〈Review〉

Treatments and management for COVID-19

Ichiro OHASHI

Department of Anesthesiology & Intensive Care Medicine 3, Kawasaki Medical School

ABSTRACT Humans have experienced three deadly pandemics in the twenty-first century which are associated with novel coronaviruses: severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19. In this review, the treatments and management of COVID-19 were discussed. Cytokine storm mechanisms and therapy, there is no doubt that the elucidation of the mechanisms of the cytokine storm is an important key to conquer this pandemic. Many clinical trials have indicated the inhibitory effects of interleukin-6 (IL-6) for the treatment of COVID-19. Although no survival benefit was demonstrated in randomized, placebo-controlled studies, non-blinded, randomized studies have supported a survival benefit with IL-6 blockade. Inhibition of the excessive immune response in severe COVID-19 pneumonia undoubtedly improves the survival of patients, particularly through glucocorticoids given to those with oxygen requirements. From this point of view, timing of the administration of immunosuppressive or immunomodulatory agents is key issue. Prone position therapy was originally used to treat patients with severe acute respiratory distress syndrome (ARDS) resulting from pneumonia or sepsis. In the critically ill patients with severe pneumonitis, the prone position has been recommended as one of the most promising treatment options to improve mortality outcomes. Overall, this review covers, the epidemiology and the important aspects of the treatment and management against critically ill patients with COVID-19.

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Key words：COVID-19, Treatment, Cytokine storm

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. Just months after its discovery at the end of 2019, COVID-19 became a worldwide pandemic with many sudden hospitalizations for pneumonia with multiple organ dysfunction. The Omicron strain saw a significant increase in the number of cases of household transmission[1], especially in the elderly and people with organ damage[2]. SARS-CoV-2 infection can be asymptomatic or cause a variety of symptoms, from mild upper respiratory tract infection to life-threatening sepsis[1, 3－5]. In this review, the

Corresponding author
Ichiro Ohashi
Department of Anesthesiology & Intensive Care Medicine 3, Kawasaki Medical School, Kawasaki Medical School General Medical Center, 2-6-1 Nakasange, Kita-ku, Okayama, 700-8505, Japan
Phone : 81 86 225 2111
Fax : 81 86 232 8343
E-mail: i-ohashi@med.kawasaki-m.ac.jp

epidemiology, treatments and management of COVID-19 were discussed.

Current knowledge of COVID-19 epidemiology

This review highlights findings regarding the pathophysiology, transmission, diagnosis, and management of COVID-19. Forty-five percent of cases were infected by a pre-symptomatic individual (i.e., a person who later developed symptoms), 40% were infected by symptomatic individuals, 10% from contact with a contaminated environment, and 5% were infected by asymptomatic individuals, who are considered to have low levels of viral load and excrete less virus compared to symptomatic cases. Transmission of COVID-19 is common from pre-symptomatic and asymptomatic people[1)].

Severity of SARS-CoV-2 would depends on the amount of virus in the lower respiratory tract and infectivity depends on the amount of virus in the upper respiratory tract. It is important to note that mildly infected individuals have a higher amount of virus immediately after the onset of illness, and severity does not necessarily correlate with infectivity[1, 3)]. The amount of virus excreted affects the amount of virus in the upper respiratory tract. It is known that infectivity is age-dependent and that adolescents have been shown to carry exceptionally higher viral loads than elderly people. Therefore, regardless of age, it is highly likely that infected individuals with more active infections but less severe symptoms, such as a sore throat or a low-grade fever, are likely to be a factor in the formation of clusters[1, 5)].

Infection clusters at live music venues and gyms cannot be explained by droplet or contact infection, and the possibility of aerosol (microdroplet) infection associated with increased respiration due to vocalization and exercise has been raised[1, 3)]. SARS-CoV-2 can remain airborne for about three hours, is known to drift through the air and may be a factor in dinner party and nightlife-related infections and cluster formations. It has long been well known that viral droplets are covered with moisture and that the evaporation of that moisture around the droplet nuclei causes aerosol infection, which is also commonly found in influenza and norovirus infections[1, 3)].

One of the most striking features of COVID-19 is a higher level of virus in the saliva than in other viral infections. This is because SARS-CoV-2 is known to bind to anti-angiotensin-converting enzyme 2 (ACE2) receptors and to enter several kinds of cells. ACE2 expression is high in the oral cavity, especially on the tongue. The abundant viruses in the saliva increases the risk of infection during eating and loud speaking. It is a certain key to block the infection pathways of the mucous membranes of the eyes, nose, and mouth where aerosols and droplets might invade[1, 3, 4)].

Recent progress of treatments for SARS-CoV-2

1)Anti-viral drugs

The suppressing effects against the host response too early during rapid viral replication is probably detrimental[6)]. Although there were few effective therapeutic agents at the beginning of the pandemic, it has gradually become possible to prevent infection and severe disease by means of vaccines, neutralizing antibody drugs, and oral medications[6–10)]. However, once infection and severe disease occur, effective therapeutic agents are limited. Data on the efficacy of the antiviral ribonucleic acid (RNA) polymerase inhibitor Remdesivir in COVID-19 came from a randomized controlled trial in adults in which Remdesivir reduced the recovery time compared to a placebo, but there was no statistically significant difference in mortality by day 29[11)].

Remdesivir is the only drug that is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir (Paxlovid), molnupiravir, and certain

anti-SARS-CoV-2 monoclonal antibodies (mAbs) have received Emergency Use Authorizations from the food and FDA for the treatment of COVID-19[12].

