Guideline

Heat stroke management during the COVID-19 pandemic: Recommendations from the experts in Japan (2nd edition)

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Both coronavirus disease 2019 (COVID-19) and heat stroke have symptoms of fever or hyperthermia and the difficulty in distinguishing them could lead to a strain on emergency medical care. To mitigate the potential confusion that could arise from actions for preventing both COVID-19 spread and heat stroke, particularly in the context of record-breaking summer season temperatures, this work offers new knowledge and evidence that address concerns regarding indoor ventilation and indoor temperatures, mask wearing and heat stroke risk, and the isolation of older adults. Specifically, the current work is the second edition to the previously published guidance for handling heat stroke during the COVID-19 pandemic, prepared by the

Working group members (committee members and external committee members) are presented in Appendix 1.

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"Working group on heat stroke medical care during the COVID-19 epidemic," composed of members from four organizations in different medical and related fields. The group was established by the Japanese Association for Acute Medicine Heatstroke and Hypothermia Surveillance Committee. This second edition includes new knowledge, and conventional evidence gleaned from a primary selection of 60 articles from MEDLINE, one article from Cochrane, 13 articles from Ichushi, and a secondary/final selection of 56 articles. This work summarizes the contents that have been clarified in the prevention and treatment of infectious diseases and heat stroke to provide guidance for the prevention, diagnosis, and treatment of heat stroke during the COVID-19 pandemic.

Key words: COVID-19, diagnosis, heat stroke, prevention, treatment

INTRODUCTION

THE SPREAD OF the novel coronavirus disease 2019 (COVID-19) has greatly changed people's lives. To avoid the three Cs of crowded spaces, close contact, and closed spaces, governments have enforced physical distancing, adequate indoor ventilation, and mask wearing in people's daily lives, and these actions have become widespread among citizens. However, in carrying out these actions, precautions are needed in terms of heat stroke prevention and treatment. For example, when preventing both COVID-19 spread and heat stroke, concerns regarding indoor ventilation and rising indoor temperatures, mask wearing and heat stroke risk, and the isolation of older adults who live alone as they refrain from going out may cause confusion. Furthermore, COVID-19 and heat stroke both have symptoms of fever or hyperthermia—immediately distinguishing them is not easy, which could lead to a strain on emergency medical care. In 2020, when the COVID-19 pandemic began in Japan, the country was not at the peak of summer. At the time, academic organizations acknowledged the need to take responsibility for gathering accurate knowledge.

Therefore, in 2020, the Japanese Association of Acute Medicine Heatstroke and Hypothermia Surveillance Committee, Tokyo, Japan, decided to review scientific articles available at the time and create a guidance for medical treatment. This involved the establishment of the "Working group on heat stroke medical care during the COVID-19 epidemic" jointly with the Japanese Society for Emergency Medicine, which has emergency medical personnel as members, including paramedics and nurses; the Japanese Association for Infectious Diseases, an academic organization of infectious disease experts; and the Japanese Respiratory Society, an academic organization of respiratory specialists. The working group also decided to collect many expert opinions from each specialized field.

In June 2020, the first edition of the Recommendations for heat stroke prevention considering the novel coronavirus disease pandemic was published. Our working group received many opinions from concerned parties, asking us to touch on both prevention and treatment. Therefore, we decided to release the first edition of the Guidance for handling heat stroke during the novel coronavirus pandemic (henceforth, "Guidance") in July 2020.

At the time, there were no papers in the literature that directly investigated the relation between heat stroke and COVID-19. Therefore, this Guidance was published amid a scarcity in scientific evidence. There were many unresolved problems and clinical questions for which clear guidelines could not be given owing to insufficient evidence.

Two years have passed since the publication of the first edition of this Guidance. Since then, many articles and reports have been published that have investigated the relation between heat stroke prevention and treatment and COVID-19. At the very least, more knowledge has been consolidated compared with 2 years ago. This time, we included new knowledge and conventional evidence, and summarized the contents that have been clarified in the prevention and treatment of infectious diseases and heat stroke. These guidelines are intended for physicians and other healthcare professionals.

We express our sincerest gratitude to the editorial committee members and task force members who have contributed to the preparation of this Guidance and to the working group members of academic organizations who have reviewed the content and provided valuable feedback:

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Tetsuya Sakamoto, Chairperson, Japanese Association for Acute Medicine;

Yasumitsu Mizobata, President, Japanese Society for Emergency Medicine;

Hiroshi Yotsuyanagi, President, Japanese Association for Infectious Diseases;

Toyohiro Hirai, Chairman, Japanese Respiratory Society; and

Shoji Yokobori, Director and Chairperson, Heatstroke and Hypothermia Surveillance Committee, Japanese Association for Acute Medicine.

CLINICAL QUESTION LIST

Prevention (masks and air conditioners)

Q-1: Does wearing a mask raise body temperature?
A-1: Wearing a mask has no effect on body temperature during mild exercise for about 1 h in a hot environment or intense exercise for 20 min, such as running.
Q-2: Does wearing a mask increase the incidence of heat stroke?
A-2: There is no evidence that wearing a mask is a risk factor for heat stroke in healthy adults.
Q-3: How should an air conditioner be used to prevent heat stroke while avoiding a "closed" space for COVID-19 prevention?
A-3: Measures should be taken to avoid making indoor spaces where people gather, such as workplaces and classrooms, into closed spaces. Windows should be opened in two directions to allow for natural air flow and the temperature setting of the air conditioner should be adjusted with consideration for the room temperature. It is desirable to have measures against both heat stroke and COVID-19.

