INTRODUCTION

Coronavirus disease COVID-19 caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. SARS-CoV-2 causes severe hypoxia and lung damage in the peripheral airways and vascular endothelial cells to induce sudden death. The current emerging viral infection lacks established clinical evidence based on clinical research findings. Therefore, treatment concepts against RNA virus infections are needed in the contexts of virology, pathophysiology, and pharmacology. We can also have the method of constructing and assigning traditional drugs in safety management of COVID-19. We describe the four main bundles and nine sub-bundles we consider useful in COVID-19 management, namely, healthcare personnel protection, early detection and treatment, open lung strategy, analgesia/sedation/sleep, careful management of secondary infections, anticoagulant therapy, nitric oxide inhalation, extracorporeal membrane oxygenation, anti-oxidant therapy, excretion of inflammatory ligand, anti-inflammatory therapy, immunoglobulin, and prevention of exacerbation interstitial pneumonia. Many excellent drugs may be used to treat the pathological conditions described in the COVID-19 bundles. This article could thus serve as a reference for the application of traditional drugs in the management and treatment of COVID-19.

As COVID-19 is an emerging infectious disease, clinical evidence is lacking regarding the initial medical care. In such situations, in addition to a virologic understanding of SARS-CoV-2, we must also observe and grasp the emerging pathophysiology and, in the context of pharmacology, apply a “deductive method” to devise a therapeutic system by identifying the necessary contents for the treatment of COVID-19 and prescribing conventional “traditional drugs” according to the pathology of COVID-19. In Japan as well as globally, available drugs and devices that have already been confirmed to be safe for treating critically ill patients and without recognized life-threatening adverse events have been applied for the early treatment of patients with COVID-19, in an attempt to prevent mortality.

Currently, there are about only 6,500 licensed intensive care units (ICUs) in Japan. Many COVID-19 patients are expected to recover without progressing to a severe respiratory condition requiring ICU care. This review presents pathophysiological conditions as a management bundle during the critical care of COVID-19 from the present to the future. The COVID-19 management bundle 2020 comprised four main bundles and nine sub-bundles, including a total of 13 aspects for continuous clinical research. We introduce the bundles as one treatment strategy for the COVID-19 crisis for the future.
PATHOPHYSIOLOGY OF COVID-19

SARS-CoV-2 has a transtracheal affinity for the peripheral airway such as the alveolar region. CT imaging shows that SARS-CoV-2 tends to infiltrate the end of the alveolar sac region, increase mucin production, and lead to vasculitis in the peripheral lung region [2-4]. The typical CT features of COVID-19 include pure ground-glass opacities (GGO), GGO with consolidation, rounded opacities, bronchiolar wall thickening, interlobular septal thickening, and peripheral distribution.

Four coronavirus receptors have been reported, namely, angiotensin-converting enzyme-2 (ACE-2), carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), aminopeptidase N receptor (APN), and dipeptidyl peptidase-4 (DPP-4) [5,6]. SARS-CoV-2 has a high affinity for ACE-2, which may contribute to its easy invasion of the peripheral airway and pulmonary blood vessels. Therefore, while the upper respiratory tract symptoms do not progress rapidly, sudden breathing difficulty may occur, hypoxemia may progress, and patient life may be threatened. Overexpression of ACE-2 owing to smoking, hypertension, and diabetes may be associated with an increased COVID-19 risk. In this process, vascular hyperpermeability and coagulation abnormality associated with inflammation and fibrinolysis may occur because of the RNA virus itself, with vascular endothelial cell damage progressing locally in the lungs. It is also important to note that dissemination of SARS-CoV-2 into the blood can accelerate multiple organ failure and result in disseminated intravascular coagulation (DIC) as observed during bacteremia.

In an acute lung injury, pulmonary fibrosis progresses along with increased levels of growth factors such as tumor growth factor-beta (TGF-ß), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) in the following stages of lung inflammation [7]. Considering the long-term prognosis that does not leave the lungs organized, we will manage shortening the inflammatory phase and fibroblast proliferation phase as well as early rehabilitation that does not leave disuse disorders in COVID-19. The 13 contents considered necessary for early recovery from COVID-19 are summarized as a management bundle in Table.

FOUR MAIN BUNDLES (BUNDLES 1–4)

The implementation and explanation of the four important bundles for the treatment are described below.

