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Clinical Management of Patients with COVID-19

A guide for front-line healthcare workers

Version 2.1

2020

- This guide (Version 2.1) was prepared based on information available as of June 16, 2020. Corrections to the content may be required according to future findings. Please keep up to date with the latest information by accessing websites such as those of the Ministry of Health, Labour and Welfare and the National Institute of Infectious Diseases.

Clinical Management of Patients with COVID-19: A guide for front-line healthcare workers (Version 2.1)

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Introduction to Version 2

Two months have passed since Version 1 of this guide was released. While there have been outbreaks in Europe and the USA, the number of patients in Japan has increased since the end of March and an emergency declaration was issued on April 7 in accordance with the Revised Act on Special Measures for Pandemic Influenza and New Infectious Diseases. As of May 13, 2020, 15,908 cases and 687 deaths have been reported in Japan, although the number of deaths is low compared to Europe and the USA. Nosocomial infections and an inadequate supply of personal protective equipment have placed a heavy burden on medical institutions. However, progress has been made in diagnosis and treatment because of the accumulation of cases and further understanding of the disease nature.

To respond to these changes in the situation, we have prepared Version 2 of this guide in cooperation with the Japanese Association for Infectious Diseases, the Japanese Respiratory Society, and the Japanese Society of Intensive Care Medicine through the participation of specialists in the review board. This guide provides considerably more useful information on the clinical management of patients with COVID-19.

The number of patients in Japan has been decreasing since its peak in early April, but there is still a risk that we will have an outbreak again, so the situation remains unpredictable. We hope that this guide will prove to be a widely used reference in the clinical field and that it will help to improve patient prognosis and control the outbreak.

Introduction to Version 1

In December 2019, an outbreak of pneumonia with unknown etiology was reported in Wuhan, Hubei Province, the People's Republic of China. It was later confirmed that the pneumonia was caused by a novel coronavirus (SARS-CoV-2). Despite the adoption of strong measures, such as the lockdown of Wuhan city, the SARS-CoV-2 infection spread throughout the world and the WHO declared it a Public Health Emergency of International Concern on January 30, 2020. The first case in Japan was reported on January 16, and SARS-CoV-2 disease (COVID-19) was classified as a designated infectious disease on February 1. Furthermore, in response to an increase in the number of patients, the government's basic strategy has included measures aimed at preventing the spread of infection through Border Control Measures on February 25, 2020.

As of March 4, it is reported that there are 257 patients in Japan (246 domestic cases and 11 cases of returnees who arrived by chartered plane). Although medical institutions in the metropolitan area have accepted patients from the cruise ship (Diamond Princess) anchored off the Port of Yokohama and gained experience examining them, some regions in Japan have not seen any patients yet. The situation is such that even healthcare workers are worried about how to handle this novel infectious disease.

When a novel infectious disease occurs, the role of medical institutions is to provide optimal medical care for patients. Prior preparation is essential to ensure that this role can be fulfilled by avoiding nosocomial infection. Fortunately, Chinese physicians and researchers have promptly shared relevant information, such as the clinical features of the patients. In Japan too, case reports are being published. At the same time, so many notifications from the government and guidelines from academic societies have been issued that there seems to be a trend towards too much information.

This guide summarizes the current information in a format that is as easy to comprehend as possible. We hope that this guide will be used as a reference by healthcare workers and government-related staff to improve patient prognosis and control the outbreak.

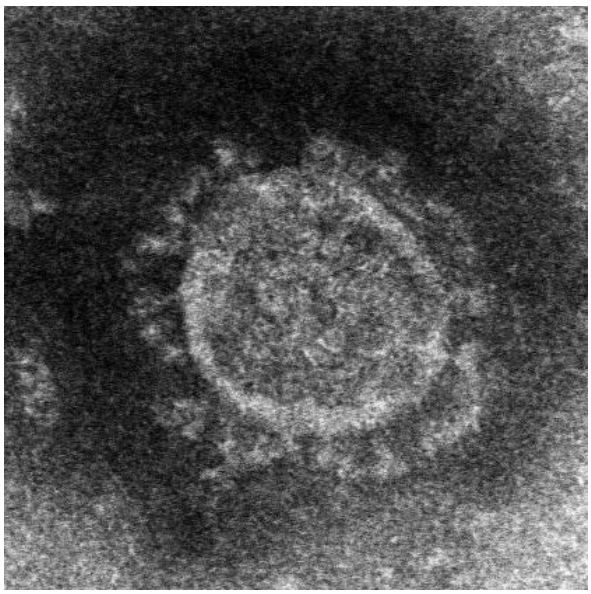
KATO Yasuyuki, Research Representative

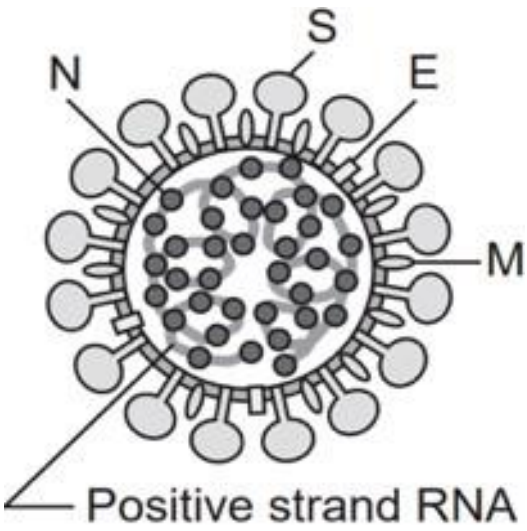
1 Pathogen and Clinical Features

Four types of coronavirus are known to infect humans. A coronavirus is the causal pathogen for about 10 to 15% of common colds in general. In addition, some coronaviruses infect animals, such as dogs, cats and pigs. In 2002, Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV-1 spread from Guangdong Province (China). In this case, humans were infected with SARS-CoV from bats via masked palm civets, with human-to-human infections leading to over 8,000 SARS patients. Furthermore, Middle East Respiratory Syndrome (MERS) caused by MERS-CoV was reported in the Arabian Peninsula in 2012, when it was found that humans had been infected with MERS-CoV from dromedary camels. In 2019, it was determined that the outbreak of pneumonia due to unknown causes that began in Wuhan, Hubei Province (China), from December 2019 was caused by a novel coronavirus (SARS-CoV-2) (Figure 1-1).

SARS-CoV-2 might be a coronavirus of animal origin that, like the pathogens for SARS and MERS, was classified as a β-coronavirus group. The host animal has yet to be found. The disease is currently spreading globally through human-to-human infection. The disease caused by infection with SARS-CoV-2 is called COVID-19 (referred to as the “novel coronavirus infection” in the Infectious Diseases Control Act).

Figure 1-1: SARS-CoV-2 (Coronavirus of Animal Origin)





(National Institute of Infectious Diseases)

The spike like structures on the SARS-CoV-2 virion makes SARS-CoV-2 look like a crown (“corona” in Greek). As with the pathogen for SARS (SARS-CoV-1), it enters human cells using ACE2 as a receptor. Similar to SARS-CoV-1, it is considered to remain infectious on surfaces in the environment for about 3 days.

(van Doremalen N, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020.)

1 Transmission Modes

Route of Transmission

The main mode of transmission is considered to be droplet infection, but in environments with poor ventilation, SARS-CoV-2 is thought to be infectious even in the absence of coughing and sneezing. It is also considered to spread through direct and indirect contact. Persons with symptoms are the main source of virus transmission. However, there is a risk of infection from asymptomatic pathogen carriers, as well.

Incubation Period and Infectious Period

The incubation period is 1 to 14 days, and symptoms usually appear about 5 days after exposure (WHO). The pathogen is infectious from prior to onset and its high infectivity in the early phase of the disease is one of the main causes of community-acquired infections, a characteristic that differs from those of SARS and MERS.
SARS-CoV-2 replicates in both the upper and lower respiratory tracts, and there is a tendency towards higher virus shedding and a longer excretion period in severe cases. The genetic material of SARS-CoV-2 can be detected 3 to 4 weeks after onset. However, detection of the pathogen gene in a patient is not equivalent to that patient being infectious. The infectious period is considered to be from 2 days prior to onset until about 7 to 10 days after onset. It is of note, however, that infectious SARS-CoV-2 is rarely detected in blood, urine and stool samples.

(Wölfel R, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020.)

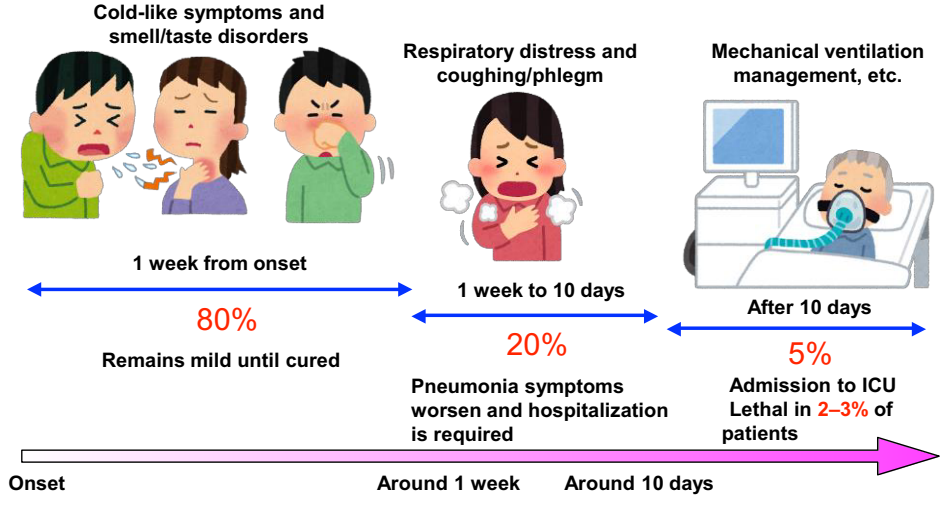
Seasonality

Coronavirus infections generally spread during the winter season in temperate climates. However, it is unknown whether this can be applied to COVID-19.

2 Clinical Features

Patients with COVID-19 usually present symptoms such as fever, respiratory symptoms (coughing, throat pain, runny nose, nasal stuffiness, etc.), headaches and fatigue. Gastrointestinal symptoms such as diarrhea and vomiting are seen in less than 10% of patients, which is considered to be less than that in patients with SARS or MERS. The initial symptoms are similar to those for influenza and the common cold, making it difficult to distinguish COVID-19 from them. It is becoming apparent that patients experience altered sense of smell and taste. According to a report from Italy, about 30% of patients experienced smell and/or taste disorders and this was particularly commonly seen in younger people and women. In China, it has been reported that the period from onset until a visit to a medical institution and that until hospitalization were about 5 days and 7 days, respectively. It is thought that some cases become severe within a week from disease onset. In even more severe cases, patients tend to be admitted into the intensive care unit after the tenth day (Figure 1-2).