Diagnosis (clinical symptoms, blood test, chest computed tomography examination)

Q-4: Can heat stroke and COVID-19 be distinguished from clinical symptoms?
A-4: Both heat stroke and COVID-19 present with various systemic symptoms. It is difficult to differentiate them with only clinical symptoms.
Q-5: Is a blood test useful for distinguishing between heat stroke and COVID-19?
A-5: There are no blood test items that are useful for differentiating between the two.
Q-6: Is a chest computed tomography (CT) examination of patients suspected of heat stroke due to hyperthermia and consciousness disorder useful for differential diagnosis of COVID-19?
A-6: A chest CT scan is inappropriate for use in confirming and excluding diagnoses.

Treatment (cooling method)

Q-7: Can the patient be cooled using evaporative plus convective cooling, as in the past?
A-7: Active cooling using evaporative plus convective cooling may be conducted after taking normal infection control measures. It is desirable to select a cooling method that can be used quickly at each facility.

LITERATURE COLLECTION AND REVIEW PROCESS

THE SAME CLINICAL questions from the first edition published in June 2020 were addressed in the second edition. We set the following six items, which are the same as in the first edition, to clarify the discussion points.

1. What are the precautions for wearing a mask to prevent heat stroke?
2. How should an air conditioner be used to prevent heat stroke while avoiding a "closed" space for COVID-19 prevention?
3. Can heat stroke and COVID-19 be distinguished from clinical symptoms?
4. Is a blood test useful for distinguishing between heat stroke and COVID-19?
5. Is a CT examination of patients suspected of heat stroke due to hyperthermia and consciousness disorder useful for differential diagnosis of COVID-19?
6. Can the patient be cooled using evaporative plus convective cooling, as in the past?

Literature collection involved extracting all the articles that compared heat stroke and COVID-19, with the cooperation of the International Medical Information Center. The search formula is shown in Table 1 (MEDLINE), Table 2 (Cochrane), and Table 3 (Ichushi). As such, this collection represents the primary selection. Using a search formula that included the terms "heat stroke" and "COVID-19," we collected 60 articles from MEDLINE,[1] one article from Cochrane,[2] and 13 articles from Ichushi.[3] Subsequently, the literature that was adopted in the primary selection underwent abstract review by at least three task members, and if at least one member deemed an article worthy of actual literature review, it was obtained and adopted for secondary selection.

Six review groups were organized according to the abovementioned clinical questions and each group added a few articles as needed to the 56 articles collected in the abovementioned secondary selection. If the literature needed for the clinical question review could not be supplemented, we investigated the reports of heat stroke and COVID-19 as follows, and integrated and investigated the information. In this case, review articles and conference presentations were also searched as needed. In particular, for the first clinical question (CQ 1)—"Does wearing a mask raise body temperature?"—there was a need to clarify the rationale that "there is no evidence that wearing a mask is a risk factor for heat stroke in healthy adults," but there was the possibility that literature on heat stroke when wearing a mask (regardless of COVID-19) may not have been collected in the abovementioned primary selection. Therefore, with the cooperation of the International Medical Information Center, we decided to

Table 1. Search formula for MEDLINE

MEDLINE		
Date Run	24/05/2022	
ID	Search	Hits
1	COVID-19+NT/CT OR SARS-COV-2+NT/CT OR "COVID-19 VACCINES"+NT/CT	163,337
2	(COVID OR CORONAVIRUS?)(W)19 OR (2019 OR NOVEL)(1A)(CORONA? OR NCOV) OR SARS(W)COV(W)2 OR COVID19 OR SARS2 OR SEVERE(W)ACUTE(W) RESPIRATORY(W)SYNDROME(W) CORONAVIRUS(W)2	256,353
3	HEAT STRESS DISORDERS+NT/CT	6,577
4	HEATSTROKE? OR HEAT(2W)STROKE? OR HEAT(2W)(ILL ? OR ATTACK? OR CRAMP? OR EXHAUST? OR STRESS OR DISORDER? OR DISEASE) OR SUNSTROKE? OR SUN (2W)STROKE? OR HEAT(2W)STRESS(2W)D ISORDER? OR SIRIASIS OR CALENTURE OR HELIOSIS	22,238
5	(1 OR 2) AND (3 OR 4)	62
6	5 AND (ENGLISH OR JAPANESE)/LA	62
7	6 AND AB/FA	60

Search date: May 24, 2022.

Table 2. Search formula for Cochrane

Cochrane		
Date Run	24/05/2022	
ID	Search	Hits
1	[mh "COVID-19"] or [mh "SARS-COV-2"] or [mh "COVID-19 VACCINES"]	1,734
2	(COVID OR CORONAVIRUS OR COVID19 OR NOVEL near/1 (CORONA OR NCOV) OR SARS next COV OR SARS2 OR SEVERE next ACUTE next RESPIRATORY next SYNDROME next CORONAVIRUS):ti,ab,kw	10,866
3	[mh "HEAT STRESS DISORDERS"]	200
4	(HEATSTROKE* OR SUNSTROKE* OR SUN next STROKE* OR HEAT near/2 STRESS near/2 DISORDER* OR SIRIASIS OR CALENTURE OR HELIOSIS):ti,ab,kw	173
5	HEAT near/2 (STROKE* OR ILL* OR ATTACK* OR CRAMP* OR EXHAUST* OR STRESS OR DISORDER* OR DISEASE):ti,ab, kw	725
6	(1 or 2) and (3 or 4 or 5)	2
7	clinicaltrials.gov:so	228,563
8	6 not 7	1

Search date: May 24, 2022.

collect additional literature that directly investigated the relation between mask wearing and heat stroke. A search formula that included "heat stroke" and "mask" yielded 34 articles from MEDLINE (Table 4), four articles from Cochrane (Table 5), and eight articles from Ichushi (Table 6) for the primary selection. For CQ 1, at least three task members conducted abstract reviews, and if at least one member deemed an abstract worthy, it was adopted for additional secondary selection. However, no literature was deemed necessary.

