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Review

Seven recommendations to rescue the patients and reduce the mortality from COVID-19 infection: An immunological point of view

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ABSTRACT

Now COVID-19 is causing a severe public health emergency and the mortality is rapidly increasing all over the world. In the current pandemic era, although there have been many efforts to diagnose a number of patients with symptoms or close contacts, there is no definite guideline for the initial therapeutic approach for them and therefore, many patients have been dying due to a hyperinflammatory immunological reaction labeled as "cytokine storm". Severe patients are hospitalized and the treatment is done, though they have not been established yet. Currently, however, no treatment is provided for those who are isolated at home or shelter until they get severe symptoms, which will increase the harms to the patients. In this review, we discuss some important points dedicated to the management of patients with COVID-19, which should help reducing morbidity and mortality. In this era, we suggest 7 recommendations to rescue the patients and to reduce the morbidity and mortality due to COVID-19 based on the immunological point of view.

1. Introduction

Coronavirus Disease 2019 (COVID-19) is a severe public health emergency worldwide caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. The number of confirmed cases and the mortality rate are increasing worldwide and the World Health Organization (WHO) acknowledged COVID-19 as a pandemic on March 11, 2020 [2]. Currently, there have been many efforts to diagnose a number of patients with symptoms or close contacts to prevent the spread in the community. This may prevent some spreading of the virus, but not perfectly. Moreover, many confirmed cases are occurring through diagnosis, but there is no definite guideline for the initial therapeutic approach for them and therefore, many patients have been dying. If the COVID-19 symptoms are severe, the patients are hospitalized and the treatment is done, though they have not been established yet. Currently, however, no treatment is provided for those who are isolated at home or shelter. Among them, there will be also some cases in whom severe lung injury or cytokine storm has progressed [3], leading to sudden death. Case fatality rates in some countries, especially Italy and Spain, are high and effective therapeutic measures are urgently needed [4]. In this review, we discuss some important points dedicated to the management of patients with COVID-19, which should help reducing morbidity and mortality.

2. How much do we know about the pathophysiology of COVID-19-associated lung injury and death?

Patients with COVID-19 have higher leukocyte numbers, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, and an imbalance of pro−/and anti-inflammatory cytokines and chemokines with increased levels of interleukin (IL)-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factor (FGF)2, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interferon (IFN)-γ, IFN-γ induced protein (IP)-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)1-α, MIP1-β, platelet derived growth factor (PDGF)-B, tumor necrosis factor (TNF)-α, and vascular endothelial growth factor (VEGF)-A [5]. Higher expression levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP1-α, and TNF-α were found in individuals admitted to the intensive care unit (ICU) [5]. These cytokines may indicate patients

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at risk to develop acute lung injury, followed by acute respiratory distress syndrome (ARDS) and eventually death. This circumstance is called cytokine release syndrome (CRS) or "cytokine storm" [6].

The main pathogenesis of COVID-19 may be similar to that of other viruses such as influenza or others. However, there have been few efforts to make a potential hypothesis why COVID-19 could cause a higher incidence of acute lung injury, ARDS, cytokine storm and death than other viruses. We are going to make a simple hypothetical model for the inflammatory processes and "cytokine storm" for COVID-19 to understand the pathophysiology of COVID-19 and its associated lung injury, ARDS and cytokine storm.

- First, COVID-19 (SARS-CoV-2) is first attached to the angiotensin converting enzyme 2 (ACE2) receptors in the nasopharynx and respiratory epithelium [7].
- Second, host immune responses are initiated after entry of COVID-19 into the cells and the pro-inflammatory cytokines induced by COVID-19 are formed by various kinds of immune cells such as T cells, B-cells, and macrophages, and others [8,9].
- Third, the degree of increase in pro-inflammatory cytokines determines the degree of COVID-19-induced lung injury. The more increase in pro-inflammatory cytokines, the higher the injury to lung tissue and the more severe the ARDS, which could be related to higher mortality.
- Fourth, the degree of increase in pro-inflammatory cytokines in COVID-19 is higher as induced by other viruses. Especially, this effect is more pronounced in older age and comorbid conditions.
- Fifth, the reason why this effect is less pronounced in younger age groups may be obscure, but it could be due to the immaturity of immune system and the predominance of Th2 immunity than Th1 in these groups.
- Sixth, the reason why this effect is more pronounced in older age groups and those with comorbid conditions may be obscure, but it could be due to pre-existing subclinical or subtle inflammations, represented by increased high-sensitive CRP (hsCRP) in these groups.
- Seventh, the exaggerated increase in pro-inflammatory cytokines in COVID-19 could be due to hyperactivation of various kinds of immune cells in response to N-protein of COVID-19, which is called "cytokine storm".
- Eighth, this increase in pro-inflammatory cytokines induced by COVID-19 ("cytokine storm") can cause acute lung injury, ARDS and eventually multiorgan failure.
- Ninth, "cytokine storm" may start from the early course of disease to later stage according to the degree of activation of host immune response and it may be rapidly progressive at any time.
- Tenth, there may be clinico-pathologic non-correlations between them [3]. The patient may be asymptomatic or have mild symptoms despite severely progressed conditions, which will delay the appropriate treatment at an early stage.