Figure 1-2: Clinical Course of COVID-19



National Epidemiological Surveillance of Infectious Diseases, National Institute of Infectious Diseases, January 14, 2020 to May 25, 2020

In Japan, the number of cases epidemiologically linked to overseas travel increased from the beginning of March. In addition, cases with unidentified infection sources occurred sporadically and the number and ratio of such cases increased continuously from mid-March. By the end of March, infection clusters (groups for which relationships exist among the patients) were being reported one after another, mainly in urban areas, and the number of infected patients increased rapidly. As of May 27, according to NESID, the day with the highest number of reported cases was April 9 (647 cases) and the day with the highest number of onsets was April 1 (419 cases: cases with a confirmed date of onset only). This epidemic is considered to have increased rapidly from mid-March, with a peak in early April, after which the number decreased until it had settled by mid-May (Figure 1-3, Figure 1-4).

No. of cases: 16,386 cases (14,605 confirmed cases, 1,753 asymptomatic pathogen carriers, 28 cases which were confirmed through postmortem examination)

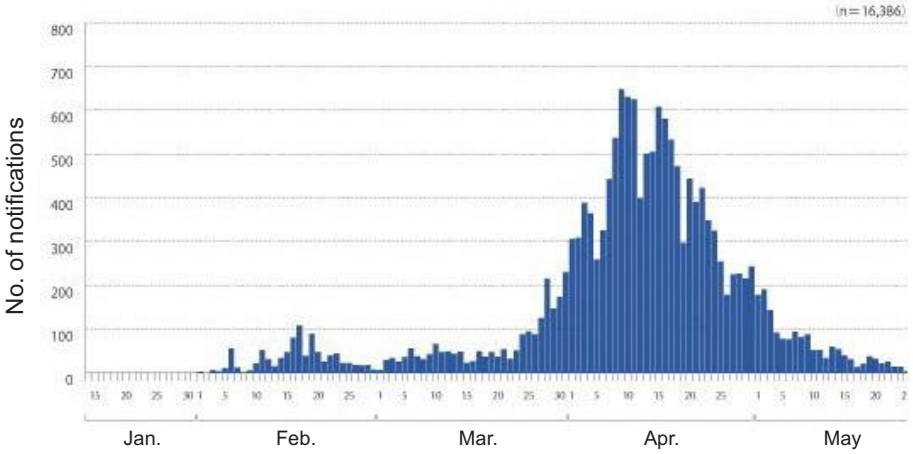
Gender: Male = 9,009 cases, female = 7,376 cases, unknown = 1 case (male/female ratio = 1.2:1)

Age: Median = 49 years old (Range 0 to 104)

The ICU admission rate and the percentage of patients receiving mechanical ventilation increases significantly for patients aged over 60. The ratio of severe cases is low for patients up to 59 years of age, and the fatality rate becomes increasingly high with age for patients aged over 60. (Figure 1-5)

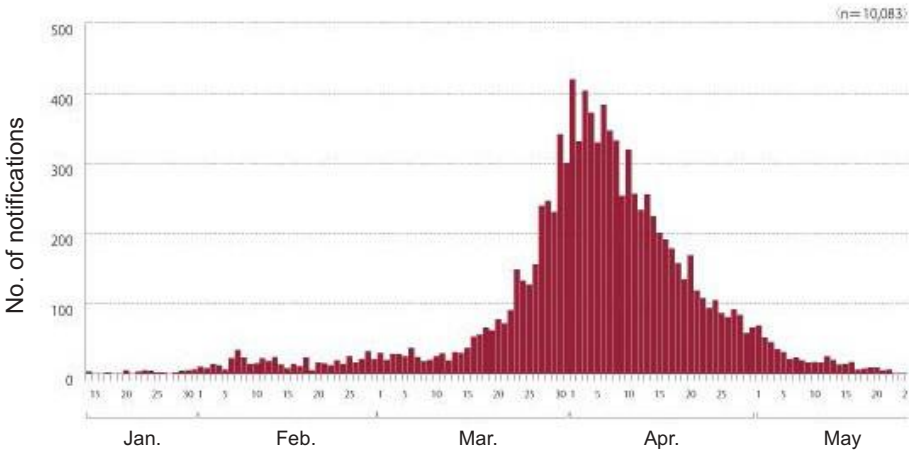
Symptoms (overlapping): Fever = 12,340 cases (75.3%), coughing = 7,005 cases (42.7%), acute respiratory symptoms other than coughing = 1,458 cases (8.9%), serious pneumonia = 1,131 cases (6.9%).

Figure 1-3: Number of COVID-19 Notifications by Reported Date (January 14, 2020 to May 25, 2020)



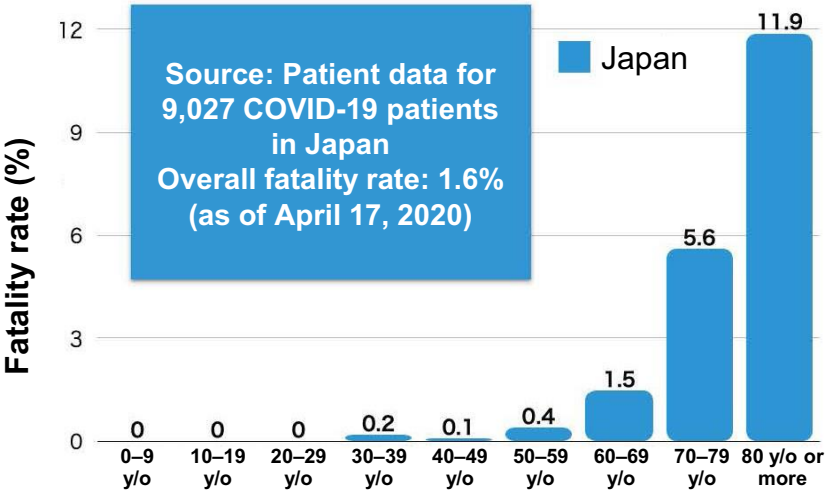
* This graph should be interpreted with caution because recent reports are not completely reflected due to the time required for reports to be confirmed.

Figure 1-4: Number of COVID-19 Notifications by Onset Date (January 14, 2020 to May 25, 2020)



* This graph should be interpreted with caution because recent onsets are not completely reflected due to the time lag between onset and reporting.

Figure 1-5: Fatality Rate for Patients with COVID-19 by Age



Ministry of Health, Labour and Welfare. Trends in the Occurrence of COVID-19 (published April 17, 2020)

Risk factors for severe cases

Elderly patients and patients with underlying diseases (heart failure, diabetes, chronic respiratory diseases, etc.) have a high fatality rate (Table 1-1).

Complications

Cases of cerebral infarction in young patients have been reported, and thrombosis as a pathophysiology for causing such cerebral infarction has been suggested. In addition, it has been suggested that thrombosis may be related to the sudden death of patients with mild cases under observation. Cases of pediatric COVID-19 patients with Kawasaki disease-like symptoms have been reported in Europe and the USA.

Table 1-1: Risk Factors for Severity

Aggravation risk factors	Underlying diseases to beware of despite there being insufficient information to determine whether they are aggravation risk factors
• Elderly patients aged 65 years and above	• Use of biological agents
• Chronic respiratory disease	• Immunodeficiency after organ transplantation or other causes
• Chronic renal disease	• HIV infection (particularly CD4 < 200/L)
• Diabetes	• History of smoking
• Hypertension	• Pregnancy
• Cardiovascular disease	• Malignant tumor
• Obesity (BMI of 30 or higher)	

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3 Prognostic Markers

Table 1-2: Summary of 191 Cases in Two Hospitals in Wuhan
(Cases of death or survival and discharge between December 29, 2019 and January 31, 2020)

	Death cases (n = 54)	Survival cases (n = 137)	p-value
White blood cells (/μL)	9,800	5,200	< 0.0001
Lymphocytes (/μL)	600	1,100	< 0.0001
Hemoglobin (g/dL)	12.6	12.8	0.30
Platelets (x104/μL)	16.55	22.00	< 0.0001
Albumin (g/dL)	2.91	3.36	< 0.0001
ALT (U/L)	40.0	27.0	0.0050
LDH (U/L)	521.0	253.5	< 0.0001
CK (U/L)	39.0	18.0	0.0010
High-sensitivity troponin I (pg/mL)	22.2	3.0	< 0.0001
Prothrombin time (s)	12.1	11.4	0.0004
D-dimer (μg/mL)	5.2	0.6	< 0.0001
Serum ferritin (μg/L)	1435.3	503.2	< 0.0001
IL-6 (pg/mL)	11.0	6.3	< 0.0001
Procalcitonin (ng/mL)	0.1 (0.1-0.5)	0.1 (0.1-0.1)	< 0.0001

* Only the medians of the test values are shown (the interquartile range is also shown for procalcitonin).

(Zhou F, et al. Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: retrospective cohort study. Lancet 2020)

- Several other articles have been published, and the following may be useful as markers for assessing prognosis.

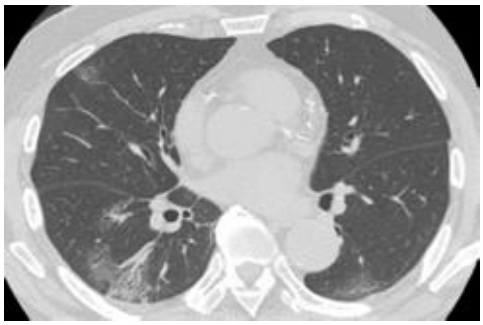
(1) Increase in D-dimer, (2) Increase in CRP, (3) Increase in LDH, (4) Increase in ferritin, (5) Decrease in lymphocytes, (6) Increase in creatinine, and (7) Increase in troponin

- Focus on the general clinical features and use them as part of the clinical decision-making process.

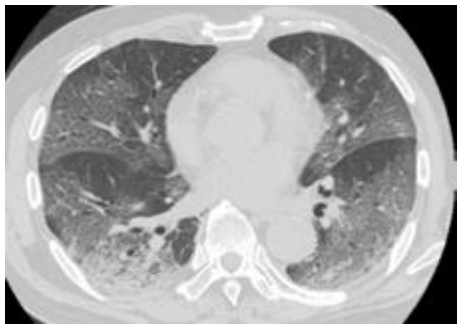
4 Imaging Findings

- The sensitivity of chest CT scan is high in diagnosis of COVID-19, and abnormal pulmonary findings can be detected even in patients before developing symptoms.
- In a summary of chest CT findings for patients in Wuhan (81 cases), opacities on both sides were found in 79% and this was distributed to the peripheral lung field in 54%. Abnormalities were found in all lung fields, but there tended to be more in the right lower lobe.
- Changes from ground glass-like opacities to infiltrative opacities at 1 to 3 weeks after onset. The peak of pulmonary CT image worsening is often on around Day 14 of the disease.
- CT imaging findings are not directly associated with pulmonary oxygenation.