Prevention (mask)

Q-1: Does wearing a mask raise body temperature?
A-1: Wearing a mask has no effect on body temperature during mild exercise for about 1 h in a hot environment or intense exercise for 20 min, such as running.

Explanation

Research that assumed the hottest season in Hong Kong and investigated the heat stress that was potentially amplified by wearing a surgical mask[1] found that wearing a surgical mask reduces the perceived physiological temperature of mask wearing (i.e., magnitude of thermal stimulus that is calculated based on body heat storage and internal mean radiant temperature under clothing) by 5.0°C. However, research that predicted the amount of heat release from breathing using model calculations[2,3] showed that the amount of heat release from breathing when not wearing a mask was only ~5% to 10% of the metabolic heat that was produced in the body.

Several studies have investigated the relation between mask wearing, exercise intensity, and temperature rise using healthy adult volunteers. Research that compared oral and eardrum temperatures in 93 participants when not wearing a mask and after 30 min of wearing a surgical or N95 mask during non-exertion[4] showed that oral and eardrum temperatures increase when wearing either mask, but that the only statistically significant increase in oral temperature is when wearing an N95 mask (mean increase of 0.27°C).

Research that investigated the core body temperature with different samples yielded nearly similar results. A study with 20 participants who were asked to walk on a treadmill for 1 h with and without surgical masks at a speed of 5.6 km/h in an environment with a room temperature of 25°C and

Table 3. Search formula for Ichushi

Date Run ID	24/05/2022 Search	Hits
1	Heat Stroke (Japanese)/TH or Heatstroke (Japanese)/AL or Sunstroke (Japanese)/AL or Heliosis (Japanese)/AL or Depressive Fever (Japanese)/AL or Depressive Heat (Japanese)/AL or Heatstroke (Japanese)/AL or Heat Stress Syndrome (Japanese)/AL or Heat Fatigue (Japanese)/AL or Heat Stress Disorder (Japanese)/AL or heatstroke/al or "heat stress"/al or "Heat Ill"/al or "heat Cramp"/al or "heat Fatigue"/al or "heat Syncope"/al or "heat STROKE"/al or "heat EXHAUST"/al or "heat ATTACK"/al or "heat DISORDER"/al or "heat DISEASE"/al or "heat INJUR"/al	5,505
2	COVID-19/al or "COVID 19"/al or COVID19/al or nCoV/al or "Novel Corona"/al or "SARS-CoV 2"/al or SARS-CoV-2/al or SARS2/al or "Severe Acute Respiratory Syndrome Coronavirus 2"/al or covid-19 (Japanese)/al or covid-19 (Japanese)/al or novel corona (Japanese)/al or novel corona (Japanese)/al or SARS coronavirus-2 (Japanese)/al or SARS coronavirus 2 (Japanese)/al or "SARS coronavirus 2" (Japanese)/al or ((@disease epidemic (Japanese)/th and @COVID-19 (Japanese)/th) or coronavirus (Japanese)/al)	29,164
3	1 and 2	67
4	(3) and (AB=Y)	13

Search date: May 24, 2022.

Table 4. Search formula for MEDLINE

Date Run ID	15/06/2022 Search	Hits
1	HEAT STRESS DISORDERS+NT/CT	6,607
2	HEATSTROKE? OR HEAT(2W)STROKE? OR HEAT(2W)(ILL ? OR ATTACK? OR CRAMP? OR EXHAUST? OR STRESS OR DISORDER? OR DISEASE) OR SUNSTROKE? OR SUN(2W)STROKE? OR HEAT(2W)STRESS(2W)DISORDER? OR SIRIASIS OR CALENTURE OR HELIOSIS	22,360
3	MASKS+NT/CT OR MASKS OR MASK OR FACEMASK?	50,314
4	(1 OR 2) AND 3 NOT RESERV?(3A)MASK?	36
5	4 AND (ENGLISH OR JAPANESE)/LA	35
6	5 AND AB/FA	34

Search date: June 15, 2022.

Table 5. Search formula for Cochrane

Date: Run ID	15/06/2022 Search	Hits
1	[mh "HEAT STRESS DISORDERS"]	203
2	(HEATSTROKE* OR SUNSTROKE* OR SUN next STROKE* OR HEAT near/2 STRESS near/2 DISORDER* OR SIRIASIS OR CALENTURE OR HELIOSIS):ti,ab,kw	175
3	HEAT near/2 (STROKE* OR ILL* OR ATTACK* OR CRAMP* OR EXHAUST* OR STRESS OR DISORDER* OR DISEASE):ti,ab,kw	731
4	[mh Masks]	1,687
5	mask or masks or facemask*	12,534
6	(1 or 2 or 3) and (4 or 5)	5

Search date: June 15, 2022.