Bundle 1: Healthcare Personnel Protection

Implementation: It is important for healthcare workers to protect themselves from SARS-CoV-2 and bacterial infections; thus, the appropriate use of personal protective equipment (PPE) is required. We request that the Japanese government and the Ministry of Health, Labor and Welfare distribute PPE appropriately.

Explanation: The WHO recommends droplet and contact precautions (i.e., a surgical mask with eye protection, a gown, and gloves) for healthcare workers who are caring for patients with confirmed or suggested COVID-19 [8]. Strict adherence was emphasized both in Japan and at our institution, as described in the Australian and New Zealand Intensive Care Society (ANZICS) Intensive Care Guidelines [9,10]. However, the demand for PPE for COVID-19 management exceeded the supply owing to the pandemic and the supply of PPE kits was not enough. For this reason, methods such as fixing medical personnel in the management field of COVID-19 and irradiating PPE for reuse have been proposed. The Cabinet Office of Government and the Ministry of Health, Labor and Welfare in Japan was encouraged by the Japanese Society of Intensive Care Medicine to distribute PPE [11] and their administrative response progressed. The inability to provide PPE and medical care was declared a “medical crisis” in Japan.

Zoning of clinical spaces was also emphasized for for the treatment and management of COVID-19. The COVID-19 space is defined as the red zone and is separated from the green zone defined for the management of patients not affected with SARS-CoV-2. The treatment space and flow of patients suggested of having SARS-CoV-2 infection were appropriately divided by setting a yellow zone between the designated COVID-19 and non-COVID-19 spaces. According to the SARS-CoV-2 report of the US National Institutes of Health, SARS-CoV-2 remains viable in aerosols for 3 hours, on copper surfaces for 6 hours, on iron surfaces for 13 hours, on polypropylene for 16 hours, on cardboard for 24 hours, and on plastic and stainless steel for 2–3 days [12]. Many institutions also took care to disinfect the environment with 70% alcohol and 0.05% hypochlorous acid.

In Japan, the guidance of the emergency medical center at the national public university hospital was required under the guidance of the government and the Ministry of Health, Labor and Welfare. Emergency outpatients with fever (37.5°C or higher before arrival) and symptoms (dry cough, dyspnea, increased respiratory rate, or taste or olfactory disorders) were placed in appropriate clinical zones. Different entry routes and anterior rooms (yellow) and negative pressure rooms (red) were set up for the medical treatment of fever patients separate from the areas for usual patients.

Bundle 2: Early Detection and Treatment: Early Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and Early Administration of RNA Polymerase Inhibitors

Implementation: If COVID-19 is suspected, acquire saliva and plasma samples for RT-PCR testing. Thereafter, for early reduction of SARS-CoV-2, oral administration of favipiravir (Avigan®) should be started immediately.

Explanation: The recommendations for the management of sepsis owing to bacterial infection include performing a
blood culture test immediately and administering a broad antibacterial agent set within 1 hour in cases with suggested infection [13]. When COVID-19 is suggested because of symptoms of fever, dry cough, taste disorder, and olfactory disorder, saliva collected after coughing with the mouth closed is used for RT-PCR testing. We consider RT-PCR testing of saliva and plasma to be useful to evaluate COVID-19, although we often used nasal discharge and sputum.

Avigan® Tablets 200 mg were developed in Japan and are used as a therapeutic agent for influenza virus infections [14,15]. This drug targets emerging influenza viruses by inhibiting RNA polymerases involved in viral amplification and activity. As SARS-CoV-2 is also an RNA virus similar to the influenza virus, favipiravir was considered to be effective in the treatment of COVID-19. Favipiravir is metabolized in infected cells to favipiravir-ribofuranosyl-triphosphate, which selectively inhibits RNA-dependent RNA polymerases. In Japan, favipiravir can be used under in-hospital approval to reduce the viral load in COVID-19.

The translocation of favipiravir to organs has been assessed in cynomolgus monkeys, with a single oral dose of [14] C-favipiravir (20 mg/kg) reaching the maximum lung translocation at 0.5 hours after administration [14]. The ratio of favipiravir concentrations between the plasma and lung was 0.51 or more because of the drug’s rapid transfer to the lung without comparison with the other RNA polymerase inhibitors. The key to the use of favipiravir in the treatment of COVID-19 is setting an effective concentration in the lungs and trachea based on consideration of the pharmacokinetics/pharmacodynamics (PK/PD).