Figure 1-6: Male patient in his 80s (Case at Toshima Hospital, Operated by the Tokyo Metropolitan Health and Hospitals Corporation)



▲ Day 6



▲ Day 12

2 Case Definition, Diagnosis, and Notification

1 Case Definition

The initial system used for COVID-19 surveillance had been through suspected disease surveillance performed by the sentinel medical institutions that conducted etiological diagnosis and notification. However, COVID-19 surveillance has been conducted by making COVID-19 a designated infectious disease that requires notification under the Infectious Disease Control Act since February 1, 2020.

Classification	Definition	Specific example
Patient (confirmed case)	SARS-CoV-2 is detected in patient suspected of infection	
Asymptomatic pathogen carrier	No symptoms, but SARS-CoV-2 is detected	When etiological diagnosis for person in close contact with infected person was conducted, etc.
Suspected patient	Clinically high probability of infection among patients suspected of infection	Typical clinical features were found in person in close contact with infected person before completion of etiological diagnosis, etc.
Cases confirmed or suspected through postmortem examination	Death or suspected death due to COVID-19 diagnosed through postmortem examination	Death due to pneumonia with unknown cause, etc.

Table 2-1: Criteria for Suspected Patients

Conduct differential diagnosis if any of conditions **A** to **E** below are applicable and the patient is suspected of having COVID-19 with no other apparent infectious or disease causes.

A Patient who has a fever or respiratory symptoms (including mild cases) as well as a history of close contact with a person confirmed as having COVID-19

B Patient who has a fever of 37.5°C or higher, respiratory symptoms, and a history of travel to or residence in an area confirmed as a COVID-19 outbreak area within 14 days before the onset of symptoms

C Patient who has a fever of 37.5°C or higher, respiratory symptoms, and a history of close contact with a person having a history of travel to or residence in an area confirmed as a COVID-19 outbreak area within 14 days before the onset of symptoms

D Patients with symptoms such as fever, respiratory symptoms, and other symptoms suggesting an infection as well as patients who present symptoms that require intensive care or equivalent treatment based on medical knowledge generally acknowledged by physicians when it is determined that immediate diagnosis of a particular infection cannot be made (equivalent to suspected cases specified by the Order of the Ministry of Health, Labour and Welfare under the provisions of Article 14, paragraph 1 of the Infectious Diseases Control Act) and that differential diagnosis of COVID-19 is required

E Other than conditions A to D above, any of the following conditions are applicable and the physician suspects COVID-19

- Patient who has a fever of 37.5°C or higher as well as respiratory symptoms and is suspected of pneumonia requiring hospitalization (give this active consideration particularly if the patient is elderly or has underlying diseases)
- Patient who is suspected of having COVID-19 and has tested positive in pathogen testing for a general respiratory infection other than COVID-19, but the response to treatment is poor and symptoms worsen
- Patient who is suspected of having COVID-19 based on a comprehensive analysis by the physician

* Criteria for Reporting to Governors for Physicians and Managers at Designated Reporting Institutions (revised on May 13, 2020)

Table 2-2: Definition of Close Contact with COVID-19 Patients

Persons who come into contact with a patient (confirmed case) during the infectious period (from 2 days prior to onset) are defined as those who fall under the following criteria.

- Person who lives with or had prolonged contact with (including traveling together in a vehicle or airplane) a patient (confirmed case)
- Person who examined, nursed or cared for a patient (confirmed case) without taking any appropriate protective measures against infection
- Person who is likely to have had direct contact with contaminated substances, such as the respiratory secretions or bodily fluids from a patient (confirmed case)
- Other: Person having had more than 15 minutes of contact with a patient (confirmed case) within touching distance (about 1 m) without taking the necessary protective measures against infection (comprehensively determine the infectivity of the patient based on the various situations, such as the surrounding environment, contact, etc.)

* Guidelines for Active Epidemiological Investigation (revised on April 21, 2020)

Table 2-3: Guidance on When to Consult a Call Center for Japanese Returnees and Potential Contacts

If any of the conditions below apply, contact the call center. Even if none of these conditions apply, you can consult the call center as well.

☆ Presenting severe symptoms of shortness of breath (respiratory distress), strong fatigue (feeling of weariness), or high fever

☆ Having relatively mild cold-like symptoms with a high risk of developing into a severe case (*)

(*) Persons who are elderly, have underlying diseases such as diabetes, heart failure, or respiratory disease (COPD, etc.), have undergone hemodialysis, and are using immunosuppressants or anti-cancer drugs

☆ Other than the above, persons with relatively prolonged mild cold-like symptoms, such as persist fever or coughing

(Please make sure that you consult the call center if symptoms persist for 4 days or longer. Symptoms depend upon the individual, so please consult the call center immediately if you think you have severe symptoms. Similarly, please consult the call center if you need to continue taking antipyretics.)

* Guidance on Consulting and Visiting a Physician Regarding COVID-19 (revised May 13, 2020)

2 Etiological Diagnosis

Etiological tests should be performed for patients with symptoms such as fever who consulted the Call Center for Japanese Returnees and Potential Contacts and then visited the Outpatient Facilities for Japanese Returnees and Potential Contacts. A nucleic acid amplification test such as the PCR method or an antigen test is conducted if the outpatient facility physician deems it necessary.
Other than the Outpatient Facilities for Japanese Returnees and Potential Contacts, if the examining physician comprehensively determines that COVID-19 is suspected, the physician shall consult with the public health center to determine whether a test should be conducted. Furthermore, it is possible in some regions to conduct the test by means of a direct referral from a clinic to the regional outpatient or test center operated by a medical association or the like.
For persons suspected of having COVID-19, virus isolation, SARS-CoV-2 genome detection or antigen detection is conducted using sputum, respiratory tract secretions, alveolar lavage fluid, nasopharyngeal swab, saliva* or autopsy material. This provides a definitive diagnosis if the result is positive. (An antigen test should be conducted using a nasopharyngeal swab.) There is a sensitivity limit to etiological tests so the test results should be comprehensively combined with the clinical features to achieve a proper diagnosis.
* PCR tests can be conducted using saliva if the patient is tested within 9 days of the onset of symptoms. The PCR tests should not be recommended for persons without any symptoms currently. Saliva samples are not adequate for antigen tests at present.

Order of priority for sample transportation	Sample type	Amount
1	Lower respiratory tract samples (sputum or respiratory tract secretions including aspiration fluid)	1 to 2 ml
2	Nasopharyngeal swab	1 swab
3	Saliva	1 to 2 mL

Note: Take one sample in accordance with the order of priority.

* Refer to the “Manual for Sample Collection and Transportation” for details.
https://www.niid.go.jp/niid/images/pathol/pdf/2019-nCoV_200602.pdf

3 Antigen Test

Since an antigen test detects the SARS-CoV-2 antigen that is specifically produced in cells infected with SARS-CoV-2, a positive result leads to an accurate diagnosis. Together with PCR tests, the antigen test can be used to provide a definitive diagnosis (May 13, 2020).

○ Positive antigen test: Definitive diagnosis of COVID-19

○ Negative antigen test: Physician decides whether to conduct a PCR test.

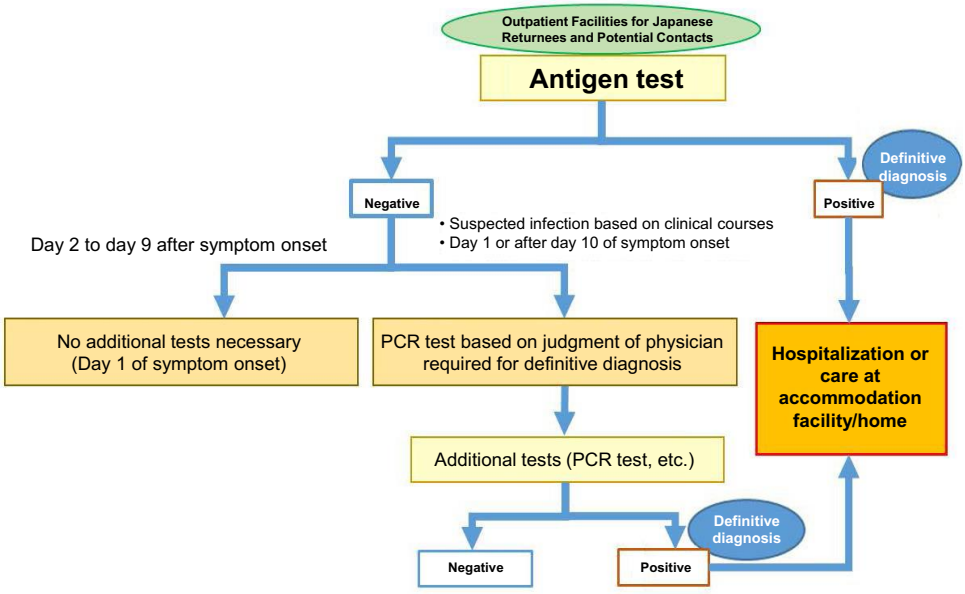
Characteristics of antigen test kit (product name: ESPLINE SARS-CoV-2)

This test quickly and easily detects the antigen of SARS-CoV-2 in a nasopharyngeal swab by using the immunochromatography method, whose measurement principles are based on an enzyme immunoassay. This kit does not require any special test equipment. In addition, the test results can be obtained easily and rapidly (approx. 30 minutes).
If a positive result is obtained using this kit, a definitive diagnosis can be given. Please note, however, that if a negative result is obtained using this kit for a person on day 2 to day 9 after the onset of suspected COVID-19 symptoms (day 1 being the date of onset), doctors should determine whether additional PCR tests are necessary or not.

However, detection requires a higher viral amount compared to the PCR method so, at present, this is not suitable to be used for detection of and screening for asymptomatic COVID-19 cases because it cannot demonstrate an appropriate detection ability.

Interpretation of results and points to consider

If a positive result is obtained, a definitive diagnosis can be given. Please note, however, that if a negative result is obtained and infection is suspected through clinical courses or if it is on day 1 or after day 10 of symptom onset, additional PCR tests are recommended if doctors suspect the patients as having COVID-19 to provide an accurate diagnosis.



Reference: Guidelines Regarding Use of SARS-CoV-2 Antigen Detection Kits (revised on June 16, 2020)

Clinical studies

(1) Correlation using domestic clinical samples

The study results (n = 72) for the RT-PCR method using domestic clinical samples showed that negative and positive result concordance rates were 98% (44/45 cases) and 37% (10/27 cases), respectively. When the positive result concordance rates for positive samples are compared by converting them to the RNA copy number (estimate) per RT-PCR test sample, the concordance rate was 83% (5/6 cases) for samples with 100 copies/reaction or higher and 50% (6/12 cases) for 30 copies/reaction or higher.