relative humidity of 70%[5] showed that core body temperature increases by an average of 0.08°C when wearing a mask; the study found no significant difference compared with when not wearing a mask. A study with 12 participants who walked on a treadmill for 30 min with and without surgical masks at a speed of 6 km/h in an environment with a room temperature of 35°C and relative humidity of 65%.[6] showed that core body temperature increases regardless of mask wearing, but that the two groups have no significant difference. Another study used an internal capsule-type core thermometer to measure the body temperature of six participants who completed tasks of standing, walking, and running for 20 min each when not wearing a mask (control), wearing a surgical mask, and wearing a sports mask in an environment with a room temperature of 28°C.[7] This study conducted two-way repeated measures analysis of variance and Friedman's rank-based repeated measure analysis of variance measurements, and the results showed that core body temperature increased with increasing exercise intensity in all groups (control: 37.4°C → 38.8°C, surgical mask: 37.2°C → 38.7°C, sports mask: 37.3°C → 38.7°C), but no significant differences were found among the three groups.

The above research indicates that, even if mask wearing affects the physiologically perceived temperature, mask wearing itself has no effect on body temperature in light exercise for about 1 h in a hot environment or in intense exercise for 20 min, such as running.

Table 6. Search formula for Ichushi

Date Run ID	15/06/2022 Search	Hits
1	Heat Stroke (Japanese)/TH or Heatstroke (Japanese)/AL or Sunstroke (Japanese)/AL or Heliosis (Japanese)/AL or Depressive Fever (Japanese)/AL or Depressive Heat (Japanese)/AL or Heatstroke (Japanese)/AL or Heat Stress Syndrome (Japanese)/AL or Heat Fatigue (Japanese)/AL or Heat Stress Disorder (Japanese)/AL or heatstroke/al or "heat stress"/al or "Heat Ill"/al or "heat Cramp"/al or "heat Fatigue"/al or "heat Syncope"/al or "heat STROKE"/al or "heat EXHAUST"/al or "heat ATTACK"/al or "heat DISORDER"/al or "heat DISEASE"/al or "heat INJUR"/al	5,513
2	2 mask(Japanese)/TH or mask(Japanese)/al or mask/ta	12,846
3	3 1 and 2 not Reservoir(Japanese)/ta	32
4	4 (3) and (AB=Y)	8

Search date: June 15, 2022.

Q-2: Does wearing a mask increase the incidence of heat stroke?

A-2: There is no evidence that wearing a mask is a risk factor for heat stroke in healthy adults.

Explanation

Research that measured the core body temperature of six young adult participants with an internal capsule-type core thermometer when not wearing a mask (control), wearing a surgical mask, or wearing a sports mask after the participants were asked to stand, walk, and run for 20 min each in an environment with a room temperature of 28°C [7].. showed that increased exercise intensity can increase the core body temperature, respiratory rate, and pleth variability index (an index of dehydration), and decrease SpO_2, but no significant differences were found among the three groups. Research that evaluated the motor cognitive performance at baseline and after 45 min of light work, physiological indices (rectal, skin, and facial temperature), and sensory indices (heat discomfort, and dyspnea) of eight young adult participants when not wearing (control) or while wearing a KN95 mask in an environment with a room temperature of 28°C and relative humidity of 20%.[8] showed that wearing a KN95 mask increased the number of participants who complained of dyspnea after light work by 36%, but had no effects on motor cognitive performance, physiological indices, and thermal discomfort. The KN95 mask was made in accordance with the Chinese standard GB2626-2006 and cleared the same standards as the N95 mask in terms of filter performance.

As explained in A-1, wearing a mask has no known impact on body temperature. Although it may affect the feeling of dyspnea, there is no evidence that mask wearing itself is a risk factor for heat stroke when exercise intensity increases. However, all these studies,[7,8] focused on healthy young adults (mean age of 23 ± 3 years.[7], median age of 19.5 years [interquartile range, 19.0–21.0 years]).[8] There are no reports on whether mask wearing is a risk factor for heat stroke in older adults and children. However, an investigation on the impacts of age and maximum daytime temperature on heat stroke.[9] showed that older adults 65 years and older and young people 7–17 years old tend to have lower maximum daytime temperatures at which heat stroke can occur, compared with adults 18–64 years old. Infants are also at a higher risk for respiratory failure compared with adults because their respiratory muscles are underdeveloped, and their anatomical dead space is large.[10]

Aerobic exercise while wearing an N95 mask is associated with an increase in end-expiratory carbon dioxide concentration among those with a history of lung disease.[11] Although there are no reports on its associations with the onset of heat stroke, care must be taken during mask wearing.

Regardless of mask wearing, exercising in a hot environment has a large impact on core body temperature.[4–7] With the interpretation of the above results that the risk for heat stroke is not sufficiently reduced in a hot environment even if a mask is not worn, it is especially important that older adults, children, and those with lung disease take measures against heat stroke in a hot environment, such as ensuring air conditioning and hydration.

Prevention (air conditioner)

Q-3: How should an air conditioner be used to prevent heat stroke while avoiding a "closed" space for COVID-19 prevention?

A-3: Measures should be taken to avoid making indoor spaces where people gather, such as workplaces and classrooms, into closed spaces. Windows should be opened in two directions to allow for natural air flow, and the temperature setting of the air conditioner should be adjusted with consideration for the room temperature. It is desirable to have measures against both heat stroke and COVID-19.

