Interim Guideline for Clinical Management of SARS-CoV-2 Infection (5th edition)

Translation Editor-in-Chief: Prof. Wang-Huei Sheng, M.D. PhD
Translation Team Coordinator: Hsien-Wei Hsiao
Deputy Translation Team Coordinator: Yi-Hsuan Yen, Li-Tien Hsu
Translation Editor: Li-Tien Hsu
Translator: (arranged in Chinese alphabetical order)
Yen-Yi Sung, Yu-Chung Wu, Cheng-Yen Li, Chang-Yu Hsu, Chia-Yen Hsu, Shi-Tin Liang, Wei-Chieh Huang, Kung-You Pan, Jun-Hong Tsai, Yi-Hsuan Yen
Affiliation: Department of Medicine, National Taiwan University

Table of Contents

I Preface

Since December 2019, multiple cases of viral pneumonia have emerged in Wuhan, the capital of Hubei province, China. On January 7th, 2020, it was subsequently proven to be a novel coronavirus strain through viral subtype testing, and viral RNA genome sequencing was completed on January 10th. It was named as 2019 novel coronavirus (2019-nCoV) by the World Health Organization (WHO) on January 12th, 2020, which subsequently declared the outbreak a Public Health Emergency of International Concern (PHEIC) on January 30th, 2020. The International Committee on Taxonomy of Viruses (ICTV) then officially named 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on February 11th, 2020, whereas the WHO officially named the disease caused by SARS-CoV-2 as Coronavirus Disease 2019 (COVID-19).

The epidemic soon advanced to involve other Chinese provinces, while imported cases and secondary outbreaks were also reported in multiple countries. The first confirmed imported case in Taiwan was reported on January 21st, 2020. Although the epidemic slowed down in most Chinese provinces after implementing a series of control measures, cases increased significantly in Western and Middle Eastern countries. Meanwhile, imported cases from China also rose rapidly in Taiwan, leading to elevated risks of infections in community.

Given the absence of specific medication or vaccine to treat or prevent SARS-CoV-2 infection, along with very limited research literature on clinical diagnosis and treatment of COVID-19 worldwide, the WHO published a clinical management guideline for suspected SARS-CoV-2 infected cases on January 28th, 2020. The above WHO guideline was based on relevant published literature, including acute and critical illness patient care guidelines, management experience of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) patients, as well as expert advice from those who have treated patients with Middle East Respiratory Syndrome Coronavirus (MERS) or Severe Acute Respiratory Syndrome (SARS).

This guideline, published by Taiwan Centers for Disease Control (hereinafter referred to as Taiwan CDC), is based on the aforementioned WHO guideline (updated on March 13th, 2020, and latest international literature. It is intended to provide recommendations for clinicians involved in caring patients with suspected SARS-CoV-2 infection. It is not meant to replace clinical judgment or specialist consultation but rather to strengthen clinical management of these patients and to provide up-to-date guidance. Best practices for infection prevention and control (IPC), triage and optimized supportive treatment are also included.

As clinical evidence-based literatures of SARS-CoV-2 are continually updated, this guideline will also be revised on a regular basis. Please always refer to the latest version.

Remarks: The following symbols are used to flag interventions

V Do: the intervention is beneficial (strongly recommended) OR the intervention is a best practice statement.
X Don't: the intervention is known to be harmful.
! Consider: the intervention may be beneficial in selected patients (conditional recommendation) OR the risks and benefits should be evaluated on a case-by-case basis.

References:
Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected ─ Interim guidance 13 March 2020. WHO/2019-nCoV/clinical/2020.4

II Summary of clinical manifestations

As reported by limited retrospective case series, symptoms of patients with COVID-19 are not easily distinguishable from other infections. Most patients develop symptoms of fever, dry cough, fatigue, with a third presenting with shortness of breath. Other symptoms include myalgia, headache, sore throat, and diarrhea. Some cases also report abnormal sense of smell (anosmia) and taste (dysgeusia).