(2) Studies using regulatory examination samples

The study results (n = 124) based on the RT-PCR method using regulatory examination samples showed positive, negative, and overall concordance rates were 66.7% (16/24 cases), 100% (100/100 cases), and 94% (116/124 cases), respectively. When the positive result concordance rates for positive samples were compared by converting them to the RNA copy number (estimate) per RT-PCR test sample, the concordance rate was 100% (12/12 cases) for samples with 1,600 copies/reaction or higher, 93% (14/15 cases) for samples with 400 copies/reaction or higher, and 83% (15/18 cases) for samples with 100 copies/reaction or higher. However, the sample solution used for the RT-PCR method was used as the sample group (the swab was kept in a virus transport solution beforehand).

* The converted RNA copy number was estimated by converting the cycle threshold (Ct) value obtained when assuming that the RNA extraction rate from the sample (nasopharyngeal swab suspended in virus storage solution) was the same as the standard.

4 Antibody Test

Antibody tests are not implemented as regulatory examinations, and they are not designated as a test for definitive diagnosis.

Currently, various antibody test kits, such as those that employ rapid antibody detection by means of the immunochromatography method, are marketed as reagents for research, but careful consideration is necessary because these tests may use methods that cannot deliver the anticipated level of precision. In addition, no antibody tests have obtained approval as an in vitro diagnostic within Japan, and the WHO does not recommend the sole use of antibody tests for diagnosis. Instead, they suggest the possibility of using them in epidemiological investigations.

The investigation results produced with patient serum at the National Institute of Infectious Diseases are shown here (using Company A detection kits). Detection of the IgM antibody using a single serum is considered to be of little use in making a diagnosis within 12 days of onset, so it is necessary to evaluate a significant increase in the IgG antibody level using paired serum. This is currently under development.

Table 2-4: Anti-SARS-CoV-2 IgM or IgG Antibody Positive Rate by Days after Onset

Days after onset	IgM antibody			IgG antibody			IgM or IgG antibody		
	No. of samples	No. of positives	Positive rate (%)	No. of samples	No. of positives	Positive rate (%)	No. of samples	No. of positives	Positive rate (%)
Day 1–6	14	0	0.0	14	1	7.1	14	1	7.1
Day 7–8	20	2	10.0	20	5	25.0	20	5	25.0
Day 9–2	21	1	4.8	21	11	52.4	21	11	52.4
Day 13 onward	32	19	59.4	32	31	96.9	32	31	96.9

5 Notification

The diagnosing physician shall immediately notify the nearest public health center (notification is also required for suspected patients).

Based on this notification, the patient receives a recommendation for hospitalization at an infectious disease designated medical institution or other measures are taken. According to the outbreak status in each region, the patient may be advised to stay at an accommodation facility or at home (MHLW Administrative Notice dated April 2, 2020).

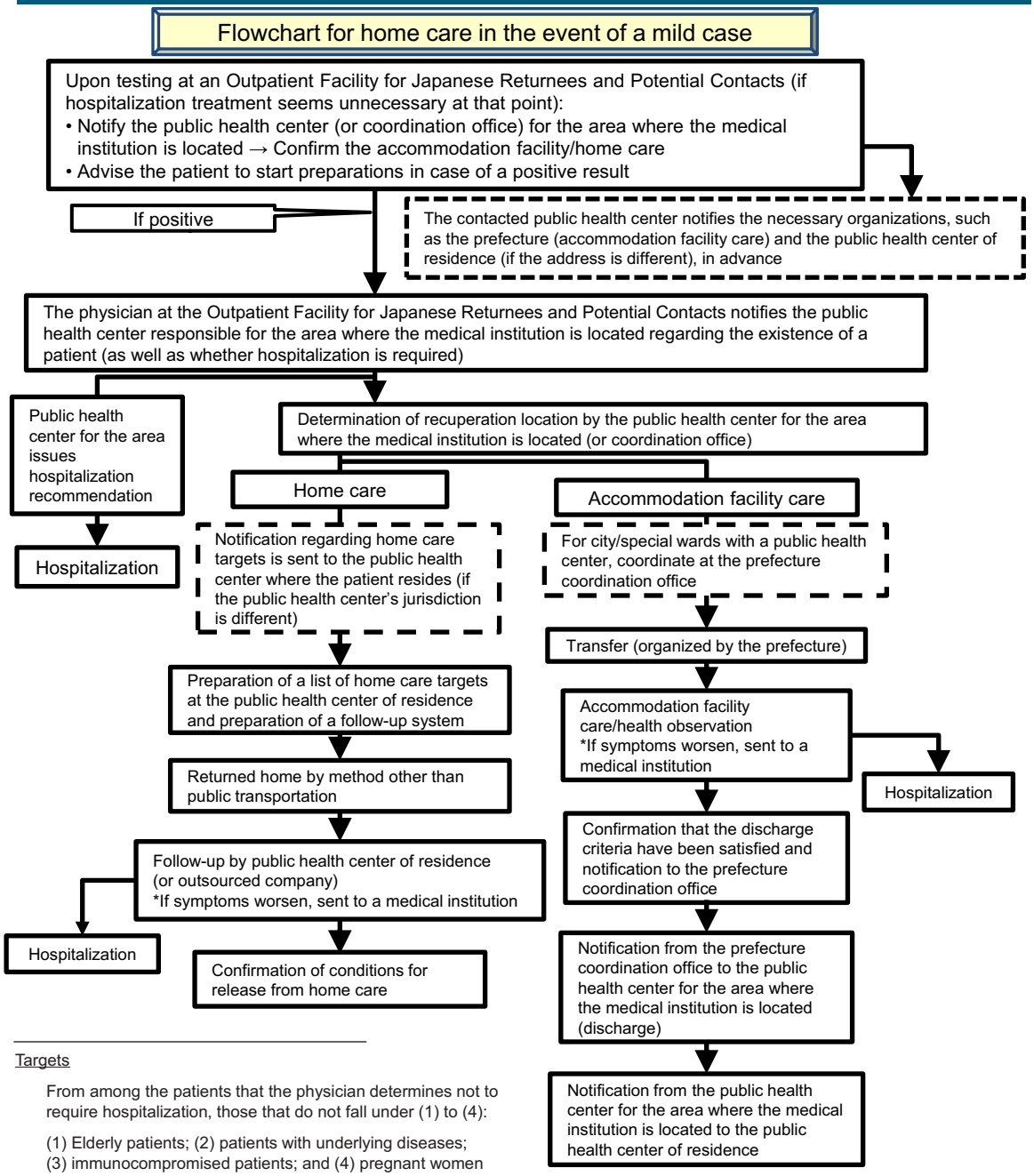
In addition to the conventional fax-based notification method, Japan's Ministry of Health, Labour and Welfare developed and introduced the Health Center Real-time information-sharing System on COVID-19 (HER-SYS) to reduce the burden imposed by public health center tasks and increase the speed of information sharing. Using HER-SYS allows public health centers, local government (divisions other than public health centers), medical institutions and contracted workers engaged in related tasks to share information among themselves instantaneously.

The same applies to a notification issued when a person who has died due to COVID-19 (included suspected cases) is examined.

Reference

Health Center Real-time information-sharing System on COVID-19 (HER-SYS):
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00129.html

Figure 2-1: Home Care for Mild Cases



Appended Form 6-1

COVID-19 Occurrence Notification

FAO: Governor (Mayor/Special Ward Head of Public Health Center)

In accordance with Article 12, paragraph 1 of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (including the conditions stipulated under Article 12, paragraph 6), I hereby declare the following.

Report Date: MM/DD/YYYY

Physician's name Seal

(Sign or write name/affix seal)

Name of affiliated hospital/clinic

Location of above hospital/clinic (*)

Telephone No. (*) ( ) –

(* If physician is not affiliated to a hospital/clinic, write address and telephone number)

1 Type of diagnosed (examined) patient (dead body)				
• Patient (confirmed case) • Asymptomatic pathogen carrier • Suspected patient • Dead body of infected patient • Dead body of suspected infected patient				
2 Patient's name	3 Gender	4 Date of birth	5 Age at diagnosis (in months for 0-year-olds)	6 Occupation of patient
	M / F	MM/DD/YYYY	years (months)	
7 Patient's address Phone: ( ) –				
8 Patient's location Phone: ( ) –				
9 Guardian's name	10 Guardian's address (complete 9 and 10 only if patient is a minor) Phone: ( ) –			

11 Symptoms

- Fever • Coughing
- Acute respiratory symptoms other than coughing
- Pneumonia image • Serious pneumonia
- Acute respiratory distress syndrome
- Multiple organ failure • Systemic feeling of fatigue
- Headache • Nausea/vomiting
- Diarrhea • Conjunctivitis • Smell/taste disorder
- Other ( )
- None

12 Diagnostic method

- Detection of pathogen by isolation/detection
  Sample: Sputum, respiratory tract aspiration fluid, alveolar lavage fluid, pharyngeal swab, nasal aspiration fluid, nasal swab, nasopharyngeal swab, stool, saliva, autopsy material, others ( )
  Sampling date (MM/DD)
  Result (Positive / Negative)

- Detection of pathogen gene from sample using a nucleic acid amplification method (PCR method, LAMP method, etc.)
  Sample: Sputum, respiratory tract aspiration fluid, alveolar lavage fluid, pharyngeal swab, nasal aspiration fluid, nasal swab, nasopharyngeal swab, stool, saliva, autopsy material, other ( )
  Sampling date (MM/DD)
  Result (Positive / Negative)

- Detection of pathogen antigen (immunochromatography method, etc.)
  Sample: Nasopharyngeal swab
  Sampling date (MM/DD)
  Result (Positive / Negative)

18 Infection cause/route/region

(1) Infection cause/route (definitive / estimate)

1 Droplet/droplet nuclei infection (infection source type/situation:)

2 Contact infection (type/situation of contact person/object:)

3 Other ( )

(2) Infection region (definitive / estimate)

1 Japan (prefecture: ; city/ward/town/village:)
2 Overseas (country: ; specific region:)
* If multiple countries or regions apply, enter all.
Travel period
(Date of departure from Japan: MM/DD/YYYY;
date of arrival in Japan: MM/DD/YYYY;
overseas residents need only give their date of arrival in Japan)

19 Other items that the physician deems necessary to prevent the spread of infection and care for the patient

13 Initial visit date	MM/DD/YYYY
14 Diagnosis (examination*) date	MM/DD/YYYY
15 Estimated date of infection	MM/DD/YYYY
16 Date of onset (**)	MM/DD/YYYY
17 Date of death (*)	MM/DD/YYYY

• Hospitalized at time of notification? (Yes / No)
Hospitalized cases only
(hospitalization date: MM/DD/YYYY)

Please process this notification immediately after diagnosis.

(Circle the relevant number in sections 1, 3, 11, 12, and 18 and enter the age/date for sections 4, 5, and 13 to 17.

(*) This section is applicable only if a death case has been examined. (**) This section is applicable only if the patient has been diagnosed (confirmed case). Enter all applicable information in sections 11 and 12.)

