immunity, while the slower transmissibility (and/or lower pathogenicity) appears in the younger people who have higher innate immunity. It can also be expected that individuals with allergic disorders may show a different clinical course and/or more severe symptoms than the general population.

To prevent infection and initiate appropriate immunity to the virus, a sufficient level of air circulation indoors, cough etiquette and maintenance of hand hygiene are required. Furthermore, social and physical distancing among people should help prevent the breakdown of the medical system. It also seems reasonable to allow a temporary increase in patient numbers to the level which can be managed by the current medical system. These strategies also include appropriate healthcare policies, for example acquisition of herd immunity, which has been adopted in Sweden [49]. With proper measures, it is quite possible that we should be able to overcome the expected second wave predicted in the northern hemisphere in the coming late fall and winter [4].

It is quite unlikely that adaptive immunity would be activated with a vaccine that induces IgG via antibody-dependent immune enhancement, similar to the one observed in case of infection with the Dengue virus [50]. It should also be noted that convalescent serum therapy may be harmful. Therefore, increasing of nonspecific innate immunity is needed surely for the elderly and the people with defective innate immunity. Increasing innate immunity in the epithelium as the first line defense is as follows. Moderate mountain hiking can lead to the increase of muscle tissue and strengthen the lung capacity [51]. Being exposed to nature will

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lead to an increase of innate immunity by the sound microbiome [52]. In addition, spending time on the beach such as, playing, reading, or swimming would be effective in reducing the viral load infected to upper respiratory tracts [53].

It is well known that probiotics such as *Lactobacillus* spp. can enhance immunity. Vitamin D supplements also reinforce the resilience against the virus as it enhances immunity [54]. Antibiotics of macrolides kinds, metronidazole, trimethoprim/sulfamethoxazole, dapsone may help increase the immunity as well [55]. Rosiglitazone and pioglitazone can promote innate immunity as a PPAR-γ agonist [56]. Cimetidine which is helpful in the case of heartburn will enhance immunity [18]. BCG vaccine can stimulate the immune system [57]. Also, the innate immunity of T lymphocyte can be elevated by the application of RNA delivery into cells [58].

PERSPECTIVE FOR THE FUTURE RESEARCH

The precise therapeutic mechanisms of the medications recommended in this review should be clarified in future studies, and the efficacy of antiviral agents and anticoagulants needs to be confirmed in randomized controlled trials. A bulk of clinical and research data cannot be interpreted at present. Considering that the infection can be asymptomatic and as it can rapidly spread across national borders, studies—to elucidate the life cycle of SARS-CoV-2, innate and adaptive immune responses to the virus, and side effects of medications—should be conducted on a global scale; this would help in developing appropriate treatment strategies. Studies pertaining to the lifestyle, including diet, living conditions, and working environment, and hospital policies are also necessary. Considering the high intracellular concentration of TDF/FTC in the epithelium, short-term preexposure and postexposure prophylaxis with TDF/FTC or rilpivirine for healthcare workers and high-risk groups could be useful [59, 60] and its effectiveness should be evaluated. In addition, the short course of TDF/FTC can contribute to decrease viral shedding in stool.

Vaccine development is urgent. As it is challenging to produce a proper vaccine that takes into consideration the interaction between the immune system and coronaviruses such as SARS-CoV-2, comprehensive studies should be attempted using several viral strains and up-to-date techniques as well as conventional approaches, including inactivated whole virus. Furthermore, the efficacy of different inoculation methods should be compared.

There are several reports on the status of SARS-CoV and MERS-CoV survivors, including their low lung capacity and cognitive problems [61-63]. Systematic studies are required to address these complications. Isolation restricts motor activity, which would add considerable physical and mental problems for patients with deteriorated lung function, especially those in intensive care units. If possible, various rehabilitation activities are recommended at the beginning of the isolation rather than after recovery. Considering that SARS-CoV-2 is less virulent in the younger population, employment of young healthcare workers should contribute to prevention of secondary infections and accelerate patient recovery.

CONCLUSION

SARS-CoV-2 is a virus that causes common cold and various hypersensitivity reactions. The lack of immunity against SARS-CoV-2 results in the worldwide spread of COVID-19, a novel

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disease with diverse clinical manifestations and pathophysiological mechanisms. After the initial confusion among the scientific community and healthcare professionals, extensive basic and clinical research has been conducted to understand the course of COVID-19 and reactions triggered by SARS-CoV-2 in the host. These findings could contribute to our understanding of the pathophysiology not only of COVID-19 but also of other infectious diseases.

We need to analyze the data obtained through evaluation of COVID-19 survivors as well as COVID-19-related deaths, so that the losses associated with the pandemic can be minimized. It is also necessary to evaluate our natural environments and review the extensive scientific data obtained in the past, so that better solutions for combating the next wave could be identified. Strategies developed through analysis of the current pandemic should prepare us for future crises caused by pathogens more lethal than SARS-CoV-2.

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