One of the effective administrations of favipiravir is shown in Figures 1 and 2 as the PK/PD data [14] during the development of favipiravir. The effective concentration (EC50) of favipiravir against the influenza virus is 1.6 μg/mL for the H7N2 New York strain and 3.5 μg/mL for the H1N1 strain. The EC50 of the N3N2 Aichi strain is as low as 0.12 μg/mL. Based on this background and these reported therapeutic effects, an EC50 of 3 μg/mL for SARS-CoV-2 allows effective trough lung tissue concentrations of 15 μg/mL. The estimated favipiravir inhibitory concentration in the bone marrow and hepatic mitochondria is approximately 500 μg/mL in vitro [14]. A trough concentration of 15 μg/mL in the lung tissue is safe, as confirmed in clinical trials in influenza virus infections.

The major metabolic pathways of favipiravir are urinary excretion of metabolites by aldehyde oxidase, xanthine oxidase, and aldehyde dehydrogenase as well as bile excretion after glucuronidation in the liver. The main side effect of favipiravir is an elevated uric acid level. Favipiravir may increase xanthine oxidoreductase (XOR) activity, which increases plasma uric acid levels. In contrast, in patients with hyperuricemia who have been administered allopurinol, oxypurinol, topiroxostat, etc. to inhibit XOR, the metabolism of favipiravir may be delayed and its blood concentration may increase. Finally, favipiravir is contraindicated for pregnant women because of placental transit and fetal teratogenicity. In Japan, favipiravir is expected to be administered earlier for suggested COVID-19 with early recovery and good outcomes. This may be due to its high transferability to the lungs.

**Bundle 3: Open Lung Strategy**

Implementation: In emergency of breathing management for COVID-19, Jackson-Rees breathing management [16] is an essential open lung strategy with proper PPE and zoning. High-flow nasal oxygen therapy (HFNT) [17] and non-invasive positive pressure ventilation (NPPV) [18] also require proper PPE use and red clinical zone. A pulse oximeter is necessary to evaluate SpO2. In addition, inhaled corticosteroids such as Orvesco® (ciclesonide) [19] are also used as an adjunct to open the lungs. Consider mechanical ventilation under tracheal intubation in cases with PaO2/FIO2 ≤ 200 by arterial blood gas analysis with proper PPE and zoning.
Explanation: Attention must be paid to mucinous asphyxia in the end bronchiolar and alveolar regions as well as cardiac arrest due to hypoxia in COVID-19. As an expansion strategy for the peripheral airways, it is important to cultivate medical personnel with experience with techniques to ventilate patient lungs using Jackson-Rees circuits [16] in patients with spontaneous breathing for the prevention of cardiac arrest in asthma. We recommend manual positive expiratory end-pressure using Jackson-Rees circuits instead of bag valve masks. In hypoxia, where there is a risk of cardiac arrest in asthma and cardiogenic pulmonary edema, Jackson-Rees breathing will be an essential manual technique for the rescuing COVID-19 patients, with appropriate PPE and zoning. In the treatment of COVID-19, manual open lung will be first recommended against sudden hypoxemia and lung emergency. HFNT and NPPV should be used for patients with non-emergency airway status only in private rooms with ventilation windows or negative pressure rooms in the red zone because of the risk for aerosol diffusion of SARS-CoV-2.

Ciclesonide [19], developed by ALTANA Pharma in Germany, is expected to reduce viral airway inflammation as a steroid precursor with antiviral activity in COVID-19. The routine administration of ciclesonide (Olvesco®) 200 μg Inhaler (56 puff/kit) is three times daily, with two inhalations each time. When ciclesonide is hydrolyzed by esterase in inflamed lungs, it is converted to a deisobutyryl derivative that is an active metabolite with a 100-fold or more increased binding affinity to the glucocorticoid receptor (GR). The complex bound to GR can translocate into the nucleus to bind the glucocorticoid responsive element of DNA to inhibit activating protein-1 (AP-1) and nuclear factor-κB (NF-κB), which are associated with inflammation and cell death in alveolar type-II epithelial cells and vascular endothelial cells [20].