3 Severity Classification and Management

The following is a summary of the severity classifications and supportive therapy depending on the severity classification. In addition, points to note when performing mechanical ventilation by tracheal intubation are also summarized. If severe cases cannot be treated in an infectious disease ward, consult with the prefecture or responsible public health center regarding the use of other wards, such as an intensive care unit (ICU), or transfer the patient to a different medical facility.

1 Severity Classification (Evaluation Criteria Used by Healthcare Workers)

Severity	Oxygen saturation	Clinical state	Examination points
Mild	$SpO_2 \geq 96\%$	No respiratory symptoms Coughing only; no shortness of breath	• Condition will resolve naturally in most cases, but may also suddenly worsen • Patients with risk factors should be hospitalized
Moderate I Patient does not suffer respiratory failure	$93\% < SpO_2 < 96\%$	Shortness of breath and pneumonia findings	• Careful observation under hospitalization • Patient sometimes does not complain of respiratory distress even with hypoxemia • Also important to deal with patient anxiety
Moderate II Patient suffers respiratory failure	$SpO_2 \leq 93\%$	Oxygen administration required	• Estimate the cause of respiratory failure • Consider transferring patient to a hospital that offers advanced medical treatment • Avoid using nasal high-flow and CPAP where possible and suppress aerosol generation
Severe		Admission to ICU or mechanical ventilator required	• Two classifications of severe pneumonia based on mechanical ventilator management (L-type and H-type) • L-type: Lungs are soft and ventilation amount increases • H-type: Introduction of ECMO should be considered because of the positive pulmonary edema • Difficult to determine the progress from L-type to H-type

Note

- Classification of severity is made based on respiratory symptoms (particularly shortness of breath) and oxygenation because respiratory failure is common in fatal cases due to COVID-19.
- Ideally, SpO_2 should be measured to objectively determine the state of oxygenation.
- Respiratory failure is defined as the condition where $PaO_2 \leq 60$ mm Hg and is equivalent to $SpO_2 \leq 90\%$, but it is set to $SpO_2 \leq 93\%$ because a 3% margin of error is expected for SpO_2.
- To determine whether the patient has pneumonia, a chest CT should be taken if possible with measures implemented to prevent nosocomial infection.
- Even for mild cases, care must be taken to monitor any aggravation signs of the symptoms and the appearance of new symptoms.

2 Mild Cases

○ Most mild cases will resolve spontaneously without medical treatment; monitoring of the patient's condition is required.
○ Symptomatic treatments, such as antipyretics and cough remedies, should be given only when necessary. If the patient can eat and drink, infusion is not always necessary.
○ Even if the case is determined to be mild through the examination, the disease may worsen quickly within 2 weeks from onset. In most cases, disease progression manifests as the progression of hypoxemia.
○ Patients with risk factors such as the following should be hospitalized based on the assumption that the disease may progress: old age, underlying diseases (diabetes, heart failure, chronic respiratory disease, hypertension, and cancer), immunosuppressive state, and pregnancy.
○ In the case of home care and recuperation at accommodation facilities, explain to the patient the disease conditions that would require them to visit a medical facility.
○ Because mild patients are infectious prior to onset, they should avoid contact with others. If the patient lives with other family members, instruct them to use separate living areas and recommend that they wear masks and wash their hands properly.

Table 3-1: Vital Signs Suggesting Progression to Moderate Severity or Higher

Respiratory rate	Under 1 year: Over 50/min 1–4 years: 40/min or more 5 years onward: 30/min or more
Pulse	Under 1 year: Over 180/min 1–4 years: 160/min or more 5–11 years: 140/min or more 12 years onward: 130/min or more
SpO_2	< 96%

References

• Clinical care for severe acute respiratory infection: toolkit. COVID-19 adaptation. Geneva: World Health Organization; 2020 (WHO/2019-nCoV/SARI_toolkit/2020.1).
• Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts: interim guidance. World Health Organization; 17 March 2020.
• COVID-19 Treatment Guidelines Panel. Coronavirus Diseases 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/ (accessed 11 May 2020).

3 Moderate Case

○ Moderate cases should be hospitalized for treatment. The objective is to provide symptomatic treatment, prevent aggravation, and facilitate early intervention. When patients are treated in isolation units under hospitalization, it is also important to relieve their anxieties.

Moderate I: Patients without respiratory failure

○ Bed rest and sufficient nutritional intake are necessary. In addition, the patient should drink sufficient water to avoid dehydration.

○ Measure vital signs and oxygen saturation (SpO_2) about three times a day. The patient may not complain of shortness of breath even if the disease advances to the point where hypoxemia is observed.

○ Moderate cases develop pneumonia, but if the patient has the following risk factors,* specific caution is required because it is more likely to become severe.

* Old age, underlying diseases (diabetes, heart failure, chronic respiratory disease, hypertension, and cancer), immunosuppressive state, and pregnancy

○ Persons who smoke should be advised to quit smoking.

○ Conduct the following as necessary: general blood test and urinalysis; biochemical test; serum test; coagulation-related test; and blood culture. Factors that are known to be related to poor prognosis are lymphopenia count and an increase in CRP, ferritin, D-dimer and LDH.

○ If bacterial infection is suspected based on blood test results and radiological imaging findings, conduct a sputum test and empirically start administering anti-microbial agents.

○ Provide symptomatic treatment of any fever, respiratory symptoms, and underlying diseases.

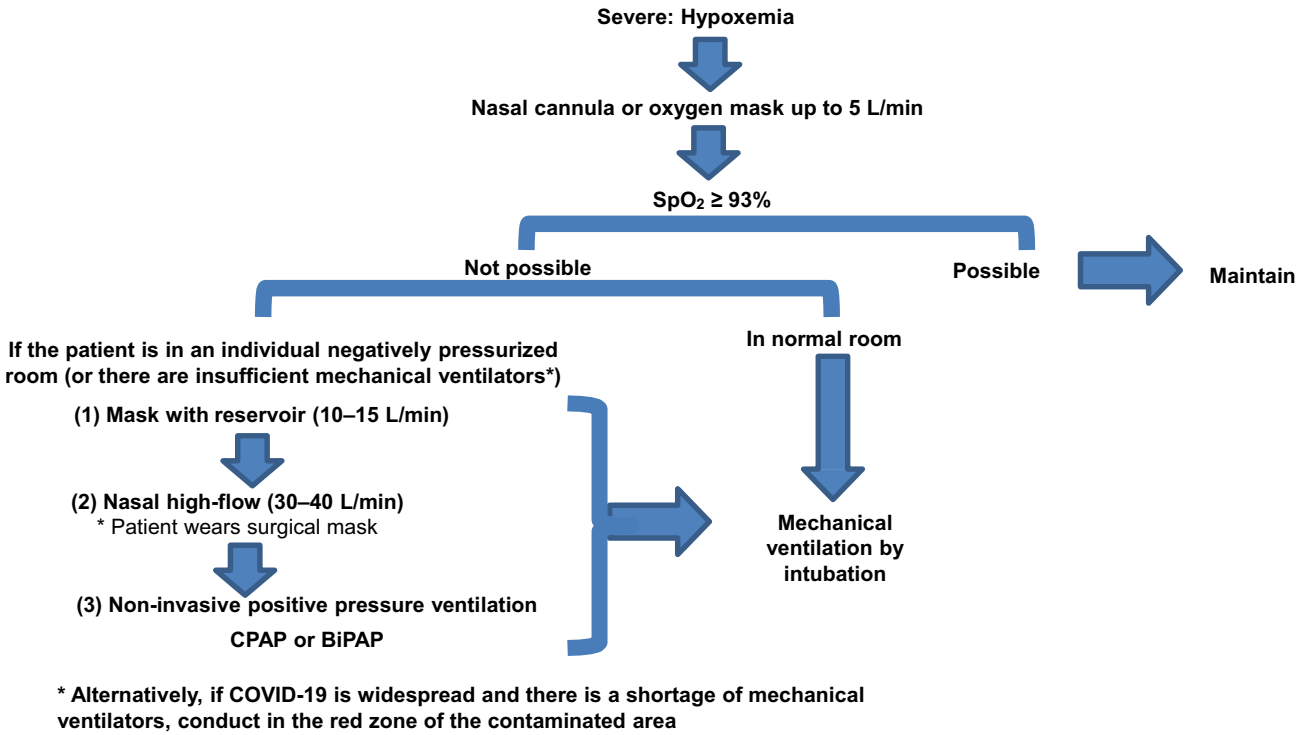
○ Consider the use of anti-viral drugs (refer to pp. 25 and 26).

Moderate II: Patients with respiratory failure

- Due to respiratory failure, oxygen should be administered. To estimate the cause of the respiratory failure, conduct an arterial blood gas test (PaO_2 and $PaCO_2$) prior to oxygen administration. In addition, consider transferring the patient to a facility that offers more advanced medical care, such as mechanical ventilators and ECMO.
- The patient may experience a quick worsening of their condition, such as a rapid progression of an infiltrative shadow in their lungs in a pulmonary CT. In this case, steroids and tocilizumab (off-label) can be used (refer to p. 26).
- Ordinarily, $SpO_2 \geq 93\%$ should be maintained by a nasal cannula up to O_2 5 L/min or an oxygen mask up to O_2 10 L/min.

  * Note: When a nasal cannula is used, the patient should wear a surgical mask to suppress aerosol generation.
- Consider intubation if $SpO_2 \geq 93\%$ cannot be maintained even with O_2 administration by means of an oxygen mask. In addition, intubation or mechanical ventilation management should ideally be performed earlier than usual.

  * Note: Although not recommended due to the risk of environmental pollution, masks with a reservoir (10–15 L/min), nasal high-flow, and non-invasive positive pressure ventilation are normally considered at this stage. There is a risk of nosocomial infection due to aerosol generation so the use of individual negatively pressurized rooms is desirable. Confirm that the flow is between 30 and 40 L/min when using high-flow and that the cannula is within the nasal cavity. In addition, the patient should wear a surgical mask to suppress aerosol generation.



- Be careful of complications in the form of bacterial pneumonia, ARDS, septicemia, myocardial disorder, arrhythmia, acute renal injury, thromboembolism, gastritis or gastroduodenal ulcers, and ischemic enteritis.

4 Severe Case

1. Characteristics of Severe COVID-19 Pneumonia

- ○ COVID-19 pneumonia is classified as L-type (relatively mild) or H-type (severe).
- ○ Although both types require relatively high PEEP, the management strategies (e.g. respiratory therapy, the use of sedatives) are different.
- ○ Some cases of L-type change to H-type, but clinical detection of this transition is difficult.
- ○ For appropriate treatment, expertise and a close monitoring system in intensive care are essential.