3. Understanding of the pathogenesis of COVID-19: more immunological activation than other usual respiratory viruses

The pathogenesis of COVID-19 is summarized in Fig. 1. Regarding our immunity, there are 3 states: (1) immunosuppressive state, (2) normal immune state (this is also classified as lower normal, normal, and upper normal), and (3) hyperimmune state. If there are 100 normal persons, they are distributed from 0 to 100 on a scale according to the degree of anti-viral immunity, which will be mostly represented by Th1 response. If the person is immunocompromised, he/she will have minus points on the scale. The lower the minus number is located, the more severe the immunosuppressive condition will be. If the number is higher than 100, the person will get hyperactivated host immune response and will have lung injury, ARDS and multiorgan failure.

If the person is infected with other usual respiratory viruses, such as rhinovirus or influenza, he/she will have fever and sore throat caused by host immune response. However, the degree of increase in inflammatory reaction will be 3–5. So, if the person who has the number of immunity scale of 90 and infected by other viruses, the number on a scale will increase to 93–95. However, the degree of increase in inflammatory reaction in patients with the current COVID-19 will be 10–15. Therefore, if the person who has the number of immunity scale 90 is infected by COVID-19, the number on a scale will increase to 100–105, which means that there will be a high probability that this patient will progress to "cytokine storm" due to hyperactivated immune response, which might lead to death.

Because younger age groups' immune system may be immature and they may have the predominance of Th2 immunity than Th1 [10], they might have the number of immunity scale 0–30. Therefore, even though they are infected by COVID-19 and the number is increased by 10-15 by COVID-19, their number will be located between 10 and 45. Therefore, there is a lower possibility that they will be progress to severe "cytokine storm", which may explain less mortality in this group.

However, the person in an older age group will have multiple comorbidities by aging process such as atherosclerosis, hypertension, diabetes mellitus, metabolic syndrome and chronic kidney disease and they might have pre-existing subclinical or subtle inflammations, represented by increased hsCRP in these groups [11]. Therefore, they might have a number of immunity scale 85–95. Therefore, if they are infected by COVID-19 and the number of 10–15 is increased by COVID-19, their number will be located between 95 and 110. Therefore, there is high possibility that they will progress to severe "cytokine storm", which may explain high mortality in this group. Surely, there will be additional factors that influence the susceptibility and severity of COVID-19, such as genetic variant of different polymorphisms or environmental factors as smoking.

In addition to this basic 10–15 increase in the degree of inflammatory reaction, if the patient progressed to "cytokine storm", the number will rapidly increase to 200–300. We are going to discuss the use of steroids later, but the basic increase of 10–15 in various pro-inflammatory cytokines induced by COVID-19 might be suppressed by short-course low dose steroids in an early stage of disease, but steroids may not be effective in a later stage of disease such as ARDS and multiorgan failure to suppress "cytokine storm" because 200–300 cannot be suppressed even though high dose of steroids are used. Recently, hydroxychloroquine has been shown to be effective in COVID-19 [12], and this drug may reduce the increase in the degree of inflammatory reaction. However, we do not know which agent may be better in decreasing inflammatory reactions and how much the number might be decreased by steroids or hydroxychloroquine.

In addition to these, the rate of bacterial complications will increase in accordance with the progression with time after COVID-19. We think if bacterial complication is combined with "cytokine storm", there will be more severe inflammatory reactions. Although this theory may not be perfect, this may be helpful to understand the pathogenesis and potential harms of COVID-19 and guide how patients should be treated.

4. Can we apply evidence-based medicine for the treatment of COVID-19?

Evidence based medicine (EBM) is the conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients [13]. EBM integrates clinical experience and patient values with the best available research information [13]. Many clinicians are applying the treatment to the current coronavirus (COVID-19) based on the previous experiences for MERS or SARS. However, this is not exactly evidence-based, since COVID-19 is different. To be evidence-based, a large-scale randomized placebo-controlled trial for COVID-19 should urgently be conducted. However, it is too difficult to find an appropriate drug for COVID-19 in a pandemic state, because it will take a long time, although this effort