2)Immunomodulatory drugs

SARS-CoV-2 infects cells via the ACE2 receptor and induces activation of nuclear factor-κB (NF-kB) and signal transducer and activator of transcription (STAT3) transcription factors via the innate immune system and the angiotensin II / angiotensin Ⅱ type 1 receptor (Ang II / AT1R) signaling pathway. STAT3 enhances the production of inflammatory cytokines such as IL-6 by enhancing NF-kB activation. This amplification circuit is termed the IL-6 amplifier and plays an important role in the development of chronic inflammatory diseases such as rheumatoid arthritis. The anti-IL-6 receptor antibody tocilizumab (trade name, Actemra) is effective in the treatment of chronic inflammatory diseases[13, 14].

ARDS is a potentially lethal effect of cytokine storms related to chimeric antigen receptor T cell (CAR-T) therapy, used to treat leukemia and other cancers, and ARDS after a cytokine storm can also be seen in COVID-19 cases[15]. Tocilizumab has also proven to be effective against cytokine storms[13]. COVID-19 increases the production of inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-alpha) and IL-6. Since respiratory damages, such as ARDS, in COVID-19 is caused by a cytokine storm, the suppression against cytokine production in immune systems is one of the promising therapeutic stratages[15]. IL-1 and IL-6 are believed to play a central role in cytokine storms and tocilizumab has been shown to effectively suppress storms and has also been suggested to be effective in the treatment of severe pneumonia in COVID-19[13, 14].

The activation of the local innate immune system following infection of the lungs with SARS-CoV-2 and the subsequent activation of the virus-specific acquired immune system results in the production of large amounts of cytokines through T cell activation, interleukin-6 amplifier (IL-6 AMP) activation in alveolar epithelial cells and vascular endothelial cells, and the activation of the NF-kB pathway. The production of cytokines, chemokines, and growth factors leads to T-cell anergy and possibly fatal multi-organ dysfunction and damage[14]. Veerdonk *et al*. stated that the quandary in immunotherapy is that COVID-19 heterogeneity is not clearly understood and that there are a certain number of patients who do not respond to glucocorticoids, such as dexamethasone, or anti-IL6 therapy, and it is difficult to set up randomized controlled trials to test the clinical application of immunotherapy[16]. However, Shankar-Hari M. *et al*. showed that their prospective meta-analysis of clinical trials of patients hospitalized for COVID-19, administration of IL-6 antagonists with glucocorticoid therapy, compared with usual care or placebo, was associated with lower 28-day all-cause mortality[17]. Inhibition of the excessive immune response in severe COVID-19 pneumonia undoubtedly improves the survival of patients, particularly through glucocorticoids given to those with oxygen requirements. From this point of view, timing of the administration of immunosuppressive or immunomodulatory agents is key factor[6].

In a large, randomized, controlled trial of the efficacy of glucocorticoid therapy for COVID-19, patients receiving 6 mg of dexamethasone once daily for 10 days[18]. Dexamethasone was effective in patients on ventilators and those who received oxygen supplementation only, but not in those who did not require respiratory support[18]. A meta-analysis of glucocorticoid use in the treatment of COVID-19 showed a significant reduction in mortality from all causes[19].

3)Physical therapy

Prone position therapy was originally used to treat patients with severe ARDS resulting from

pneumonia or sepsis[20]. The lungs, which are responsible for ventilation, oxygenate the blood and release carbon dioxide through respiration. This function is largely dependent on the dorsal lungs. When a patient is continuously supine, gravity causes blood flow to collect on the dorsal side, and pressure collapses the dorsal side of the lungs, decreasing oxygenation of the blood. The upper lobes of the lungs are also more susceptible to damage. Changing to a prone position may improve the situation[20].

There is still no established treatment for severe ARDS[1, 3]. In this context, the prone position has been recommended as one of the most promising treatment options to improve mortality outcomes. In particular, recent studies have begun to show improved survival rates in similar conditions. It is believed that the keys are to target only the most severely ill, start early, and keep patients prone for at least 12 hours a day. The guidelines point out that, "prone position management for short periods of time may be inadequate". In addition, the use of the prone position in critically ill COVID-19 patients requires a sufficient number of staff already skilled in severe ARDS therapy.

The pathogenesis of severe COVID-19 pneumonia is similar to that of severe ARDS, and it has been shown that treatment in the prone position has had some success[21]. In Europe and the U.S., the prone position has been reported to be a safe and useful technique in patients without endotracheal intubation and under noninvasive respiratory management such as high-flow nasal oxygenation[22]. The prone position has the potential to be used in clinical practice in general and non-ICU emergency wards.

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CONFLICTS OF INTEREST

The author has no conflicts of interest to disclose.

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ABBREVIATIONS

SARS: severe acute respiratory syndrome
MERS: Middle East respiratory syndrome
IL-6: interleukin-6
ARDS: acute respiratory distress syndrome
SARS-CoV-2: severe acute respiratory syndrome coronavirus-2
ACE2: anti-angiotensin-converting enzyme 2
RNA: ribonucleic acid
FDA: Food and Drug Administration
mAbs: monoclonal antibodies
NF-kB: nuclear factor-kB
STAT3: signal transducer and activator of transcription 3
Ang II / AT1R: angiotensin II / angiotensin Ⅱ type 1 receptor
CAR-T: chimeric antigen receptor T cell
IL-1: interleukin-1
TNF-alpha: tumor necrosis factor-alpha
IL-6 AMP: interleukin-6 amplifire