In addition, ciclesonide has antiviral and anti-inflammatory effects that do not involve the GR [19]. Inhaled ciclesonide is transferred to the systemic blood circulation by two absorption routes, via the lungs and via the digestive tract, when substances adhering to the oral cavity and pharynx during inhalation are swallowed. However, the deisobutyryl derivative is rapidly metabolized in the liver mainly by cytochrome P450 CYP3A4. The early administration of the combination of favipiravir and ciclesonide may reduce the severity and mortality in nontracheal-intubated COVID-19; however, clinical studies of the effect are needed.

**Bundle 4: Managements of Analgesia, Sedation, Delirium, and Sleep**

Implementation: Relieve sympathetic nerve activity and maintain day-night sleep rhythms in accordance with the corresponding protocols for analgesia, sedation, delirium, and sleep.

Even when patients are not intubated, we carefully manage the sympathetic action because of the sustained tachypnea. Analgesia and sedation emphasize not only the superficial interpretation of “pain” suppression but also the understanding that the secretion of endogenous catecholamines is brought closer to normal. When respiratory or heart rates increase, the endogenous catecholamine concentrations in the blood may be high. Under these enhanced sympathetic conditions, lymphocytes are prone to apoptosis and lymphocyte function tends to decline.

**NINE SUB-BUNDLES (BUNDLES 5–13)**

As a supplement to the four important main bundles, nine bundles (5–13) are also carefully recommended. The following is supplementary content describing the recommendations and the explanations.

**Bundle 5: Attention to Secondary Infections**

Recommendation: Be aware of ventilation-associated pneumonia (VAP), secondary infections from catheters and urinary systems. For sudden fevers of 38.4°C or higher, collect at least two sets of blood samples for bacterial culture testing. In such cases, antibiotics should be used according to sepsis protocols.

Explanation: SARS-CoV-2 may proliferate in the oral cavity as the tongue; thus, cleaning the oral cavity is important. However, enhanced oral hygiene interventions [25] and long-term tracheal intubation may be a risk for VAP. When the fever type of COVID-19 changes, considering the potential...
for concomitant bacterial infection, two or more sets of blood culture samples are collected, and broad-spectrum antibacterial drugs are administered. Based on information on cultured bacteria obtained within several days, the use of antibacterial agents may be discontinued or de-escalated [13].

Moreover, be aware of bloodstream infections such as *Candida* species and mycosis in patients with compromised cell mediated and humoral immunities. In Japan, (1→3)-β-D glucan can be measured in the blood using a colorimetric method with a chromogenic synthetic substrate. If the fungus is detected directly in the blood or if the fungus is detected from more than one site such as the lungs and the β-D glucan level is elevated, antifungal drugs are administered.

Strains associated with VAP including *Candida* species also inhabit the digestive tract such as the duodenum. We emphasize the maintenance of gastrointestinal immunity by oral or enteral nutrition against bacteria and *Candida* species in the duodenum to prevent VAP.

**Bundle 6: Anticoagulation Therapy**

Recommendation: Consider continuous heparin administration or its combination with recombinant thrombomodulin if plasma RT-PCR is positive for SARS-CoV-2 or D-dimer levels are >4 times baseline such as 2 μg/dL. We note thrombosis in the presence of elevated D-dimer and thrombin-antithrombin complex (TAT) in COVID-19.

Explanation: Regarding thrombotic hemostasis in COVID-19, coagulation and fibrinolysis abnormalities are deeply involved in the pathophysiology of COVID-19 and significantly impact prognosis [26,27]. The International Society on Thrombosis and Haemostasis (ISTH) has published ISTH Guidance [28], which emphasizes the importance of coagulation and fibrinolysis management in COVID-19.

In our management of severe COVID-19 cases, we confirmed increased C-reactive protein (CRP) and interleukin 6 (IL 6) levels; moderately decreased platelet count; prolonged prothrombin time (PT); decreased fibrinogen level; and high D-dimer, FDP, and TAT levels. Attention should be paid to local coagulation and fibrinolytic reaction as a condition similar to DIC. In the early stage of COVID-19, fibrinogen levels increase, platelet counts decrease to the normal range, and PT prolongation and fibrinolysis as high D-dimer and FDP were noted. RNA viruses such as influenza virus and SARS-CoV-2 may cause pathologic fibrinolysis because of enhanced conversion of plasminogen to plasmin and suppression of urokinase such as serpin family E member 1 (Serpinel1) [29,30]. In contrast, as inflammatory activity in vascular endothelial cells increases in COVID-19 as evidenced by increased CRP level and neutrophil/lymphocyte ratio (NLR) [31], von Willebrand factor, tissue factor, and plasminogen activator inhibitor-1 (PAI-1) are transcriptionally activated and accelerate the fibrinolysis-suppressed DIC with vascular endothelial cell injury [20]. We must be aware of the risk of multiple thromboembolic complications [32] such as deep vein thrombosis, coronary artery injury, cerebral infarction, pulmonary thromboembolism, and gastrointestinal ischemia.