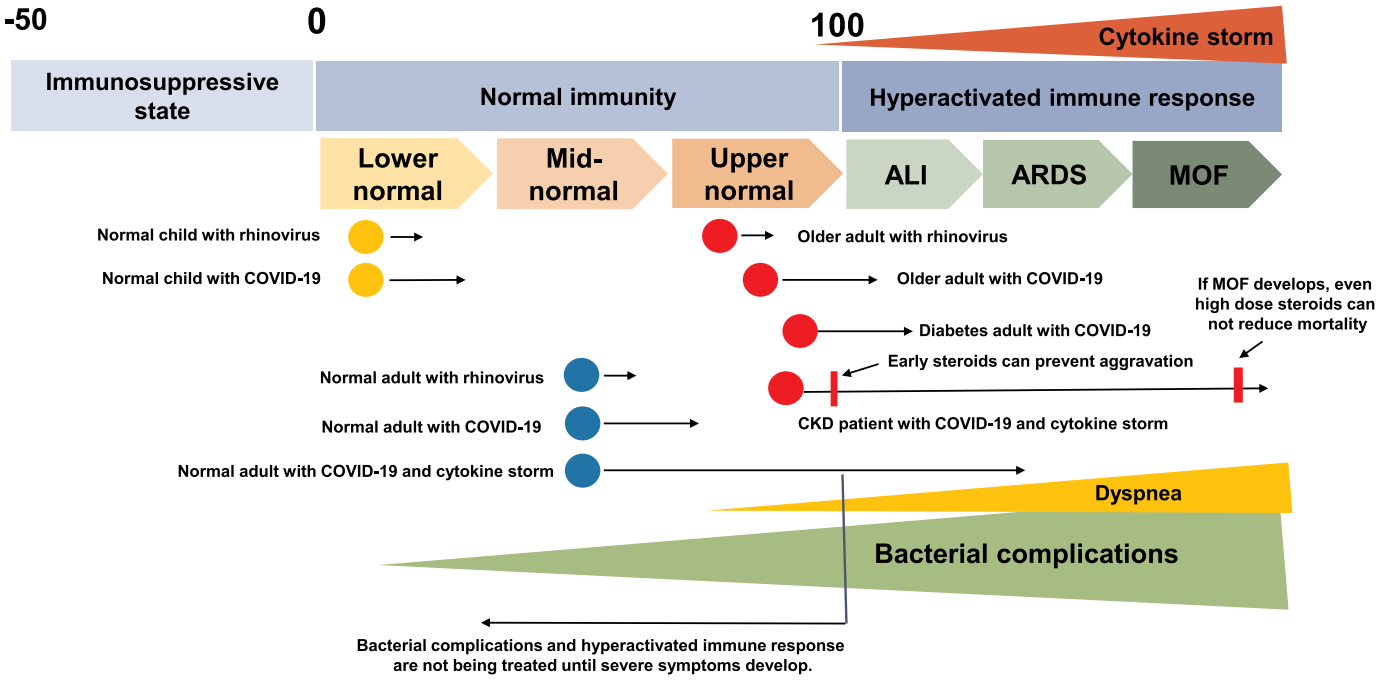

Fig. 1. The pathogenesis of COVID-19 infection and cytokine storm. ALI: acute lung injury; ARDS: acute respiratory distress syndrome; MOF: multiorgan failure; CKD: chronic kidney disease.

should also be done concurrently.

In addition, even if the results of small RCTs are meaningful, those are often reversed when a larger RCT is performed [14]. Moreover, although the results of meta-analysis may be considered to be the best evidence, this should be interpreted with caution, because the meta-analysis results can be significant even though all the results of individual RCTs have no statistical significance [15]. Furthermore, it has been claimed that most published research findings are false and not useful [16,17] (though this should also be interpreted with caution) and numerously published meta-analyses are also misleading [18]. In addition, guidelines suggested by experts can also have a mistake [19]. In this context, we should find what is the best strategies to protect the humans form the harms of COVID-19. Even though we apply several therapeutic strategies investigated in SARS or MERS, it should be interpreted with caution. If we cannot apply EBM immediately in this COVID-19 pandemic, we should also make every effort to find wise ways to solve the problems. In this situation, an experience-based approach may be also important in this pandemic era and many publications should urgently be published even though they are case reports or case series.

5. The basic principle for the treatment of patients: "Do no harm"

COVID-19 is causing a severe public health emergency all over the word and the mortality is rapidly increasing all over the world. We would like to remind of the basic principle for the treatment of patients, but we often forget this: "Do no harm" [20]. We should think of what "harms" means and what "do no harms" would look like in this pandemic. We have thought and summarized the potential harms and the things we are doing now regarding COVID-19 and it is summarized as below and Table 1.

(1) Continuing smoking is a significant harm to respiratory epitheliums. If so, why don't we recommend cessation of smoking at this time? Not doing so is causing a significant harm to the patients.
(2) "Cytokine storm" is considered to be a significant harm and an important cause of death. If so, why don't we make every effort to prevent this process at an early course of disease? Not doing so is causing a significant harm to the patients.
(3) Currently, some asymptomatic patients or those with mild symptoms have severe radiologic findings and bacterial complications which can lead to sudden death, but no radiologic examinations and treatment are done for these patients until severe symptoms develop. This may be considered to be a significant harm. If so, why don't we make every effort to detect these patients and treat them at an early course of disease? Not doing so is causing a significant harm to the patients.
(4) Currently, COVID-19 infected patients are divided into two groups: one is the person who is isolated at home, but no medications are provided and the other is the person who developed severe symptoms with time and admitted to the hospital. Currently, many patients with COVID-19 are recommended to be at home until severe symptoms develop, due to infectivity to others. We think there will be a patient group with moderate symptoms in whom if early treatment is done with steroids and antibiotics, they will not progress to severe conditions. To let them at home will be a significant harm. If so, why don't we provide medications such as steroids or antibiotics at the time of COVID-19 test and monitor the patient even by phone, considering it is practically difficult for the patient

Table 1
Points of current potential harms in the novel COVID-19 disease.

- Smoking cessation has not been recommended in this pandemic era, which may be a significant harm.
- Although "Cytokine storm" is considered to be a significant harm and an important cause of death, there have been few efforts to prevent this process at an early course of disease.
- The person with COVID-19 who is isolated at home does not receive any medications or treatment until severe symptoms such as dyspnea develops.
- Although some asymptomatic patients with COVID-19 or those with mild symptoms have severe radiologic findings, no radiologic examinations are given to these patients until severe symptoms develop.
- Although some mild patients with COVID-19 have bacterial complications at any stage, no treatment is given until severe symptoms develop.
- Misinterpretation of the results from various studies including systematic review without considering the biases will lead to a false guidance for the treatment of COVID-19, which will be a significant harm

to visit the clinic again? If so, policy should be changed in this pandemic era as medications should be given to the patients more liberally than in usual situations. Not doing so is causing a significant harm to the patients and hesitating for the use of steroids and antibiotics may be a harm to the patients with COVID-19.