Current data suggest that the majority of patients present with mild symptoms or are asymptomatic, but near 14% of infected patients have severe symptoms which require hospitalization and oxygen therapy, while 5% require intensive care. The median age of infected patients is around 50, while half of the infected patients carry underlying diseases. There are few cases of children infection, who are mostly contacts of confirmed adult patients or part of a family cluster. Children mostly present with mild symptoms or are asymptomatic, and recover within 1 to 2 weeks after symptoms onset.

Routine blood tests may reveal normal or decreased white blood cell counts and lymphocytopenia, while prothrombin time prolongation and elevated lactate dehydrogenase (LDH) may also be present. Although most cases are mild, some present with more severe respiratory conditions like pneumonia, where infiltration on chest X-ray (CXR) and ground glass opacities (GGO) on computed tomography (CT) can be seen, mostly with bilateral lesions. Studies of CT image evolution throughout the disease course suggest that CT changes could be observed even among asymptomatic patients. The most drastic changes on CT appear about 8 to 14 days after symptoms onset, in accordance with a median time of 10 days from the onset of symptoms to intensive care unit (ICU) admission as reported by other studies.

However, these CT patterns of COVID-19 such as GGO and lung consolidation lack specificity. Despite evident interstitial change during the later course of the disease, sequelae of pulmonary fibrosis has yet to be confirmed.

It has been reported that the patient's condition may deteriorate in the second week after initial symptom onset. A report has shown that shortness of breath develops in half of the patients on the 8th day (range: 5~13 days) after initial symptoms onset. Approximately one-third of infected patients had progressed to acute respiratory distress syndrome (ARDS), while 20%~30% require intensive care. The latter typically involves patients with chronic diseases including diabetes mellitus, hypertension, and cardiovascular disease. Complications of arrhythmia and shock may also appear in severe cases, while acute cardiac injury and acute kidney injury have also been reported. The mortality rate is as high as 10% among inpatients with pneumonia. However, the above estimation may be updated when more clinical evidence and epidemiology data are available. A study comparing the characteristics of clinically severe patients (including ICU admission/use of ventilator/mortality) with other patients indicates that the former group tends to be of older age (63 vs 46 years old), with higher rates of mortality (22.4% vs 0%), presence of underlying disease (58.2% vs 21.5%), and CXR abnormality (76.9% vs 56.2%). However, the proportion of abnormal CT imaging are similar (87.7% vs 86.1%). Another study has demonstrated age, sequential organ failure assessment (SOFA) score, and D-dimer value upon admission as risk factors of inpatient mortality among COVID-19 patients.

References:

1. CDC. Interim Clinical Guidance for Management of Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) Infection. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
2. Chen N, Zhou M, Dong X, Qu J, Gong F. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Jan 30.
3. Wang, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. Published online February 7, 2020. https://jamanetwork.com/journals/jama/fullarticle/2761044
4. del Rio et al. 2019 Novel Coronavirus—Important Information for Clinicians. JAMA. Published online February 5, 2020. doi:10.1001/jama.2020.1490. https://jamanetwork.com/journals/jama/fullarticle/2760782
5. Song et al. Emerging Coronavirus 2019-nCoV Pneumonia. Radiology. 2020 Feb6:200274. https://pubs.rsna.org/doi/10.1148/radiol.2020200274
6. Shen et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus

infection in children: experts' consensus statement. https://www.ncbi.nlm.nih.gov/pubmed/32034659
7. Wei et al. Novel Coronavirus Infection in Hospitalized Infants Under 1 Year of Age in China. https://jamanetwork.com/journals/jama/fullarticle/2761659
8. Shi et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30086-4/fulltext
9. Guan et al. Clinical Characteristics of Coronavirus Disease 2019 in China NEJM. Published online February 28, 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa2002032
10. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. https://www.thelancet.com/pb-assets/Lancet/pdfs/S014067362305663.pdf

III. Screening and triage: early identification of patients with suspected COVID-19

✔Screening and triage: Screen and isolate all patients with suspected COVID-19 at first point of contact with the healthcare system (eg. emergency department or outpatient department/clinic). Consider COVID-19 as a possible etiology of patients with acute respiratory infection based on all relevant history of travel, occupation, animal contact, cluster (TOCC) as well as community epidemiological data. After triage, treat and isolate patients accordingly by disease severity.