Explanation

We reviewed 13 articles from the perspectives of heat stroke and ventilation. Air conditioner use was a significant prognostic factor in multivariate analyses in Chicago in 1999,[12] the heat wave in France in 2003,[13] and meta-analyses that included them.[14] Similar trends have been reported in Japan,[15–17] and the use of air conditioners is effective in preventing heat stroke. However, there is no clear evidence regarding the appropriate room temperature for the prevention of heat stroke outbreaks.[18–20]

Avoiding closed indoor spaces as a measure against COVID-19 infection requires frequent ventilation in indoor spaces where people gather, such as workspaces and classrooms. The Ministry of Health, Labour and Welfare of Japan also recommends that windows be opened in two directions for a few minutes and that ventilation be conducted at least twice an hour.[21,22]

Research that compared the ventilation rate and infection risk when opening windows in one direction and two directions used the tracer gas attenuation method with CO_2 as the tracer gas to calculate the ventilation efficiency; the study evaluated infection risk using the Wells–Riley model, which is a simple and rapid method for evaluating airborne infection risk.[23] The study reported that ventilation efficiency is better when windows are opened in two directions than when windows are opened only in one direction; notably, ventilation rates are higher when windows opened in two directions are opened wider. Regarding infection risk, the probability of infection can be reduced to 1% or less by opening windows in two directions by 15% for 30 min of exposure and while wearing masks.[23] However, this research may be intended to present a positive evaluation of the infection control measures of the South Korean government.

For improving "closed spaces with poor ventilation" while considering heat stroke prevention by the Ministry of Health, Labour and Welfare of Japan, the recommended ventilation method is to open windows in two directions to the extent possible to keep the room temperature and relative humidity at the maximum values of 28°C and 70%, respectively, and to allow air to pass continuously through the room.[21] In buildings with mechanical ventilation and air conditioning equipment that can ensure the legislated ventilation level, such as whole-building and commercial air conditioning, it is important to maintain and manage mechanical ventilation and air conditioning equipment so that the temperature does not exceed the legally stipulated environmental hygiene management standard value of 28°C and to open windows and doors as appropriate to keep the temperature below 28°C.[22]

There is no clear evidence on the extent to which room temperature rises with ventilation. Therefore, the temperature setting of the air conditioner should be adjusted regularly according to measurements of the room temperature. An epidemiological study on older adults who are vulnerable to heat stroke found that visualizing temperature and humidity encourage behavioral changes, reporting changes in air conditioner usage among 60% of participants.[24] The Ministry of the Environment of Japan has proposed "COOL-BIZ" as a lifestyle that encourages light clothing and efforts to stay comfortable even when the room temperature is 28°C, but it is not a recommendation for setting the air conditioner to 28°C. It should be noted that the air conditioner setting temperature does not equal indoor temperature and that efforts should be made to manage temperature and humidity with an air conditioner while being conscious of the heat index (wet bulb globe temperature [WBGT]), and create a comfortable environment by blocking sunlight, using a circulator, and using a fan. Furthermore, setting room temperatures to lower than 28°C should be considered in environments where a physical strain is applied on the body.

Wet bulb globe temperature

The WBGT is a heat index that was proposed in the United States in 1954 for preventing heat stroke. The units are in degrees Celsius (°C), which is the same as temperature, but the values are different from that of temperature. The WBGT is an index that focuses on the exchange of heat between the human body and external air (i.e., heat balance). It incorporates three factors that have a large impact on the heat balance of the human body: (1) humidity; (2) surrounding thermal environment, such as insulation and radiation; and (3) air temperature. The calculation is based on the measurement values (globe temperature [GT], natural wet bulb temperature [NWB], and natural dry bulb temperature [NDB]) of the following three measuring devices.

- The GT is measured by inserting a thermometer into the center of a thin copper plate that is painted black (hollow inside, diameter of ~15 cm). The surface of the black ball is painted with a material that is almost completely non-reflective. This globe temperature is an observation of the equilibrium temperature inside the bulb that is exposed to direct sunlight, and it has a good correlation with the sensible temperature in the sun during light winds.
- The NWB is measured by wrapping gauze that is moistened with water around the bulb of a thermometer. This is the temperature when the moisture on the surface of the thermometer evaporates and is balanced with the cooling heat. The drier the air, the greater the difference from the

air temperature (NDB temperature). The NWB expresses the degree of coolness felt when sweat evaporates from the skin.
- The NDB is measured directly using a normal thermometer.
- Calculation formula of heat index (WBGT). The calculation formula for outdoors is WBGT (°C) = 0.7× NWB + 0.2 × GT + 0.1 × NDB. The calculation formula for indoors is WBGT (°C) = 0.7 × NWB + 0.7 × GT. - WBGT, GT, NWB, and NDB units are all in degrees Celsius (°C).

From the Ministry of Environment of Japan (https://www.wbgt.env.go.jp/doc_observation.php).

Diagnosis (clinical symptoms)

Q-4: Can heat stroke and COVID-19 be distinguished from clinical symptoms?
A-4: Both heat stroke and COVID-19 present with various systemic symptoms. It is difficult to differentiate them with only clinical symptoms.

Explanation

No study has directly compared the clinical symptoms of heat stroke and COVID-19. Therefore, we investigated the literature on each clinical symptom. The temperature, an environmental factor with the largest contribution to the onset of heat stroke, peaks from mid-July to early August[25,26]. Those with a history of working outdoors, playing sports, or being exposed to a hot environment, such as indoors without an air conditioner, are more likely to develop heat stroke. However, the possibility of COVID-19 cannot be rejected simply because of exposure to a hot environment.