(5) Doing something is better than nothing. Currently, there are no established guidelines for COVID-19 and we rely on the previous treatments for SARS, MERS or influenza or on expert opinions. Recently, some investigators are discussing the beneficial effect of hydroxychloroquine for COVID-19, but this is just based on in vitro studies and not much experience. But why don't we have more interests on the use of elderberry supplements which was shown to be effective in cold and influenza by randomized, double-blind, placebo-controlled study and meta-analysis [21–23]? If some treatments such as elderberry supplements or betadine mouth or nasal spray are not causing significant harms, we think doing something is better than nothing.

(6) Misinterpretation of the various studies including systematic review without considering the biases will lead to a false guidance for the treatment of COVID-19, which will be a significant harm [24]. The role of experts who are doing evidence-based medicine or meta-research is very important to reduce the harm to the patients in this pandemic era. (See Table 2.)

In addition to these, there may be more current harms in this pandemic era and this should also be urgently discussed.

6. Defense for COVID-19 in the pandemic era: 7 recommendations to rescue the patients from COVID-19 infection

Based on the pathogenesis of COVID-19 infection and the principles mentioned above, we would like to suggest 7 recommendations for COVID-19 which should urgently be considered in this pandemic era.

6.1. Smoking cessation

First, smoking cessation should be encouraged. This has always been recommended for general population, but it has also been very difficult for the people to do so. Because COVID-19 can predominantly damage the respiratory epitheliums and lungs, this should at least be recommended. Recently, it was also hypothesized that those individuals who have been exposed to nicotine prior to their exposure to the virus are “primed” to be at higher risk because nicotine can directly impact the putative receptor for the virus (ACE2) and lead to deleterious signaling in lung epithelial cells. [25] In addition, several cytokines including IL-2, IL-6 and TNF-α which is induced by smoking might trigger “cytokine storm” in COVID-19. We still do not know whether a short duration of smoking cessation could reduce the susceptibility or severity of COVID-19 or not, but if it is beneficial, doing something (smoking cessation) is better than nothing.

Table 2
Summary points of 7 recommendations which should urgently considered in the novel COVID-19 disease.

- Smoking cessation should be encouraged.
- Povidone-iodine (polyvinylpyrrolidone-iodine, PVP-I, betadine) mouth or nasal spray can be considered.
- The use of elderberry supplements can be considered at an early course of the disease.
- The use of low dose oral steroids should be actively considered at an early course of the disease.
- The use of oral antibiotics should be actively considered if the patient feels not good.
- Hydroxychloroquine can be used as a secondary drug in patients with worsening symptoms.
- Policy for the drug use should be changed like giving steroids and antibiotics to the patients at the time of diagnostic test or by drive through system to reduce the harms of patients.

6.2. Povidone-iodine mouth or nasal spray

Second, povidone-iodine (polyvinylpyrrolidone-iodine, PVP-I, betadine) mouth or nasal spray can be applied to kill the COVID-19 viruses and it will reduce the number of COVID-19 viruses which enter into the cells. COVID-19 is initiated by the attachment of the virus to the pharynx or respiratory epithelium and this causes sore throat. Currently, however, we do not know about whether the number of virus attached to the pharynx or respiratory epithelium will influence on the severity of COVID-19. Easily speaking, when you inhaled 10 viruses and when you inhaled 1000 viruses, will infection risk or the disease severity be same or different? Currently, this cannot be proved easily. However, considering the effectiveness of a mask that prevents respiratory infections, less exposure is likely to prevent infection by an indirect evidence. One previous meta-analysis showed that physical measures are highly effective in preventing the spread of SARS: wearing masks (odds ratio 0.32, 95% CI 0.25 to 0.40; number needed to treat (NNT) = 6, 4.54 to 8.03) vs. wearing N95 masks (0.09, 0.03 to 0.30; NNT = 3, 2.37 to 4.06) [26]. We can make a potential hypothesis: if 10 viruses were inhaled and attached to the throat, this may be cleared by host immunity. However, if 1000 viruses were inhaled and attached to the throat, it should go through a fight between the virus and host immunity. If viruses are cleared by host immunity, the person can be free from virus, but if the viruses win, they may replicate exponentially within a relatively short time and will cause viremia in the blood. In this situation, we still do not know whether the degree of viremia (viral load) might be correlated to the degree of host hyperimmune response, or whether reduction of viruses in the throat, for example, using betadine mouth spray or gargles, could decrease the degree of viremia in blood.