	L-type	H-type
Pathophysiology	• Amount of gas in lungs and compliance are normal (low elastance) • Hypoxemia may be best explained by loss of regulation of perfusion (low V/Q ratio) • No pulmonary edema (low lung weight) • No recruitable atelectasis (low lung recruitability)	• Decrease in amount of gas in lungs and compliance (high elastance) • Hypoxemia due to fraction of cardiac output perfusing non-aerated tissue (high right-to-left shunt) • Increase in lung weight on order of magnitude of severe ARDS (high lung weight) • Increased amount of non-aerated tissue is recruitable (high lung recruitability)
Treatment	• Reducing tidal volume is not essential • Prone positioning is effective • Consider use of sedatives and/or neuromuscular blockade to reduce tidal volume to prevent lung injury induced by large tidal volume	• Reducing tidal volume is essential • Prone positioning is effective • Refer to ECMOnet specialist because hypoxemia is generally refractory

(Gattinoni L, et al. COVID-19 pneumonia: different respiratory treatment for different phenotypes? Intensive Care Med 2020)

2. Tracheal Intubation Procedure

Experts in airway management should be included in the treatment team since the patient's respiratory status may suddenly worsen. Furthermore, it should be noted that intubation is a procedure that generates aerosol, so airborne infection prevention (N95 mask use) are necessary in addition to the use of face shields or goggles. To reduce the risk of aerosol generation, rapid sequence induction (RSI) without bag-mask ventilation is selected where sedatives, analgesics, and muscle relaxants are also simultaneously administered after pre-oxygenation. The use of a video laryngoscope should be considered because performing the intubation procedure via a monitor screen enables the operator to maintain a safe distance from the patient compared to direct viewing into the oral cavity.

3. Mechanical Ventilation Strategy for Severe COVID-19 Patients

1) Basic strategy
   - Use the lung protective strategy for ARDS.
   - As long as the local medical service works properly, use respiratory therapies that minimize the risk of nosocomial infections.

2) Lung protective strategy
   - Limit the plateau pressure.
   - Limit the driving pressure: The difference between the plateau pressure and PEEP should be < 14 cmH_2O.
   - Permit hypercapnia as long as pH > 7.25.
   - Set the tidal volume according to the type.
   - Set PEEP according to the type.
   - Consider the use of a neuromuscular blocking agent for excessive spontaneous breathing efforts.

3) Selection of respiratory care therapy based on the environment
   - The first line therapy is low flow oxygen therapy.
   - High flow oxygen therapy and non-invasive positive pressure ventilation are not used.
   - If esophageal pressure can be measured, tracheal intubation is recommended as soon as possible if the pressure swing is > 15 cmH_2O.
   - Use bacteria filters on the gas inlet and outlet of the ventilator.
   - Use HME/HMEF (HME + antimicrobial filter) to heat and moisturize the respiratory circuit.
   - Use a closed system for tracheal suction.
   - Avoid procedures with a high risk of aerosol generation.

4) Mechanical ventilation for L-type
   - Lung injury (VILI) occurs if the lungs are ventilated as ARDS.
   - Keep PEEP to a minimum and increase FIO_2 to deal with hypoxemia.
   - Increase tidal volume to correct hypercapnia.
   - Recruitment is not required.
   - Deep sedation is recommended after intubation.
   - Set PEEP to between 8 and 10 cmH_2O.
   - Prone positioning is recommended if refractory hypoxemia is sustained in spite of the above strategy.

5) Mechanical ventilation for H-type
   - Treat as severe ARDS.
   - Use a higher PEEP (10 to 14 cmH_2O).
   - Prone positioning is effective.
   - Consider switching to ECMO if refractory to mechanical ventilation.

6) Transition from L-type to H-type
   - A sudden transition from L-type to H-type may occur.
   - If the esophageal pressure can be measured, it is possible to detect a transition from L-type to H-type.
   - A biomarker that can predict the transition is not available.

<u>References</u>

- The Japanese Society of Intensive Care Medicine HP
  https://www.jsicm.org/news/upload/COVID&MVstrategy_ECMOnet_v2.pdf
- Video materials
  http://square.umin.ac.jp/jrcm/news/news20200415.html

* Consultation regarding mechanical ventilation therapy is available 24 hours a day at the ECMOnet Call Center for COVID-19.

4. Extracorporeal Membrane Oxygenation (ECMO)

Japan ECMOnet for COVID-19 stated in the basic considerations for ECMO management that the prognosis is extremely poor if ECMO is introduced after a long period (more than 7 days) of mechanical ventilation at a high pressure. It also stated that a careful and comprehensive decision is required for the indication of ECMO, a large number of personnel and a considerable work load are required when using ECMO treatment for COVID-19, and ECMO should be considered if there is a progressive deterioration of oxygenation with a PEEP of 10 cmH_2O and P/F < 100.

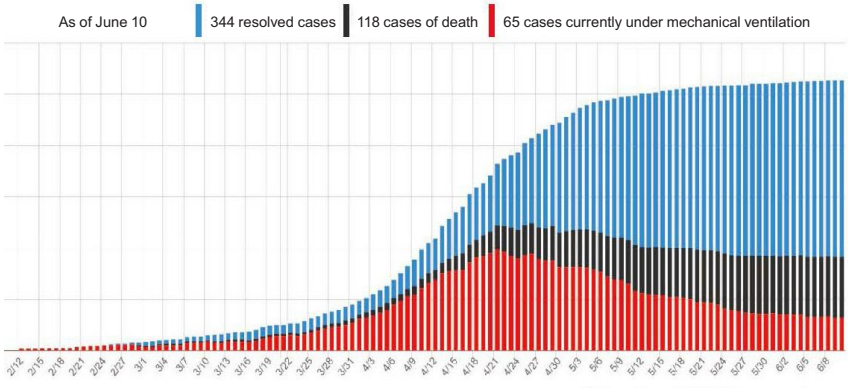
ECMO must be withdrawn if a high degree of pulmonary fibrosis develops, and informed consent for withdrawal must be provided prior to its introduction. In addition, ECMO is contraindicated or off-label for patients who have irreversible underlying diseases or are in the terminal stage of cancer. The prognosis for a patient whose condition is complicated with chronic heart failure, chronic respiratory failure, or other types of chronic organ failure in the course of treatment is worse. Since patients aged from 65 to 70 or more have a poor prognosis, they are generally excluded from ECMO indication in the aforementioned basic notes.

Japan ECMOnet for COVID-19 accepts questions and consultations on the following topics via a 24/7 phone system (the dedicated phone number has been distributed to the registered email addresses of members of related academic societies) and its active use is recommended: selection of cannula; the artificial lung or pump to be used; circuit pressure monitoring; the ventilator setting during ECMO; ECMO withdrawal or DNAR; and other detailed topics related to the stable, long-term management of ECMO.

Jinyintan Hospital (Wuhan, China) reported severe COVID-19 cases (52 cases; mean age: 59.7 years; 67% male; 40% with underlying diseases) (February 21, 2020). The 28-day mortality rate was 61.5% (7 days from ICU admission to death, median). The complications were ARDS (67%), AKI (29%), liver dysfunction (29%), cardiac dysfunction (23%), and pneumothorax (2%). ECMO was implemented for 6 cases, of which 1 survived but was difficult to wean. In addition, renal replacement therapy was conducted for 9 cases, of which 1 was a 28-day survivor.

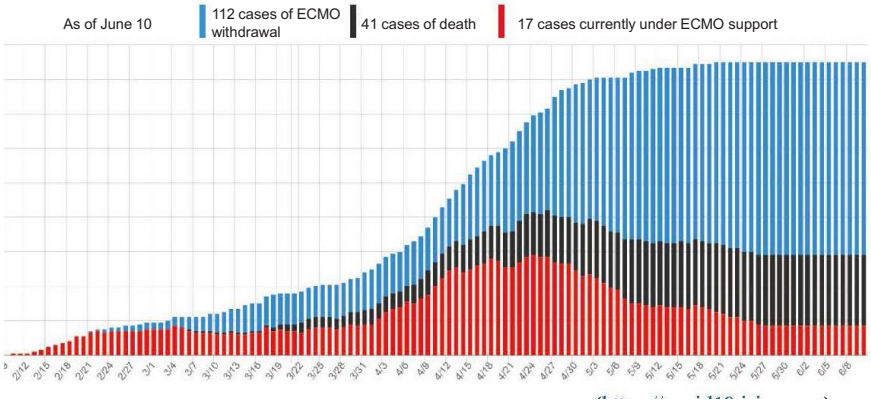
According to the report from Japan ECMOnet for COVID-19 that was tabulated on June 10, 2020, the number of patients who have received mechanical ventilation (excluding ECMO treatment) in Japan to date is 527, including 344 resolved cases, 118 fatal cases, and 65 cases currently undergoing mechanical ventilation (estimated to be about 80% of the actual nationwide number). The number of ECMO treatment patients to date is 170, including 112 improved cases, 41 fatal cases, and 17 cases currently receiving ECMO support (This figure covers cases in Japan). Furthermore, it was judged that about 1 in 5 patients requiring mechanical ventilation also require ECMO and that cases surviving ECMO require about 10 days to 2 weeks of ECMO support. ECMO is expected to be effective. ECMO should be indicated according to future increases in the number of patients and the status of medical resources in each hospital, so consultation with Japan ECMOnet for COVID-19 is highly recommended.

Accumulative results of mechanical ventilation (excluding ECMO) for COVID-19 in Japan (as of June 10, 2020)



(https://covid19.jsicm.org)

Accumulative results of ECMO treatment for COVID-19 in Japan (as of June 10, 2020)



(https://covid19.jsicm.org)

5. Blood Purification Therapy

In the initial stages prior to the progression of multiple organ failure, it is thought that there are cases where consideration must be given to the introduction of acute blood purification therapy (including CRRT and PMX-DHP using a hemofilter that has adsorption or elimination properties against various mediators, such as inflammatory cytokines).

The Joint Board for Measures against COVID-19 of the Japanese Association of Dialysis Physicians and the Japanese Society for Dialysis Therapy has reported that 108 dialysis patients in Japan (3 cases of ECMO use, 13 cases of mechanical ventilator use, and 40 cases of oxygen administration) have become infected and that there have been 19 deaths as of June 12, 2020. The implementation of blood purification therapy while taking into consideration infection prevention measures is necessary.

6. Measures against Thrombosis

- Severe infection and respiratory failure are moderate risk factors for deep vein thrombosis.
- In addition, both fibrinolysis promotion and suppression are considered to occur in COVID-19 patients due to cytokine storm and vascular endothelial damage.
- Autopsy reports have proven microthrombi formation and alveolar capillary blockade.
- If D-dimer exceeds the upper limit of normal, we recommend that an anticoagulation treatment such as heparin be used at the start.

References

- Ito M, et al. Guidelines for diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (2017 revised edition)
- Tachil J, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020.
- Sato R, et al. A new challenge of unfractionated heparin anticoagulation treatment for moderate to severe COVID-19 in Japan. Glob Health Med 2020.
- Ackermann M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020.

4 Drug Therapy

Currently, antiviral drugs for treating SARS-CoV-2 and various therapeutic agents for treating its symptoms are being developed, and clinical studies and research have been initiated for the following drug agents. In treating COVID-19 with these drugs, we recommend that you refer to guidelines such as the “Concept of Drug Treatment for COVID-19,” edited by the Japanese Association for Infectious Diseases.