In Japan, thrombomodulin can generally be used as a drug for the management of DIC in sepsis and viral diseases. The acute DIC diagnostic score [33] is used for DIC diagnosis and the use of recombinant thrombomodulin. In addition, we must check for (1) D-dimer increases of four-fold or more above the standard value, (2) acute DIC score after hospitalization. If D-dimer is over 4 times of the standard value, a heparin infusion will be need approximately at the rate of 10 units/kg/h with the target PT INR of 1.5. In accordance with acute myocardial infarction, antiplatelet drugs may be effective. If acute DIC scores is 4 or more, recombinant thrombomodulin is recommended for protection of lung and major organs.

**Bundle 7: Nitric Oxide Inhalation Therapy**

Recommendation: Consider the induction of nitric oxide (NO) inhalation therapy in the open lung strategy with bundle 3 if lung oxygenation cannot be improved with hypoxemia (PaO₂/F₉O₂ ratio ≤200 mmHg).

Explanation: NO inhalation therapy at 140–180 ppm is one choice for the management of severe respiratory failure and pulmonary hypertension in the ICU and will also be used in COVID-19 combined with hypoxemia (PaO₂/F₉O₂ ratio ≤200 mmHg), especially intubated patients. NO inhalation therapy is also used for the management of patients in the prone position when dorsal atelecataxis has progressed. Since NO inhalation therapy expands the capillaries in the alveolar region that is being ventilated, it causes a blood flow shift to the ventilated alveoli, improves ventilation-perfusion imbalance, and likely improves oxygenation [34]. NO also reduces viral protease activity [35,36]. Thus, it may suppress SARS-CoV-2 proliferation and reproduction in alveolar and bronchial areas that can be ventilated. However, it is very difficult to select an indication for NO inhalation therapy. It may be just an adjunct to the main four bundles in this article.

**Bundle 8: Extracorporeal Membrane Oxygenation (ECMO)**

Recommendation: Consider ECMO if mechanical ventilation cannot maintain lung function such as oxygenation.

Explanation: Whether or not to introduce ECHO need to be strictly discussed in the facility. The venovenous ECMO method generally removes venous blood from the femoral vein, oxygenates it, and returns it to the internal jugular vein region. However, recently, bicaval dual-lumen catheters have been used, which reduce the recirculation of oxygenated blood and allow easy management [37,38].
In Japan, the first ECMO for COVID-19 was reported on February 14, 2020; subsequently, the Japanese Society of Intensive Care Medicine and the Japanese Association of Acute Medicine provided “ECMONet [39]” for consultation and data management of ECMO in COVID-19. The efforts of Japanese intensivists have made ECMONet a great contribution to saving the lives of COVID-19 patients in Japan. However, disadvantages of ECMO include (1) the occurrence and management of thrombus in extracorporeal circulation; (2) increased bleeding tendency due to inhibition of coagulation; (3) risk of concomitant bacterial infection such as Staphylococcus species in the catheter insertion site, subcutaneous pocket, and blood flow; (4) overproduction of reactive oxygen species; and (5) excessive body water balance. While using ECMO, it is essential to strictly adhere to COVID-19 treatment according to bundles 1–4. Moreover, sufficient attention is needed to excessive body water balance and coagulation suppression in ECMO. While using ECMO, we must be clear about what we can recover in COVID-19. Regarding the production of oxygen radical species, clinical studies are expected to evaluate the efficacy of high-dose intravenous vitamin C therapy.