Currently, inhibiting angiotensin converting enzyme 2 (ACE2) and blocking angiotensin receptor 2 (AR2) is considered to be the key target for SARS-CoV-2 vaccination and COVID-19 therapy [27]. Due to this finding, some authors recommend the use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor 2 blockers (ARBs) [28]. Currently, these findings and suggestions can't be transferred into clinical practice easily. ACEI and ARBs are widely used in clinical daily practice, no clinical studies have been made in the set of COVID-19 outbreak so far. Even basic science, due to the pathophysiological mechanisms (e.g. effectiveness of blocking AR2) are limited [27]. Due to a substantiated benefit-risk evaluation a therapy with ARBs or ACEI cannot be recommended. In addition, we do not know about how many ACE2 receptors could be downregulated or blocked by antibodies or vaccines and how many entries of viruses could be inhibited by these if they are developed. However, if blocking entry of virus is a potential therapeutic target, we think that direct killing of the virus in the throat by betadine mouth or nasal spray might be more efficacious than the receptor downregulation.

Several studies showed severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) could be inactivated by PVP-I in vitro [29,30]. One phase 1 study shows application of PVP-I nasal spray to the nasal mucosa did not result in any demonstrable limitation of the nasal function nor in detectable damage to the multilayer ciliated epithelium of the nose [31]. Because anyone can buy betadine mouth or nasal spray or gargles without a prescription as over-the-counter medicines, if it does not cause any significant harm, there is no reason not to use it and it can be applied if a person feels sore throat at an early course of the disease. Although side effects of PVP-I use are rare, the adverse effect of iodine and other precautions should also be recognized. PVP-I can cause allergic reactions and should not be used in patients suffering from thyroid diseases [32]. Even there exist no studies for PVP-I and SARS-CoV-2 either due to the benefit-risk evaluation, PVP-I can be used in patients infected with SARS-CoV-2 with no or mild

symptoms without allergies to PVP-I or thyroid diseases. Or if a person is visiting more crowded places such as airport, it can also be applied easily.

6.3. The use of elderberry supplements at an early course of disease

Third, the use of elderberry supplements should be considered at an early course of the disease. Although it has not been tested in coronavirus, elderberry supplements which was shown to be effective in cold and influenza by randomized, double-blind, placebo-controlled study and meta-analysis [21–23]. Currently, there was one Cleveland clinic news reported by Emily Bamforth on the use of elderberry supplements [33]. Although there have been several reports on the beneficial effect of elderberry supplements on several viral infections [21–23], there have been few hypotheses on the potential immunologic mechanisms on the beneficial effect of elderberry supplements focusing on COVID-19.

It is well known that angiotensin-converting enzyme 2 (ACE2) is a receptor for SARS-CoV [34]. A recent study showed that SARS-CoV-2 (COVID-19) spike (S) glycoproteins also uses ACE2 to enter cells and that the receptor-binding domains of SARS-CoV-2 S and SARS-CoV S bind with similar affinities to human ACE2, correlating with the efficient spread of SARS-CoV-2 among humans. [35]. Although less discussed than ACE2, it was shown that CD209L (L-SIGN), encoded by CLEC4M, is also a receptor for SARS-CoV [36]. In this study, CD209L was expressed in human lung in type II alveolar cells and endothelial cells, both potential targets for SARS-CoV and the large S glycoprotein of SARS-CoV might use both ACE2 and CD209L in virus infection and pathogenesis [36]. In addition, Chan et al. demonstrated that individuals homozygous for CLEC4M tandem repeats are less susceptible to SARS infection and L-SIGN is expressed in both non-SARS and SARS-CoV-infected lung [37]. They also showed that compared with cells heterozygous for L-SIGN, cells homozygous for L-SIGN show higher binding capacity for SARS-CoV, higher proteasome-dependent viral degradation and a lower capacity for trans infection, suggesting that homozygosity for L-SIGN plays a protective role during SARS infection [37]. In summary, the first encounter of the virus with the host might be through binding to attachment receptors, such as these receptors, which might play an important role of infection for a large number of enveloped viruses by capturing, concentrating and transmitting infectious virions [38]. Once a virus reaches its target cell, a cascade of events generally starting with the interaction of viral envelope glycoproteins with specific entry receptors and co-receptors is necessary in order to trigger the virus-cell membrane fusion [38].

Although not much studied in coronavirus, capture and transmission of HIV-1 by the C-type lectin L-SIGN was inhibited by carbohydrate-binding agents (CBAs) [39]. In this study, both mannose- and *N*-acetylglucosamine (GlcNAc)-specific CBAs dose-dependently prevented virus capture by L-SIGN-expressing 293 T-REx/L-SIGN cells [39]. Because coronavirus also uses L-SIGN as a receptor for entry, one study suggested that influenza virus and coronavirus infections might also qualify to be treated by CBAs [40].

Keyaerts et al. evaluated the effect of 33 plant lectins with different specificities to coronavirus [41]. They showed that the plant lectins possessed marked antiviral properties against both coronaviruses with EC(50) values in the lower microgram/ml range (middle nanomolar range), being non-toxic (CC(50)) at 50–100 microg/ml and the strongest anti-coronavirus activity was found predominantly among the mannose-binding lectins. In addition, a number of galactose-, *N*-acetylgalactosamine-, glucose-, and *N*-acetylglucosamine-specific plant agglutinines exhibited anti-coronaviral activity [41]. They also found that there was a significant correlation (with an r-value of 0.70) between the EC(50) values of the 10 mannose-specific plant lectins effective against the two coronaviruses but, little correlation was seen between the activity of other types of lectins [41]. Therefore, they reported that two targets of possible antiviral intervention were identified in the replication cycle of SARS-CoV; the first target is located early in the replication cycle, most probably viral attachment, and the second target is located at the end of the infectious virus cycle [41].

