

Different clinical guidelines, common goal: To reduce COVID-19 mortality

Liqin Sun¹, Jiaye Liu², Fang Zhao¹, Jun Chen³, Hongzhou Lu^{1,*}

¹National Clinical Research Center for Infectious Diseases, The Third People's Hospital of Shenzhen and the Second Hospital Affiliated with the Southern University of Science and Technology, Shenzhen, Guangdong, China;

²School of Public Health, Shenzhen University Health Science Center, Shenzhen, People's Republic of China, Shenzhen, Guangdong, China;

³Department of Infectious diseases and Immunology, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China.

SUMMARY The tendency of the Omicron variant to rapidly became the dominant SARS-CoV-2 strain and its weaker virulence than other strains worldwide has prompted many countries to adjust their public health strategies. This work summarizes all appropriate clinical interventions to reduce the public health burden caused by COVID-19 according to guidelines from the World Health Organization and 10 countries, *i.e.*, the United States of America (USA), India, France, Germany, Brazil, South Korea, Japan, Italy, the United Kingdom (UK), and China. Five stages of COVID-19 were identified: asymptomatic infection and mild, moderate, severe, and critical illness. Most guidelines recommend antivirals starting with mild cases for those from Germany and India. Since more drugs are being developed and are becoming available to COVID-19 patients, guidelines are increasingly being updated with new pharmacological intervention strategies. Thus, a global view needs to be adopted to provide helpful options and precise treatment strategies during the lasting fight against the COVID-19 pandemic.

Keywords Covid-19, SARS-COV-2, guidelines, emerging infectious disease, public health

The coronavirus disease 2019 (Covid-19) pandemic was a global public health emergency and it remains a public health and economic burden. Over the past three years, many countries have adopted various strategies to respond to the global pandemic. Most countries have shifted their public health strategies from a strict infection prevention and control strategy (IPC) to a loose IPC strategy. From the perspective of clinical management, physicians treated the viral infection as a common respiratory infectious disease thanks to widespread vaccination, the Omicron strain being less virulent, and the accumulation of more clinical experience with treatment. The case fatality rate (CFR) has dropped to less than 0.1% since June 2022 among the countries with the highest number of new confirmed cases over the past year (*e.g.*, the United States of America (US), India, France, Germany, Brazil, South Korea, Japan, Italy and the United Kingdom (UK)). (1). The vaccine's efficiency and effectiveness, especially in terms of preventing severe disease, was widely confirmed. As of December 2022, the vaccination rates (two or more doses of vaccine per 100 people) for the aforementioned countries had reached 67.09-86.27% (1). All of these countries formulated COVID-19 treatment guidelines and updated

them according to the latest evidence (2-9). Summarized here are differences in these updated treatment guidelines from the World Health Organization (WHO) and 6 countries, including the USA, India, Germany, Japan, the UK, and China, in detail. However, treatment guidelines from France, Brazil, South Korea, and Italy were not included because their latest version was updated before the outbreak of omicron.

Patients with COVID-19 can experience a range of clinical manifestations, from no symptoms to critical illness. COVID-19 staging provides valuable frameworks and benchmarks for clinical decision-making in patient management, improved prognostication, and evidence-based treatment selection. Most countries have classified clinical stages of COVID-19 with clear criteria for each stage (Table 1, Table S1, <http://www.biosciencetrends.com/action/getSupplementalData.php?ID=132>). Guidelines from these countries (*e.g.*, the USA (5)) have detailed clinical staging for COVID-19 that includes asymptomatic infection and mild, moderate, severe, and critical illness. In specific terms, the staging criteria are mostly based on whether the patients have symptoms, or evidence of hypoxemia (shortness of breath, high respiratory rate, or low SpO₂), or whether they need