**Bundle 9: Antioxidant High-dose Vitamin C Therapy**

**Recommendation:** Consider high-dose vitamin C therapy for high-concentration oxygen supply (≥40%) and in ECMO.

**Explanation:** High-dose intravenous administration of vitamin C may be a strategy to eliminate the cytotoxic influence of reactive oxygen species in patients receiving high-concentration oxygen supply under mechanical respiratory support using ECMO. Prospective studies on high-dose vitamin C therapy have not confirmed its superiority in sepsis [40–42]. However, in COVID-19 cases with elevated mucin, Klebs von den Lungen-6 (KL-6) [43], and surfactant protein levels, there is a risk of fibroblast proliferation in the lungs due to the additional harmful effects of reactive oxygen species. At oxygen concentrations of 40% or more, high-dose vitamin C therapy may be an effective therapy for antioxidant and relative adrenal insufficiency. In high-dose intravenous vitamin C therapy for adults, 1,500 mg of vitamin C is administered every 6 hours for 6 days in the acute phase or in cases requiring high-concentration oxygen therapy. The oral administration of vitamin C supplementation has a limited ability to increase plasma and tissue concentrations due to gastrointestinal absorption and excretion; thus, the recommended daily dose of 1,000 mg is the maximum for oral or enteral nutrition.

Moreover, we must be aware that plasma levels of vitamin C may be low in patients exposed to several types of gas and smoke, including smoking. Vitamin supplementation appears to be essential in oxygen therapy for COVID-19.

The adverse effects of high-dose vitamin C administration include diarrhea, renal stones (oxalate stones), and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency [44]. The toxicity of high-dose vitamin C therapy is statistically very low. There is no evidence contraindicating the use of high-dose vitamin C in combination under high-concentration oxygen supply (≥40%) and in ECMO.

**Bundle 10: Excretion of Inflammatory Ligands**

**Recommendation:** Be alert in maintaining renal and biliary excretion. Renal function is maintained with glomerular filtration and urine output over 0.5 mL/kg/h [13], with bile excretion expected in cases with oral or enteral nutrition.

**Explanation:** Renal and biliary excretion are important for the maintenance of the excretion of drugs, inflammatory ligands, inflammatory cytokines, and proliferative cytokines. Maintenance of glomerular filtration and gallbladder function is important for normal excretion of drugs and inflammatory ligands and shortens the inflammatory and proliferative phases in COVID-19. Levels of inflammatory cytokines such as IL-6 and proliferative cytokines such as TGF-β can be measured in the urine and bile. Prolonged inflammation and proliferation may occur when oral and enteral nutrition are insufficient in COVID-19. Regarding this bundle, prospective collaborative research is needed regarding sepsis. In our department and institutes, continuous renal replacement therapy (CRRT) is available in cases with impaired renal function. Continuous hemofiltration is selected in acute kidney injury stage 2/3 in CRRT at a filtration rate of 20–30 mL/min. Our department and institutes use polymethyl methacrylate membrane (PMMA; Toray Industries, Inc.) for cytokine adsorption.

**Bundle 11: Anti-inflammatory Therapy**

**Recommendation:** Consider the concomitant use of the IL-6 receptor antibody sarilumab in patients with impaired renal function or inability to tolerate enteral nutrition and with high CRP and IL-6 levels.

**Explanation:** Sarilumab [45] was developed as a therapeutic agent for rheumatoid arthritis (RA). For the treatment of adult RA, 200 mg of sarilumab is administered subcutaneously once every 2 weeks. In adults with COVID-19, sarilumab may decrease the areas under the curves of plasma CRP and IL-6. Prolonged inflammation induces the catabolism of many proteins. Therefore, shortening the inflammatory period may reduce the progression of weight loss and weakness if the antiviral drug is appropriately administered as per bundle 2. The effect of sarilumab on the short- and long-term prognosis should be evaluated in randomized clinical trials.

**Bundle 12: Immunoglobulin Therapy**

**Recommendation:** Consider high-dose immunoglobulin therapy in severe cases of COVID-19, such as those requiring...
ECMO. We also consider immunoglobulin therapy from a group of patients with proven COVID-19 morbidity.

Explanation: In Japan, intravenous immunoglobulin (IVIG) is supplied as an immunoglobulin G (IgG) preparation without IgA or IgM. The IgG contains anti-cytokine and anti-virus antibodies against human coronavirus (HCoV)-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. We consider antibody therapy to be one virus reduction strategy for SARS-CoV-2. If we choose this bundle, IVIG therapy is recommended at 0.5 g/kg/day for 8 days (total immunoglobulin 4 g/kg) without excessive infusion volume and the plus balance. For emerging viral infectious diseases, purified convalescent plasma may also inactivate the virus [46,47].