De Clercq summarized various compounds which have been reported to exhibit in vitro activity against SARS-CoV, though they have an ill-defined mode of action but selectivity indexes up to 100 (valinomycin, glycopeptide antibiotics, plant lectins, hesperetin, glycyrrhizin, aurintricarboxylic acid, chloroquine, niclosamide, nelfinavir and calpain inhibitors). Among them, plant lectins and chloroquine (which is being discussed for the potential treatment of COVID-19) are included [42].

This hypothesis has further been tested later in MERS-CoV epidemic, because coronaviruses are enveloped viruses, with the spike proteins present on their surface responsible for virus entry into the target cell [43]. Because MERS-CoV also cause a high mortality rate of about 35%, no vaccine is available and therapeutic options for MERS-CoV infections are limited to palliative and supportive care, a search for specific antiviral treatments was urgently needed [43]. Millet et al. thought that lectins are attractive anti-coronavirus candidates because of the highly glycosylated nature of the spike protein and tested the antiviral effect of griffithsin (GRFT), a lectin isolated from the red marine alga Griffithsia sp. against MERS-CoV infection [43]. They demonstrated that griffithsin is a potent inhibitor of MERS-CoV infection without significant cytotoxicity [43]. Griffithsin inhibited entry into host cells of particles pseudotyped with the MERS-CoV spike protein, suggesting that griffithsin inhibits spike protein function during entry at the binding step [43].

The compounds found in elderberries are phenolic acids, flavonoids, vitamins, lectins and aroma compounds, etc. [44]. A very similar lectin called *Sambucus nigra* fruit specific agglutinin I (SNA-If) was identified as a minor protein in ripe elderberry fruits [45]. Although elderberry supplements have not been tested in the current COVID-19 pandemic, lectin components might inhibit spike protein function during entry at the binding step as mentioned above or have unknown other effects.

Currently, because anyone can buy elderberry supplements without a prescription as over-the-counter medicines, if it does not cause any significant harm, there is no reason not to use it and it can be applied at an early course of the disease. Although there have been some reports on the increase in some cytokines by elderberry supplements [46], elderberry supplements also have various kinds of other effects. Surely, however, we should also weigh the benefit and risk for the use of elderberry supplements like other OTCs. We know that even OTCs (eg. Tylenol) have many adverse effects on the drug information. In addition, we should also look at the Evidence-Based Systematic Review of Elderberry and Elderflower (*Sambucus nigra*) by the Natural Standard Research Collaboration [47], which could be applied to the current COVID-19 pandemic.

In this point, we should be able to guide the use of these elderberry supplements to the general population or patients with COVID-19 as this: “Elderberry supplements can be used in those with COVID-19 at an early course of disease, if you understand the previous efficacy of these and potential adverse effects”.

6.4. The use of oral steroids at an early course of disease

Fourth, the use of oral steroids should be actively considered at an early course of the disease. If the cause of death of COVID-19 is ARDS and organ failure due to “cytokine storm” by hyperactivated host immune response, why we are not considering to suppress or prevent this process at an early course of the disease? We think the increase in various pro-inflammatory cytokines induced by COVID-19 may be suppressed by short-course low dose steroids in an early stage of disease, but it may not be effective in a later stage of disease such as ARDS and multiorgan failure. This situation can be assimilated by forest fire. If a first small fire by cigarette butts can be detected by hiker early (early COVID-19), it can be extinguished by small amounts of water

(low dose steroids) easily. But if wild forest fires spread (persistent high fever, dyspnea) in the mountain without early suppression, it cannot be suppressed despite every effort by numerous fire trucks (long-term use of very high dose of steroids), and all mountains will be burned (destructed lung, requiring ECMO). There was one recent systematic review reporting that the use of steroids may be harmful to patients with COVID-19 [48]. However, this result should be interpreted with caution because the quality of the included studies is extremely low and they have many biases, many studies are missing and the included studies are not on the use of steroids vs. no use. This result should not be generalized to the patients with early course of the disease and mild symptoms.

One study investigated the structural arrangement of N protein, explaining the first steps of its interaction with nucleic acid at the initial stages of virus structure assembly [49]. The nucleocapsid (N) protein of COVID-19 has nearly 90% amino acid sequence identity with SARS-CoV and the N protein antibodies of SARS-CoV may cross react with COVID-19 but may not provide cross-immunity. In a similar fashion to SARS-CoV, the N protein of COVID-19 may play an important role in suppressing the RNA interference (RNAi) to overcome the host defense [50]. In rat models, the N-protein of SARS-CoV had pathogenicity and could induce obvious pulmonary inflammatory reaction and acute lung injury, which were related to the increase and imbalance of pro-inflammatory and anti-inflammatory cytokines. [51]. In this study, glucocorticoids could effectively alleviate the pulmonary inflammatory reaction induced by N-protein of SARS-CoV, supporting the beneficial role of steroids on the inflammatory reactions caused by N-protein of the current COVID-19 [51].