Table 1. Classification for COVID-19 from several countries and organizations

Country	Clinical characters	
	Type	Criterion
Japan	Mild	• SpO ₂ ≥ 96%, no respiratory symptoms
	Moderate 1	• 93% < SpO ₂ < 96%, shortness of breath, symptoms of pneumonia
	Moderate 2	• SpO ₂ ≤ 93%, need for oxygen
	Severe	• Need for mechanical ventilation
India	Mild	• No shortness of breath or hypoxia
	Moderate	• Any of the following: 1. Respiratory rate ≥ 24/min, breathlessness; 2. SpO ₂ : 90% to ≤ 93% on room air
	Severe	• Any of the following: 1. Respiratory rate > 30/min, breathlessness; 2. SpO ₂ < 90% on room air
WHO	Non-severe	• Absence of signs or severe or critical disease
	Severe	• SpO ₂ < 90% on room air, signs of pneumonia, signs of severe respiratory distress
	Critical	• Requires life-sustaining treatment, acute respiratory distress syndrome, sepsis, septic shock
USA	Asymptomatic or presymptomatic infection	• No symptoms that are consistent with COVID-19
	Mild illness	• Symptomatic but do not have shortness of breath, dyspnea, or abnormal chest imaging
	Moderate illness	• Having evidence of lower respiratory disease and SpO ₂ ≥ 94% on room air at sea level
	Severe illness	• Individuals who have SpO ₂ < 94% on room air at sea level, PaO ₂ /FiO ₂ < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates > 50%
	Critical illness	• Respiratory failure, septic shock, and/or multiple organ dysfunction
UK	Non-severe	• Absence of signs or severe or critical disease
	Severe	• SpO ₂ < 90% on room air, signs of pneumonia, signs of severe respiratory distress
	Critical	• Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy
Germany	Mild	• COVID-19-positive patients who did not require oxygen during hospitalization (WHO stages 1-3)
	Severe/Critical	• SpO ₂ < 90%, respiratory rate > 30/min, ARDS, sepsis, ventilation, vasopressor administration
	Early stage	• < 72 hours after the first positive PCR result and/or < 7 days after the onset of symptoms
China	Mild illness	• Symptomatic but without shortness of breath, dyspnea, or abnormal chest imaging
	Moderate illness	• Persistent high fever > 3 days or/and cough, shortness of breath, but respiratory rate (RR) < 30 times/min and at rest, oxygen saturation obtained from the finger was > 93% on room air at sea level, and imaging showed characteristic manifestations of novel coronavirus pneumonia
	Severe illness	• Individuals who have SpO ₂ ≤ 93% on room air at sea level, PaO ₂ /FiO ₂ ≤ 300 mmHg, a respiratory rate ≥ 30 breaths/min, the clinical symptoms worsened progressively, and lung imaging showed that the lesion progressed significantly > 50% within 24-48 hours
	Critical illness	• Respiratory failure requiring mechanical ventilation, septic shock, and/or multiple organ dysfunction requires ICU care

organ support. The stage of COVID-19 also determines whether the patients should be isolated at home, hospitalized, or even admitted to the ICU.

The first stage of COVID-19 is the rapid period of viral replication, in which tissue and organ damage and abnormal immune activation are not obvious and do not need to be dealt with first. Early use of antivirals to inhibit viral replication as soon as possible should significantly reduce the damage to cells and tissues caused by viral replication, which is a key point of treatment. Small molecule drugs and monoclonal neutralizing antibodies are two types of drugs with antiviral action. Antiviral therapy is recommended for

patients with COVID-19 according to the guidelines in most countries, but the recommended drugs and clinical stages vary by countries. Notably, only guidelines from the WHO (8), Japan (4), the UK (3), and the USA (5) recommended nirmatrelvir/ritonavir, remdesivir, and molnupiravir for mild cases. Several neutralizing monoclonal antibodies were recommended in the early guidelines from the USA (5) and Japan (4). However, the effectiveness of these antibodies decreased as new variants emerged, so these monoclonal antibodies were not recommended by most guidelines. Similarly, convalescent plasma is no longer mentioned or recommended in these guidelines.

For patients with hypoxemia, all of the guidelines recommend oxygen therapy, which also includes HFNC, noninvasive ventilation, machine ventilation, and ECMO. Prone position ventilation, including awake prone position ventilation, is now incorporated in several guidelines. Anticoagulants are also highly recommended by several guidelines as mounting evidence has indicated that they reduce the need for organ support and the progression to intubation and death.

During the later stage of COVID-19, the secondary immune damage becomes a major factor even though viral replication is almost undetectable. Therefore, immunomodulators, including glucocorticoids, IL-6R inhibitors, and JAK inhibitors, are supposed to prevent an excessive inflammatory response. All of these drugs are recommended to treat severe or critical ill patients while glucocorticoids and baricitinib can also be used to treat moderate COVID-19.

In summary, the guidelines in various countries have small differences in their classification of COVID-19 severity. However, the treatment principles of COVID-19 are basically the same, while the medicines vary according to the availability of drugs in each country. As more drugs become available and research results are published, the latest guidelines may include more drugs as options or they may feature more precise treatment than previous versions.

Although the CFR is declining, the impact of COVID-19 on the healthcare system cannot be ignored. With the emergence of new sub-lineages of omicron, clinicians need to pay more attention to potential disease manifestations and whether there are new high-risk groups. An important aspect of treatment is closely monitoring the antiviral action of existing and upcoming antivirals and neutralizing antibodies against new sub-lineages. Patients who may benefit from immunomodulators need to be identified and the duration of treatment needs to be determined more accurately. At the same time, clinicians need more information and guidance on managing the long-term effects of COVID-19.

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**Address correspondence to:*

Hongzhou Lu, Department of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Shenzhen Third People's Hospital, Shenzhen 518112, Guangdong, China. E-mail: luhongzhou@fudan.edu.cn

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