**Bundle 13: Prevention of the Exacerbation of Interstitial Pneumonia**

Recommendation: Consider the co-administration of drugs such as pirfenidone to diminish disability due to pulmonary fibrosis in cases with elevated plasma KL-6 and pulmonary surfactant protein levels.

Explanation: Recovery from COVID-19 must consider the long-term prognosis including pulmonary sequelae. Pirfenidone [48-50] is an antifibrotic drug used for the treatment of idiopathic pulmonary fibrosis with long-term effects of suppressing the production of type I and type II procollagen involved in organizing interstitial pulmonary fibrosis. It is used in improving the vital capacity after interstitial pneumonia.

We can also consider the combined use of the triple tyrosine kinase inhibitor nintedanib [51,52] that inhibits the proliferative actions of TGF-β, PDGF, and FGF in fibroblasts. During prolonged COVID-19 treatment, attention should be paid to the progression and organization of pulmonary fibrosis.

Long-term lung function should be evaluated after the acute phase of COVID-19. There is also a need for randomized control studies to assess how these antifibrotic agents affect lung function after acute-phase management of COVID-19.

**CONCLUSIONS**

The emergence of SARS-CoV-2 and consequent COVID-19 pandemic has resulted in the evaluation of medical care and critical care not only in Asia but also in regions such as Europe and the United States. The methods of SARS-CoV-2 infection control implemented by governments vary internationally. Likewise, the COVID-19 treatment methods also vary internationally, with differences in outcomes among countries.

This article introduced a critical care bundle describing the kinds of strategies required for the management of COVID-19 and future viral epidemics. From virological, pathophysiological, and pharmacological insights, essential strategies were “deductively” extracted as bundles.

In life-threatening medical emergency situations, we support the active use of drugs and devices with established safety profiles whose administration is inductively considered to be effective under hospital and patient approval. Future recursive prospective clinical randomized control trials will be required to provide clinical evidence. In China and Asia, many excellent drugs will be available for the treatment of the pathological conditions described in this article for COVID-19. This article will be expected to serve as a reference for the application of Chinese traditional drugs in COVID-19 and next new viral infections.

**REFERENCES**


## TABLE. COVID-19 MANAGEMENT BUNDLE CHECKLISTS

### Main Bundles 4

1. Personal defense in medical staff
   - PPE
   - Zoning
   - Air purification

2. Early detection and treatment
   - RT-PCR (saliva, plasma)
   - Favipiravir

3. Open Lung
   - Jackson-Rees breathing system
   - High-flow nasal oxygen
   - Non-invasive positive pressure ventilation
   - Ciclesonide

4. Analgesia/Sedation/Sleep
   - Sympathetic nerve suppression
   - Ramelteon

### Sub Bundles 9 (Bundles 5-13)

5. Careful management of secondary infections
   - VAP
   - Bloodstream infection
   - Cholecystitis
   - Urinary tract infection
   - Subcutaneous infection
   - Deep mycosis
   - Sepsis

6. Anticoagulant therapy
   - D-dimer
   - TAT
   - Heparin
   - Recombinant thrombomodulin

7. NO inhalation therapy
   - PaO$_2$/FiO$_2$ ratio ≤200 mmHg
   - PaO$_2$/FiO$_2$ ratio ≤100 mmHg

8. ECMO
   - PaO$_2$/FiO$_2$ ratio ≤100 mmHg
   - VV-ECMO
   - VA-ECMO
   - Bicaval dual-lumen catheter

9. High dose vitamin C therapy
   - Smoker
   - Oxygen supply ≥40%
   - ECMO
   - 1,000 mg PO a day
   - 1,500 mg DIV every 6 h

10. Excretion of inflammatory ligand
    - Diuretic management ≥0.5 mL/kg/h
    - Continue oral nutrition
    - Enteral nutrition

11. Anti-inflammatory therapy
    - Sarilumab
    - AUC$_{CRP}$

12. Immunoglobulin
    - IVIG therapy
    - Convalescent plasma

13. Prevention of exacerbation interstitial pneumonia
    - Pirfenidone
    - Triple tyrosine kinase inhibitor

### Outcomes

- Discharge to home
- 28-day mortality
- 60-day mortality
- Lung sequelae/fibrosis
- ICU-acquired weakness