According to the Chinese government's daily report, 13.2–21.3% of patients with COVID-19 developed severe or fatal illness, and therefore, the China's National Health Commission released the fifth trial version of Diagnosis and Treatment Scheme for Pneumonitis with COVID-19, and provided a systematic treatment strategy for severe cases and systematic corticosteroids treatment (methylprednisolone, $<$1–2 mg per kg body weight, for 3–5 days) was recommended to be an adjuvant therapy [52]. Zou et al. recently showed that systematic corticosteroids therapy in the first 3–5 days in severe patients could enhance oxygen saturation (SaO2) and arterial oxygen tension (PaO2)/inspiratory oxygen fraction (FiO2), but corticosteroids did not exert any intervention on survival of NCP patients complicated with both ARDS and shock or multiple organ injury [53]. Nevertheless, they concluded that corticosteroids in the phase of ARDS would effectively inhibit furious inflammatory storm and gain valuable time for controlling infection and preventing secondary multiorgan damage and shock, which implies that corticosteroids have synergistic biological effects when combined with other intensivists' treatment against severe or fatal NCP patients. [53]. However, as we mentioned above, we think the increase in various pro-inflammatory cytokines induced by COVID-19 may be suppressed by short-course low dose steroids in an early stage of disease, but it may not be effective in a later stage of disease such as ARDS and multiorgan failure because a later stage may be a big fire, which cannot be suppressed easily.

One another thing is a short course of low dose oral steroids is easily prescribed in the treatment of urticaria, but why are we afraid of prescribing the use of oral steroids in the acute COVID-19 setting even though many patients progress to severe disease, in whom there will be some patients with mild symptoms with severe radiologic findings. If we can lower the percentage of progressing to “cytokine storm” by early use of steroids, even though it is found to be statistically nonsignificant, such as *p*-value of 0.06–0.09, several patients will be rescued. Therefore, we should interpret the results based on the p-value cautiously and conversely, misinterpretation or misunderstanding of p-value will cause a significant harm to the patients with COVID-19. Recently, some groups showed the beneficial effect of hydroxychloroquine [12]. Until these reports, there was evidence of hydroxychloroquine on coronavirus just from in vitro study [54,55]. Therefore, the doctor who first used this drug in a patient with COVID-19 might have done this treatment by non-evidence-based medicine. We should try the oral steroids in patients with COVID-19 at an early course of disease.

6.5. The use of oral antibiotics

Fifth, the use of oral antibiotics should be actively considered if the patient feels not good, because secondary bacterial infection might aggravate acute immunological lung injury induced by several cytokines (eg. IL-2, IL-6 and TNF-α) in COVID-19. There are no controlled clinical trials evaluating the use of empiric antimicrobials in COVID-19 patients or other coronavirus driven diseases. Therefore, recommendations can only be based on other viral diseases like influenza [56]. Furthermore, another guideline on treating COVID-19 patients was released. Both guidelines suggest that blind or inappropriate use of antibacterial drugs, especially the combination of broad-spectrum antibacterial drugs should be avoided in patients with mild or no symptoms [57]. However, we are against these guidelines, because the current COVID-19 situation is definitely different to other usual viral infections, because some patients with mild symptoms can have severe radiologic features and sudden death. Furthermore, bacterial superinfection is hard to detect and cannot be easily diagnosed. Symptoms of COVID-19 and bacterial superinfection may overlap. Data on the prevalence of bacterial superinfection in patients with COVID-19 are very limited [58]. Influenza pneumonia is often associated with *Staphylococcus aureus* co-infection and can be especially virulent [56]. Initiating empiric antibacterial therapy in adults with community-acquired pneumonia who test positive for influenza was recommended by recent clinical practice guidelines [56]. Therefore, we suggest that according to the clinical manifestations of patients, if the accompanying bacterial infection cannot be ruled out, patients can take antibacterial drugs against community-acquired pneumonia, such as amoxicillin, azithromycin, or fluoroquinolones [57]. Empirical antibacterial treatment in severe patients should cover all possible pathogens, deescalating therapy until the pathogenic bacteria are clarified [59].

In addition, the current special situation should also be considered. Currently, if the patient is diagnosed as having COVID-19, he/she will be isolated at home and is recommended that if severe symptoms are developed, come to the hospital and no medications are provided. However, we think this is a very dangerous situation, because some persons might have no or only mild symptoms despite severe progression of lung injury. And when these patients become to feel dyspnea, and come to the hospital, the time might be late for the recovery. They will receive not only intravenous antibiotics but also various kinds of multiple drugs. We speculate that many patients who became to get severe symptoms might have bacterial complications. It has been reported that bacterial coinfection is associated with approximately 40% of viral respiratory tract infections requiring hospitalization [60]. The incidence of bacterial complications of COVID-19 is unknown yet, but considering that more patients with COVID-19 get severe symptoms than observed in other respiratory viral diseases, we speculate that more bacterial complications might be combined not only in severe conditions but also in mild conditions. If the patient is having usual other respiratory viral infections, he/she will visit the clinic and will be prescribed antibiotics. However, in the current situation, the patient with COVID-19 cannot visit an usual clinic and should wait until he will recover or get dyspnea. If virus damages the throat or lungs, other bacteria oral cavity can cause secondary infection and this cannot be exactly evaluated and diagnosed, because the laboratory examinations for bacteria such as culture or procalcitonin may not be exact due to false negative and all the bacteria cannot be examined.