Drug approved in Japan:

• Remdesivir (RNA polymerase inhibitor): Approved on May 7, 2020 under an exception to the approval pathway.

Dosage and administration

The usual dose for adult patients and pediatric patients (body weight: ≥ 40 kg) is a single loading dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg administered via intravenous infusion.

The usual dose for pediatric patients (body weight: ≥ 3.5 kg but < 40 kg) is a single loading dose of remdesivir 5 mg/kg on Day 1 followed by once-daily maintenance doses of remdesivir 2.5 mg/kg administered via intravenous infusion. The duration of administration should be up to a total of 10 days.

Note: The suggested dosage and regimen may be updated as data from clinical trials becomes available.

Precautions for administration

1. In principle, the current criteria are patients with oxygen saturation of ≤ 94% (indoor air) or requiring supplemental oxygen. Alternatively, remdesivir should be administered for severe cases requiring the introduction of ECMO or mechanical ventilation.
2. Hepatic function disorder, diarrhea, skin eruption and renal impairment have been reported with a high incidence, and reported serious adverse reactions include multiple organ failure, septic shock, acute renal injury, and hypotension.
3. Acute renal injury and hepatic function disorder may occur. Consequently, renal and hepatic function tests should be performed before treatment and every day during the treatment period and the patient should be monitored closely.
4. Remdesivir solution should be diluted with physiological saline and administered as an intravenous infusion over 30 to 120 minutes.

Procurement

1. For the time being, supply is restricted and remdesivir will be distributed to medical institutions from the Ministry of Health, Labour and Welfare
   Reference 1: MHLW Administrative Notice dated May 7, 2020, entitled “Notice on Partial Changes to Survey Items on the Status of Medical Provision by Hospitals Related to Novel Coronavirus Disease Control (No. 3)”
   Reference 2: “Establishment of the Required Amount of Remdesivir for Severe Cases in Novel Coronavirus Disease Control (Request)”
   Reference 3: “Survey Items on the Status of Medical Provision by Hospitals Related to Novel Coronavirus Disease Control (Cooperation Request)”
2. The medical institution must fax an application form to the Ministry of Health, Labour and Welfare
   Reference 4: “Distribution of Remdesivir for COVID-19 to Medical Institutions (Request)”

Off-label use of drugs available in Japan:

Various studies are currently underway in many countries to develop drugs for the treatment of COVID-19. Some of these drugs are described below. However, the efficacy and safety of these drugs have not yet been established. Therefore, in principle, appropriate procedures in the form of a study should be taken before any of the drugs are used.

Drugs for which clinical trials and specified clinical trials have been conducted in Japan

- Favipiravir (RNA polymerase inhibitor; indication: influenza)
  A sponsor-initiated clinical trial and specified clinical studies have been conducted, and an observational study is also currently underway. For details on participation in the observational study, see "Synopsis of the Observational Study of Avigan (Generic Name: Favipiravir) in Patients with COVID-19 and Provision of Drugs to Be Used in the Study" (MHLW Administrative Notice dated May 15, 2020; attachment) (https://www.mhlw.go.jp/content/000627594.pdf) (Sponsor-initiated clinical trial: JapicCTI-205238; specified clinical trial: jRCTs041190120 and jRCTs031190226)
- Ciclesonide (inhaled corticosteroid; indication: bronchial asthma)
  A specified clinical trial and an observational study are underway in Japan (jRCTs031190269).
- Nafamostat (protease inhibitor; indication: acute pancreatitis)
  A specified clinical trial is currently underway in Japan (jRCTs031200026).
- Tocilizumab (genetical recombinant) (humanized anti-IL-6 receptor monoclonal antibody; indication: rheumatoid arthritis)
  A clinical trial is currently underway in Japan (JapicCTI-No: 205270).
- Sarilumab (genetical recombinant) (humanized anti-IL-6 receptor monoclonal antibody; indication: rheumatoid arthritis)
  A clinical trial is currently underway in Japan (JapicCTI-No: 205253).

Other drugs

- Lopinavir-ritonavir combination (protease inhibitor; indication: HIV)
  Data from a Chinese clinical trial showed that this drug did not lower the fatality rate in severe cases.
- Hydroxychloroquine (immunomodulator; indication: SLE)
  Since *in vitro* data demonstrated that chloroquine exhibited antiviral activity against SARS-CoV-2, hydroxychloroquine, which is structurally similar to chloroquine, may also be expected to have a similar effect. However, healthcare professionals have been alerted to the serious arrhythmia that may occur in patients treated with hydroxychloroquine.
- Ivermectin (anthelmintic; indication: scabies)
- Steroid hormone (corticosteroid preparation)
  The efficacy of systemic steroid therapy is unknown. While some researchers reported a reduced fatality rate in COVID-19 patients with ARDS who were treated with steroids, other researchers reported that steroid therapy prolonged the time to virus shedding. Furthermore, it was also reported that steroid therapy resulted in a high fatality rate in patients with MERS or influenza.
- Azithromycin (macrolide antibiotic preparation)
- Camostat (protease inhibitor; indication: chronic pancreatitis)
- Nelfinavir (protease inhibitor; indication: HIV)

Plasma therapy is also being studied.

5 Infection Prevention and Control

Numerous cases of nosocomial infections of COVID-19 have been reported in countries all over the world, including Japan. Such cases involve not only patient-to-healthcare worker transmission, but also healthcare worker-to-patient transmission. Therefore, it is critical that preventive measures against nosocomial infections be strictly implemented.

SARS-CoV-2, the causative agent for COVID-19, is transmitted mainly in the following ways: when a person touches the mucosal membrane of the eye, nose, or mouth with a hand that has touched an infected person's body fluids, such as sputum or nasal discharge, or the surface of an object contaminated with such body fluids; or when droplets from an infected person's sneeze and sputum land on the mucosal membrane of the eye, nose, or mouth of another person or are inhaled into another person's respiratory tract. Therefore, the provision of medical care for COVID-19 patients should require, in addition to standard precaution, contact and droplet precaution.

Since SARS-CoV-2 is an RNA virus with an envelope structure, heat, drying, ethanol, and sodium hypochlorite are expected to be effective for disinfection.

Table 5-1: Infection Control Measures

	Infection control measures	Duration of infection control
Early phase	Standard precaution (including the wearing of surgical masks if respiratory symptoms are present)	
Suspected cases	Standard precaution Contact and droplet precaution	Until the results of a pathogen diagnosis confirm that the patient tests negative for COVID-19
Confirmed cases	Standard precaution Contact and droplet precaution Airborne precaution (Aerosol generating procedures)	10 days have passed since the date of onset and 72 hours have passed since the resolution of symptoms Alternatively, until tested negative for PCR test twice (with at least 24 hours between tests)

Note: Standard precaution must be taken irrespective of the patients' symptoms or test results.

1 Personal Protective Equipment (PPE)

Healthcare workers involved in care for COVID-19 patients (including the collection of samples from suspected cases) should wear PPE properly, including goggles (or face shields), face masks, gloves, long-sleeved gowns, and caps. Although surgical masks are generally used, the use of N95 masks is recommended for healthcare workers who are involved in aerosol generating procedure, such as tracheal suctioning and intubation.

The movement of patients for the performance of necessary activities, such as undergoing tests, should be kept to a minimum. They should be required to wear surgical masks whenever they leave their rooms.

Explanation

Aerosol generating procedures incude tracheal suctioning, intubation or removal, NPPV attachment, tracheotomy, cardiopulmonary resuscitation, manual ventilation, bronchoscopy, nebulizer therapy, induced sputum collection, etc.

2 Ventilation

The use of a negatively pressurized room as a consultation room or ward for COVID-19 patients (including suspected cases) is recommended but not required as long as sufficient ventilation is ensured. The ventilation conditions (e.g., ventilation frequency) of the medical institution should be examined in advance. If possible, rooms for radiography or computed tomography (CT) should be used at the end of the healthcare activities for the day.

The potential risk of secondary infections can be reduced by encouraging patients to wear face masks, performing environmental disinfection after tests, and carrying out air ventilation for about 30 minutes.

3 Environmental Cleaning

The ambient environment of the patient, including the nurse call button, table, bed rails, and bedside cabinet should be disinfected by wiping with alcohol or disinfectant.

Explanation: Medical instruments such as stethoscopes, thermometers, and manometers should be used exclusively for each individual patient and disinfected after each use. In test rooms used for patients (e.g., radiography rooms or CT scan rooms), any areas that may be touched by the patients, the testing instruments used to examine samples collected from patients, and the surrounding areas should be cleaned using disinfectant.

Staff involved in the cleaning of patient rooms should wear gloves, face masks, gowns, and goggles (or face shields).

Explanation

The National Institute of Technology and Evaluation (NITE) reported that the five types of surfactants listed below were effective in treating SARS-CoV-2. This was reported as a non-alcohol disinfection method for use in the home and workplace, but it may be considered for use in making daily environmental improvements at a medical institution in the event of a shortage of alcohol and other disinfectants.

(1) Linear sodium alkylbenzene sulfonate (over 0.1%)
(2) Alkyl glucoside (over 0.1%)
(3) Alkylamine oxide (over 0.05%)
(4) Benzalkonium chloride (over 0.05%)
(5) Polyoxyethylene alkyl ether (over 0.2%)

Reference

• Japanese Society for Infection Prevention and Control. Guide for Handling COVID-19 in Medical Institutions, Third Edition

http://www.kankyokansen.org/uploads/uploads/files/jsipc/COVID-19_taioguide3.pdf

• National Institute for Infectious Diseases. National Center for Global Health and Medicine. COVID-19 Management

(Revised on June 2, 2020). https://www.mhlw.go.jp/content/000635967.pdf

4 Waste Management

Waste from the room for COVID-19 patients (including suspected cases) should be discarded as infectious waste. When such waste is discarded, the surfaces of the waste containers should be disinfected with alcohol or a cloth impregnated with antiviral disinfectant. Medical institutions are recommended to ask the relevant contractors in advance about the conditions for waste disposal.

5 Linens

Linen that is or may be contaminated with SARS-CoV-2 should be disinfected (including by washing in hot water) within the hospital facilities.

Note: The “Handling of Linen That May Be Contaminated with SARS-CoV-2 in Medical Institutions” (MHLW Administrative Notice dated April 24, 2020) states that the washing of bedding may be outsourced to avoid imposing an excessive burden on the medical institution.

6 Dishware

Dishes used by one patient need not necessarily be distinguished from dishes used by another patient. After use, dishes should be washed using a neutral detergent, disinfected in hot water at a temperature of 80°C for at least 5 minutes, and then dried.