Table 7 summarizes the symptoms of heat stroke and COVID-19, according to the Japanese Association for Acute Medicine heat stroke classification.

Table 8 summarizes the incidence of characteristic clinical symptoms. A comparison of the incidence of each show that heat stroke is often accompanied by an increase in body temperature, but fever is also seen with COVID-19[30]. Among the first-degree heat stroke symptoms, muscle pain is also observed with COVID-19[30], although there are few reports of muscle cramps[32]. Among the second-degree heat stroke symptoms, headache, general fatigue, and nausea are also seen with COVID-19[30]. Furthermore, 1% to 20% of patients with COVID-19 are also affected by consciousness disorders, which appear in second- and third-degree heat stroke[33]. Therefore, when differentiating the two, muscle spasms are specific to heat stroke, but systemic symptoms, such as fever, headache, general fatigue, nausea, and consciousness disorders, appear in both heat stroke and COVID-19.

Table 7. Symptoms of heat stroke and COVID-19

	Clinical symptoms
Heat stroke[25–29]	First degree: dizziness, lightheadedness, yawning, sweating, muscle pain, muscle spasms Second degree: headaches, nausea/vomiting, general fatigue, mild consciousness disorders Third degree: severe consciousness disorders, cerebellar symptoms, seizures
COVID-19[30,31]	Fever, shivering chills, general fatigue, headache, joint pain, muscle pain, dyspnea, nasal discharge, sore throat, cough, sneezing, hoarseness, nausea, diarrhea, abdominal pain, earache, dysosmia, dysgeusia, consciousness disorders, brain fog, chest pain, palpitations, eye pain, rash

The characteristic clinical symptoms of COVID-19 are nasal discharge, sore throat, cough, sneezing, hoarseness, and dyspnea[30]. Heat stroke does not usually have these symptoms, except for dyspnea, which has been observed in some cases[28]. Furthermore, a meta-analysis reported that 47.9% of COVID-19 cases before the Omicron strain were accompanied by dysosmia as a characteristic finding[34]. However, the frequency decreased in the current mainstream Omicron strain (22.3%)[30,31]. Meanwhile, dysosmia is rarely observed in heat stroke cases. When differentiating between the two, dyspnea is observed in both heat stroke and COVID-19, but nasal discharge, sore throat, cough, sneezing, hoarseness, and dysosmia are less common in heat stroke cases. However, upper respiratory inflammatory symptoms other than dysosmia are also seen in other viral infections. Therefore, although the applicable case could be differentiated from heat stroke, it is not unique to COVID-19.

Both heat stroke and COVID-19 present with various systemic symptoms, making it difficult to differentiate with clinical symptoms alone. Symptoms such as muscle spasms in heat stroke, and nasal discharge, sore throat, cough, sneezing, hoarseness, and dysosmia in COVID-19 help distinguish between the two.

Diagnosis (blood test)

Q-5: Is a blood test useful for distinguishing between heat stroke and COVID-19?

Table 8. Incidence of characteristic clinical symptoms of heat stroke and COVID-19

Clinical symptom	Heat stroke	COVID-19 (%)	
Fever (hyperthermia)	Majority	26.7–39.2	30
Muscle pain	Definition of first degree	19.1–34.2	32
Muscle spasm	Definition of first degree	Hardly present	32
Headache	Definition of second degree	68.2–76.5	30
General fatigue	Definition of second degree	14.6–20.4	30
Nausea	Definition of second degree	12.6–19.7	30
Consciousness disorder	Definition of third degree	1–20	33
Nasal discharge	Usually absent	74.9–82.6	30
Sore throat	Usually absent	68.4–71.0	30
Cough	Usually absent	49.5–49.9	30
Sneezing	Usually absent	61.3–69.3	30
Hoarse voice	Usually absent	42.0–42.8	30
Dyspnea	6.3%–11.3%	4.3–5.1	28,30
Dysosmia	Usually absent	47.9 (conventional type) 22.3–27.7 (Omicron strain)	30,31,34

A-5: There are no blood test items that are useful for distinguishing between the two.

Explanation

We reviewed four papers related to heat stroke and eight papers related to COVID-19. At the time of the literature review, there was only one study on blood collection items for the purpose of differentiating between COVID-19 and heat stroke. When heat stroke is exacerbated, organ ischemia as well as hyperthermia itself advances organ damage, and systemic inflammatory response syndrome owing to hypercytokinemia and bacterial translocation owing to intestinal ischemia are thought to induce disseminated intravascular coagulation by the same mechanism as sepsis. Blood test findings of liver disorder, renal disorder, and coagulopathy may be observed, and these blood test findings are included in the definition of heat stroke severity classification degree III (most severe). Meanwhile, according to the Novel Coronavirus Disease Treatment Guidance 2022 Ver. 8.1, the following biomarkers (aggravation markers) that contribute to severity determination and prognosis prediction of COVID-19 patients are significantly associated with artificial respiration and death: (1) lymphocytopenia, (2) thrombocytopenia, (3) elevated D dimer levels, (4) elevated C-reactive protein (CRP) levels, (5) elevated procalcitonin levels, (6) elevated creatine kinase (CK) levels, (7) elevated aspartate aminotransferase (AST), (8) elevated alanine aminotransferase (ALT), (9) elevated creatinine (Cre), and (10) elevated serum lactate dehydrogenase (LDH[35]). Currently, there are many overlapping blood test items as markers of severity in heat stroke and COVID-19.