In this situation, based on the medical principle “Do no harm”, waiting until the patient deteriorate is a severe harm. Therefore, to prevent the deterioration of the patient with COVID-19, oral antibiotics and oral steroids should be given to the patient at the time of COVID-19

and it should be recommended if the patient has high fever and feels bad, take the antibiotics and steroids empirically and it can be acceptable in the pandemic era as many patients are dying due to complications of COVID-19. If the doctor can monitor and guide the patients with phone calls, it will be better if there are enough medical personnels, So, in the current situation, liberal and early use of oral antibiotics and steroids may be “Do no harm”, which may be a different situation than during the usual common cold situation. In our experiences, if the patient feels bad, earlier antibiotics and steroids are used, the patient's condition will recover.

6.6. The use of hydroxychloroquine

Sixth, hydroxychloroquine can be used as a secondary drug in patients with worsening symptoms in COVID-19. Chloroquine and its metabolite, hydroxychloroquine, are antimalarial agents that have demonstrated antiviral effects on SARS-CoV and SARS-CoV-2 in vitro [54,55]. Chloroquine had inhibitory effects for multiple RNA viruses in vitro. Chloroquine showed no antiviral or clinical beneficial effects in treatment of dengue and chikungunya virus infections and as influenza prophylaxis [61]. A news briefing suggested that its use in more than 100 patients showed “that it was superior to the control in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course”, but the data have not been published yet [62]. A recent consensus document recommended chloroquine phosphate 500 mg twice daily for minimum of 5 days [63]. Another study found hydroxychloroquine more potent than chloroquine in vitro. Based on these data, hydroxychloroquine for 4 days, 400 mg twice daily after a loading dose of 400 mg was recommended [54]. A recent systematic review found no published studies in COVID-19 patients [64]. Furthermore, adding azithromycin to hydroxychloroquine 600 mg daily treatment seemed to have a beneficial outcome in a small French cohort [12]. However, we should also be cautious in interpreting the results of hydroxychloroquine, because the current situation is just based on the in vitro studies and small number of case series. Also, the adverse effects of hydroxychloroquine should also be considered. In this situation, we think hydroxychloroquine should not be used as a routine treatment of COVID-19, but if the condition of the patients worsens despite the use of steroids and antibiotics, hydroxychloroquine can be used as a secondary drug.

6.7. Policy should be changed

Seventh, policy for the drug use should be changed to reduce the mortality of patients. In usual situation, the patient can visit the clinic frequently according to the condition. Therefore, steroids and antibiotics can be given timely based on the judgement of doctors. However, this pattern of examination, diagnosis and treatment cannot be done in this COVID-19 era. Doctors' prescriptions are surely important to diagnose and treat patients. However, as we mentioned above, patients are just waiting for recovery or deterioration until severe symptoms and no treatment is done in the meanwhile. If the patient is infected occur with COVID-19 and gets fever, and visit the different clinics, the treatment will not be standardized among doctors. If a doctor concerns for the fever and the nature of rapid deterioration in COVID-19, he may use steroids and antibiotics early, while other doctors may not. If so, we can make some guidelines for the practical use of antibiotics, steroids and hydroxychloroquine for the patients to use these drugs. These should also include the benefit and adverse effect for each drug. The policy we are proposing is to give these drugs to the patients freely, although the range of drug should also be more discussed. In Korea, the diagnosis of COVID-19 is being done by drive through. Our suggestion is to make another drive through place to give these drugs to the patients to avoid the dissemination of infection, because if the infected patient go to the hospital for the treatment, he/she can infect all other patients. Also, it will be good if the drugs are given to the patient who is visiting the screening clinic, for example, at the time of drive through diagnosis and explain in detail the benefit and adverse effect for each drug. And then, the doctor can check the result for COVID-19 and guides the patient for taking the drugs by phone calls. Also, the patient can take these drugs at his/her judgement. This concept is based on that (1) any treatment for COVID-19 has not been established, (2) even though the patient visits the doctor, the treatment patterns will be all different among doctors, (3) steroids have frequently been used in other mild diseases such as urticaria, (4) because we do not exactly know the presence or absence of secondary infection when the patient get fever, oral antibiotics for 3–4 days can be acceptable treatment in routine clinical practice. Further, (5) hydroxychloroquine can also be given to the patients and it can be recommended that if the patient's symptoms worsen despite the use of steroids and antibiotics, he/she can take hydroxychloroquine after recognizing all the adverse effect of the drug. But if the symptoms worsen, the patient surely visit the hospital as well.

7. Conclusions

COVID-19 is causing a severe public health emergency and the mortality is rapidly increasing all over the word. In this era, we suggested 7 recommendations to rescue the patients and to reduce the morbidity and mortality due to COVID-19 based an immunological point of view (Table 2). Ours may be personal opinions, but we believe these may be beneficial to control these complications exerted by COVID-19. In addition, there will be more other or conflicting evidences and publications regarding our opinions. However, we would like to remind of the basic principle for the treatment of patients again, but we often forget this: “Do no harm”. We all should think deeply on what is harm and what is no harm. In addition, we would like to say again: “doing something is better than nothing.” in the acceptable level of clinical practice. We hope that our opinions can be transferred to not only WHO and CDC but also clinicians, researchers and many institutions and COVID-19 could be finished as rapidly as possible.

Authorship

All authors made substantial contributions to all of the following: (1) conception and design of the study, data acquisition, or analysis and interpretation of data; (2) drafting or critical revision of the article for intellectual content; and (3) final approval of version to be submitted.

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