7 Postmortem Care

It is recommended that the body of an individual who has died of COVID-19 be treated so that no body fluids leak from the body and that the body be fully sealed in an impermeable and hermetic body bag. The surface of the body bag should be disinfected with alcohol or a cloth impregnated with disinfectant. Ideally, the body should be placed in a coffin in the medical institution and then transported out of the institution. Once the body has been placed in a coffin, no infection control measures are needed. Each deceased patient should be treated with dignity and respect.

8 Occupational Health for Healthcare Workers

It is important to manage the health of healthcare workers involved in care for COVID-19 patients. A system should be established to ensure that healthcare workers are monitored for 14 days (by measuring their body temperatures twice daily and examining them to check for symptoms such as coughing and pharyngeal pain) after they have completed their patient care activities and that they are instructed to promptly report any abnormality to the personnel in charge of infection control.

Healthcare workers wearing appropriate PPE are not regarded as having been in close contact with infected persons, so they do not need to refrain from further care activities.

9 Exceptions in the Handling of N95 Masks in Emergencies

Given that PPE is currently hard to obtain, the Ministry of Health, Labour and Welfare (MHLW) published “Exceptions in the Handling of N95 Masks” (MHLW Administrative Notice dated April 10, 2020), the content of which is summarized below.

N95 masks should be used as efficiently as possible, taking into account the following instructions.

- Endeavor to reuse N95 masks by proactively utilizing sterilizers. [Explanation 1]
- Use N95 masks when necessary, irrespective of their shelf lives.
- Use the same N95 mask consecutively when examining multiple patients. [Explanation 2]
- Write your name on the N95 mask and change it once daily.
- Handle KN95 masks and other such medical masks as equivalent to N95 masks and endeavor to use such masks. [Explanation 3]

Explanation 1: This administrative notice presents a method of reusing N95 masks by using a hydrogen peroxide plasma sterilizer or a hydrogen peroxide sterilizer as well as a method of rotating the use of five N95 masks allocated to each person during a 5-day cycle. However, N95 masks containing cellulose or cellulose-based materials cannot be reprocessed because they are not compatible with sterilizers. As alternatives to the use of sterilization as a method of disinfection, the Research Group of Occupational Infection Control and Prevention in Japan and the Centers for Disease Control and Prevention (CDC) in the USA have demonstrated specific methods of reusing N95 masks by employing methods such as heat and humidity (autoclaving), ultraviolet (UV-C) lighting, and vaporized hydrogen peroxide (VHP). Each method has its advantages and disadvantages and, needless to say, N95 masks are primarily produced as single-use products. With the above in mind, each medical institution must select the optimal method in consideration of its available disinfection methods and the potential effects of such methods on the materials and functionality of the N95 masks that it uses.

Explanation 2: The administrative notice stipulates the following two precautions concerning the prolonged use of N95 masks.

(1) Masks that are visibly dirty or damaged should be discarded.

(2) Healthcare workers should distance themselves from patient care areas if they need to remove N95 masks.

Explanation 3: The U.S. Food and Drug Administration (FDA) issued an emergency use authorization for KN95 and other such medical masks.

References

- The Research Group of Occupational Infection Control and Prevention in Japan. Webpage for information on the disinfection and reuse of N95 or DS2 masks. April 13, 2020. http://square.umin.ac.jp/~jrgoicp/index_ppewg_n95decon.html?fbclid=IwAR3O5rwgkzRyiHkEMfsk4Xe1p9L7tLPq2PkO1XeM7BIJmlQ25np0mzgNeiI
- Centers for Disease Control and Prevention. Decontamination and Reuse of Filtering Facepiece Respirators. 9 April 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/decontamination-reuse-respirators.html

10 Exceptions in the Handling of Surgical Masks, Long-sleeved Gowns, Goggles, and Face Shields in Emergencies

Given that PPE is currently hard to obtain, the MHLW published “Exceptions in the Handling of Surgical Masks, Long-sleeved Gowns, Goggles, and Face Shields” (MHLW Administrative Notice dated April 14, 2020), the content of which is summarized below.

Surgical masks, long-sleeved gowns, goggles, and face shields (hereinafter collectively referred to as “PPE”) should be used as efficiently as possible, taking into account the following instructions.

- Set priorities concerning occasions of use. [Explanation 1]
- Use the same PPE consecutively when examining multiple patients. [Explanation 2]
- Use substitutes for PPE. [Explanation 3]
- Discard PPE that is visibly dirty or damaged.

Explanation 1

(1) Surgical masks

Occasions such as those where necessary procedures or surgical interventions are performed or where close contact with suspected COVID-19 patients is inevitable

(2) Long-sleeved gowns

- Procedures that may require healthcare workers to be exposed to the patient’s body fluids, such as blood
- Procedures that may cause aerosol generation (e.g., tracheal suctioning, tracheal intubation, and sample collection from the lower respiratory tract)
- Sample collection from the upper respiratory tract (sleeveless aprons may be used if long-sleeved gowns are not available)
- Patient care activities, such as a position change or transfer to a wheelchair, during which healthcare workers’ forearms or upper arms may come into contact with the patient (sleeveless aprons may be used if long-sleeved gowns are not available)

* By cleaning and disinfecting their fingers and forearms appropriately, healthcare workers can prevent viral infection even if they wear sleeveless aprons.

Explanation 2

Goggles should be cleaned and disinfected whenever they become visibly dirty or they are removed.

Goggles should be discarded if the goggles themselves or their bands become damaged (e.g., if they cannot be positioned properly because they do not fit well or they begin to irreversibly obstruct the user’s vision).

Cleaning and Disinfection Methods:

To clean and disinfect the PPE, follow the methods recommended by the respective manufacturers. If such methods are unknown, clean and disinfect the PPE with reference to the following procedure.

(1) Wipe the inside and outside of the goggles or face shield carefully while wearing gloves.

(2) Wipe the outside of the goggles or face shield with a paper towel or a piece of gauze impregnated with alcohol or 0.05% sodium hypochlorite.

(3) Reuse the goggles or face shield when they are completely dry.

Explanation 3

(1) Long-sleeved gowns

Long-sleeved gowns may be replaced with disposable substitutes that can cover the body (e.g., raincoats). Ideally, water-repellent ones should be used.

(2) Goggles and face shields

Goggles and face shields may be replaced with substitutes that cover the eyes (e.g., snorkeling masks).

6 Hospital Discharge

Patient information should be shared with local public health centers. Before a patient is discharged, improvement of clinical symptoms should be confirmed. The MHLW administrative notice dated June 12, 2020 is summarized below.

This content will be updated as necessary when new findings and knowledge are obtained.

1 Criteria for Discharge

1. For patients with symptoms*1

(1) Discharge is possible 10 days after the date of onset*2 and 72 hours after the resolution of symptoms.*3

(2) Discharge is possible 24 hours after the resolution of symptoms if the patient has tested negative for the PCR test twice*4 with at least 24 hours between tests.

2. For asymptomatic pathogen carriers

(1) Discharge is possible 10 days after the day of sampling.*5

(2) Discharge is possible 6 days after the day of sampling if the patient has tested negative for the PCR test twice with at least 24 hours between tests.

NB: For 1 and 2 above, consider consulting the local infection specialist for patients who may have maintained infectivity for over 10 days (e.g., patients with severe immunodeficiency).

*1 If a patient does not present any aggravation risks and the physician judges that hospitalization is not necessarily required, the patient may recover through accommodation facility care, etc.

*2 The day on which symptoms started to appear. If the date of onset is not clear, it should be the day of sampling for positive diagnosis.

*3 When fever subsides without any antipyretics and respiratory symptoms improve.

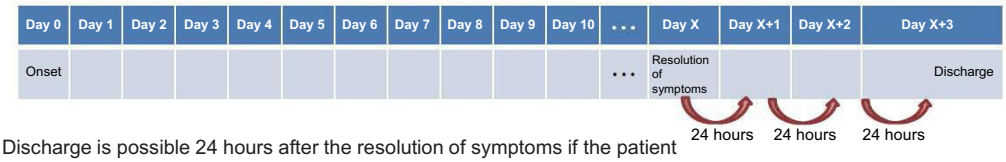
*4 Includes other nucleic acid amplification methods.

*5 Day of sampling for positive diagnosis.

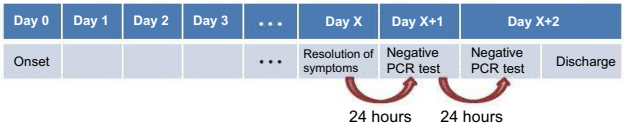
*6 Since some cases test positive after discharge, the patient should conduct self-health observations for 4 weeks after discharge or release. The patient should contact the Call Center for Japanese Returnees and Potential Contacts immediately if any symptoms present and follow their instructions to visit a medical institution.

Reference: Image Diagram for Calculation of Timing

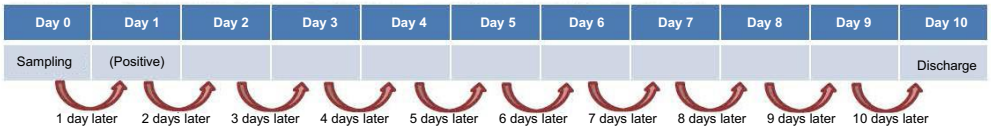
For patients with symptoms:
(1) Discharge is possible 10 days after the date of onset and 72 hours after the resolution of symptoms.



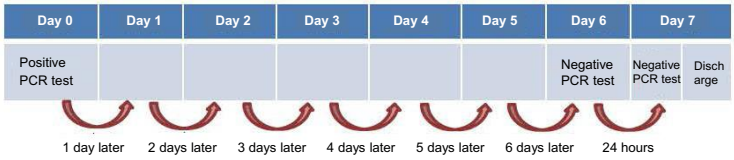
(2) Discharge is possible 24 hours after the resolution of symptoms if the patient has tested negative for the PCR test twice with at least 24 hours between tests.



For asymptomatic pathogen carriers:
(1) Discharge is possible 10 days after the day of sampling (day of sampling for positive diagnosis).



(2) Discharge is possible 6 days after the day of sampling if the patient has tested negative for the PCR test twice with at least 24 hours between tests.



2 Criteria for Release from Accommodation Facility Care

Same as the revised proposal for the above criteria for discharge.

3 Instruction to Discharged Patients

- Collaborate with the local public health center to support the smooth rehabilitation of patients. Evaluate patients, particularly in relation to the need for psychological support.
- The pathology of COVID-19, including exacerbation and late-phase complications, has not yet been fully clarified. Advise patients to visit their physicians if they experience any medical problems.
- Instruct patients to avoid the 3Cs (closed spaces with poor ventilation, crowded places, and close-contact settings; any of these 3 C's can be a risk factor for viral infection) to reduce potential risks.
- Instruct patients to follow coughing etiquette, such as wearing a mask, if they have a persistent cough.
- Provide relevant explanations to patients by referring to "For Patients to Be Discharged from Hospital after Confirmation of Negative Test Results" (MHLW Administrative Notice of the Task Force on Prevention and Control of COVID-19 dated March 6, 2020).

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