Research that investigated biomarkers to differentiate between heat stroke and COVID-19 includes a report that compared the blood tests of 90 hospitalized heat stroke patients and 86 hospitalized COVID-19 patients who were registered in the Heatstroke STUDY 2017–2019 that was conducted in Japan[36]. The results showed significant differences for the three items of white blood cells ($10.8 \times 10^3/\mu L$ versus $5.2 \times 10^3/\mu L$, $P < 0.001$), Cre (2.2 versus 0.85 mg/dL, $P < 0.001$), and CRP (0.2 versus 2.8 mg/dL, $P < 0.001$). Moreover, the finding of acute kidney injury in the prolonged COVID-19 period in the summer was deemed useful for differentiation. However, the incidence of acute kidney injury in hospitalized patients with COVID-19 was high at 36.6%[37], and COVID-19-related kidney diseases, such as nephrotic syndrome[38] and nephritis associated with antineutrophilic cytoplasmic autoantibodies (ANCA)[39], have also been widely reported. Therefore, a blood test for acute kidney injury does not lead to a recommendation as a differential test.

As previously described, heat stroke is characterized by liver damage, renal damage, and coagulopathy owing to organ ischemia and hyperthermia; however, follow-up blood tests for at least 72 h are required to avoid overlooking the exacerbation of these organ disorders[29]. According to the 2015 heatstroke treatment guideline, renal dysfunction occurs in <5% and 25% to 30% of non-exertional and exertional heat stroke, respectively. According to observational research on heat stroke[29,36,40,41], elevated CK is the most

characteristic finding, but its percentage has a wide range of 7.9% to 92.0%. Moreover, there was wide variation within the patient group, and the measured values did not appropriately reflect the severity of heat stroke and long-term prognosis. Generalizing the percentage of outliers was also difficult. Further, neither hyper/hyponatremia nor hyper/hypokalemia, which are presumed to occur during heat stroke, has been shown to have characteristic results in either exertional or non-exertional heat stroke. Additionally, the inflammation-related protein high-mobility group box 1 (HMGB1)[42] is a biomarker that reflects organ damage owing to heat stroke. It is reported to be useful for early diagnosis and treatment, but it has not been put into practical use in clinical settings.

Regarding characteristic blood test items for COVID-19, a recent meta-analysis showed that common test abnormalities are elevated CRP at 68.6% (95% CI, 58.2–78.2), lymphocytopenia at 57.4% (95% CI, 44.8–69.3), and elevated LDH at 51.6% (95% CI, 31.4–71.6)[43]. Further, observational research of patients hospitalized with COVID-19 showed that elevated AST/ALT was observed in 28% to 76%, elevated total bilirubin in 18%, elevated LDH in 76%, elevated myoglobin in 15%, and elevated D dimers in 36%. Meanwhile, blood urea nitrogen, Cre, and CK were shown to have either increased or decreased compared with standard values in some cases[35,44,45]. There are no studies that investigated electrolyte imbalances for COVID-19.

Therefore, although there are test items that may reflect the prediction of organ damage and severity attributable to heat stroke and COVID-19, the blood tests that are useful for differentiating between heat stroke and COVID-19 are not clear at present[46].

Diagnosis (chest CT test)

Q-6: Is a chest CT examination of patients suspected of heat stroke due to hyperthermia and consciousness disorder useful for differential diagnosis of COVID-19?
A-6: A chest CT scan is inappropriate for use in confirming and excluding diagnoses.

Explanation

Prompt diagnosis and therapeutic intervention are necessary because the prognosis of heat stroke worsens if diagnosis and treatment are delayed[29]. COVID-19 is included as a differential disease during the COVID-19 pandemic. Therefore, various restrictions are imposed compared with normal medical treatment, which may lead to an excessive burden on the emergency medical field and delays in treatment onset. Early differentiation of COVID-19 by plain chest CT exams would solve these problems. Therefore, we investigated the usefulness of plain chest CT exams for differential diagnosis of COVID-19 in patients suspected of having heat stroke based on hyperthermia and consciousness disorders.

We conducted a search with COVID-19 and heat stroke as key words, identified 43 Medline papers and 11 Ichushi papers, and conducted a review of these papers. We found no reports on the usefulness of plain chest CT exams in patients with hyperthermia and consciousness disorders who may have heat stroke for differentiation from COVID-19. Therefore, the findings of plain chest CT exams for heat stroke and COVID-19 are described below, and their usefulness is investigated by comparing them.

Patients with heat stroke may experience complications of acute respiratory distress syndrome (ARDS) within 24 to 48 h of the onset of heat stroke, although the frequency is unknown; and diffuse infiltrative shadows in both lungs are characteristic findings in patients with ARDS[29,47–49]. However, in ordinary heat stroke treatment, heat stroke patients who do not present with respiratory symptoms that suggest ARDS at the time of their hospital visit tend not to have specific plain chest CT imaging findings.

Meanwhile, patients with COVID-19 will have plain chest CT imaging findings that are characterized by diffuse peripheral and subpleural predominant ground-glass opacities in both lungs[50]. These imaging findings, when classified using the classification of idiopathic interstitial pneumonia, are similar to those of acute interstitial, acute fibrinous organizing, non-specific interstitial, and idiopathic organizing pneumonia[31]. However, there are cases of COVID-19 that are complicated by ARDS and caution is required as these imaging findings may not apply in these cases[31]. Regarding the characteristic findings of plain chest CT exams, the sensitivity is ~70% to 90% and specificity is ~20% to 90%, and no consensus has been reached in terms of usefulness[51]. Therefore, plain chest CT imaging may be useful as an aid to the differential diagnosis of respiratory failure, such as ARDS and COVID-19, particularly in patients with hyperthermia and consciousness disorders; the implementation of tests can be considered, despite views that it is inappropriate for use when reaching a definitive diagnosis[31,51,–9].

In Japan, the Delta strain was nationally replaced by the Omicron strain around February 2022, and the latter has become the main strain of COVID-19 infection at the time of publication of this Guidance. Retrospective research from December 2021 to January 2022 showed that typical severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia chest CT findings were present in 83% (55/66) of conventional (Delta strain) patients, compared with only 40% (16/40) of Omicron strain patients, and Omicron strain cases were reported to be more often classified as normal[10].

When differentiating between heat stroke and COVID-19, medical history and detection status are extremely important, the importance of plain chest CT images is not high and rapid therapeutic interventions are needed for heat stroke, as previously mentioned. Therefore, treatment should be prioritized in cases where plain CT exams would take time. However, when considering that cranial CT exams are required for differentiating cerebrovascular disorders in patients with consciousness disorders and abdominal CT exams are required for differentiating organic diseases in patients with multiple organ failure, whole-body CT exams, including chest CT, may be ideal, while conducting active cooling and fluid replacement. Additionally, plain CT exams cannot be used for a definitive diagnosis. Therefore, the cancellation of judgment of a COVID-19 suspected case should be carefully conducted after comprehensively considering such results as the prevalence of COVID-19, clinical symptoms, gene amplification tests (e.g., real-time polymerase chain reaction and loop-mediated isothermal amplification), and antigen tests.[8]

Treatment (cooling method)

Q-7: Can the patient be cooled using evaporative plus convective cooling, as in the past?

A-7: Active cooling using evaporative plus convective cooling may be conducted after taking normal infection control measures. It is desirable to select a cooling method that can be used quickly at each facility.

Explanation

It is difficult to distinguish between COVID-19 and heat stroke from clinical symptoms and CT findings in patients with hyperthermia and consciousness disorders. Active whole-body cooling must be conducted as an initial medical treatment for heat stroke while taking infection control measures against COVID-19. However, evaporative plus convective cooling in COVID-19 patients runs the risk of spreading the SARS-CoV-2 on the body surface and in exhaled breaths via the aerosols generated by the evaporation of water from the body surface. Therefore, the previous Guidance recommended as a general rule that evaporative plus convective cooling should not be used[52].

Active cooling methods for heat stroke patients include internal cooling, such as gastric lavage, bladder lavage, intravascular cooling, renal replacement therapy, and extracorporeal membrane oxygenation. External cooling methods include evaporative cooling, cold-water immersion, cold-water showers, local cooling with ice packs and other equipment, and cooling devices such as cooling mats. However, treatment with only extracellular fluid infusion is not included in the active cooling method, regardless of the fluid temperature of the infusion[53].

According to the Japanese Association for Acute Medicine Heatstroke STUDY, 62.6% of the cases in 2019 were treated with extracellular fluid infusion without active cooling, whereas 70.0% of the cases in 2020 were treated in this manner. Furthermore, the percentage of active cooling methods that used evaporative plus convective cooling was 77.9% in 2019, but this decreased to 61.6% in 2020[54].

Based on previous recommendations, a demonstration experiment using evaporative plus convective cooling on a doll whose surface was heated to 40°C confirmed a cooling effect on the doll surface, but also the generation of aerosols owing to water evaporation from the body surface[55]. Therefore, although there is no risk of infection through aerosols associated with the evaporation of water from the body surface by evaporative plus convective cooling, there remains a risk of infection from talking or coughing if the patient has COVID-19, as with other cooling methods. Hence, infection control measures should be continued.

Meanwhile, as an active cooling method, evaporative plus convective cooling is not recommended. A cooling method that can be used quickly in each facility should selected.

Rapid and effective cooling is thought to improve prognosis in heat stroke, but it is difficult to conduct inter-comparative research on the optimal cooling method[56]. Research that compared the prognosis of patients with severe heat stroke who were treated with extracellular fluid infusion alone and patients who received extracellular fluid infusion combined with active cooling showed that the combined use of active cooling reduced the in-hospital mortality rate[53].

The prognosis worsens when a core body temperature of 40.5°C or higher is maintained in patients with heat stroke, whereas the prognosis improves when cooling at 0.10°C or more per minute in exertional heat stroke[29]. No research has investigated the cooling target temperature and cooling time in non-exertional heat stroke, but the prolongation of hyperthermia leads to a poor prognosis. Patients must be cooled down to around 38°C as early as possible, as in the case with exertional heat stroke[53]. Of the active cooling methods, cold-water immersion is reported to achieve a cooling rate of 0.20–0.35°C/min. Further, although comparisons are difficult, given that the body temperatures at the time of introduction are different, a study has reported that intravascular cooling catheters and water-cooled body surface cooling using the gel pad method can achieve cooling rates of 0.8–1.4°C/h and 1.0–1.2°C/h, respectively[25].

Attention must be given to the occurrence of excessive cooling or arrhythmia in any active cooling. The attending

medical personnel should implement these methods under appropriate monitoring and select a cooling method that can be used quickly at each facility.

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DISCLOSURE

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APPENDIX

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