Remarks:

According to WHO guidelines, clinical syndromes associated with COVID-19 are classified as mild, moderate, or severe, the latter including severe pneumonia, ARDS, sepsis, and septic shock.

Early identification of suspected patients allows for timely implementation of appropriate IPC measures, diagnostic testing, and subsequent isolation procedures. (For definition of suspected cases and positive contact history, please refer to Taiwan CDC “Recommendations for COVID-19 Case Definition, Specimen Collection, and Diagnostic Tests”. For decision algorithm of diagnostic testing and further management, please refer to Taiwan CDC “Proposed Workflow for Healthcare Facilities on Reporting Cases of COVID-19”.) Early identification of those with severe illness (see Table 1) allows for timely and effective supportive treatment as well as safe, rapid referral to intensive care units according to standard operating protocols.

Older patients and those with comorbidities, such as cardiovascular disease and diabetes mellitus, have increased risk of severe disease and should be monitored closely. Although hospitalization may not be required for those with mild illness from a purely clinical perspective, currently all COVID-19 patients must be hospitalized in isolation per Taiwan CDC guidelines due to public health considerations and prevention of community infection. These patients may be discharged only after reaching the discharge criteria for confirmed COVID-19 cases.

Table 1: WHO Classification on Clinical Symptoms Associated with COVID-19

Mild Illness	Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Rarely, patients may also present with diarrhea, nausea and vomiting. The elderly and immunosuppressed may present with atypical symptoms. Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events, such as dyspnea, fever, GI-symptoms or fatigue, may overlap with COVID-19 symptoms.
Pneumonia	Adult with pneumonia but no signs of severe pneumonia and no need for supplemental oxygen. Child with non-severe pneumonia who has cough or difficulty breathing + fast breathing. Fast breathing (in breaths/min) < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40, and no signs of severe pneumonia.
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 ≤ 93% on room air. Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO2 < 90%; severe respiratory distress (e.g. grunting, very severe chest wall collapse); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest wall collapse, fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40. While the diagnosis is made on clinical grounds; chest imaging may identify or exclude some pulmonary complications.
ARDS	Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms. Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.

	Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/edema if no risk factor present. Oxygenation impairment in adults: ● Mild ARDS: 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O, or non-ventilated) ● Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O, or non-ventilated) ● Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O, or non-ventilated) ● When PaO2 is not available, SpO2/FiO2 ≤ 315 suggests ARDS (including in non-ventilated patients). Oxygenation impairment in children: ● Bilevel (NIV or CPAP) ≥ 5 cmH2O: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264 ● Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 ● Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 ● Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3
Sepsis	Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. Children: suspected or proven infection and ≥ 2 aged based SIRS criteria (of which one must be abnormal temperature or white blood cell count).
Septic shock	Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. Children: any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental state; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or warm vasodilation

	combined with bounding pulse; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

Abbreviations:

CPAP continuous positive airway pressure

FiO2 fraction of inspired oxygen

OI Oxygenation Index

OSI Oxygenation Index

PaO2 partial pressure of oxygen

PEEP positive end-expiratory pressure

SIRS systemic inflammatory response syndrome

SpO2 oxygen saturation

NIV Non-invasive ventilation

IV. Immediate implementation of appropriate infection prevention and control (IPC) measures

✔Infection prevention and control (IPC) plays a key role in clinical care, and should be initiated at the point of entry (usually in Emergency Departments) of the patient to hospital. Standard precautions should always be routinely applied in all areas of healthcare facilities, which include hand hygiene, the use of personal protective equipment (PPE) to avoid direct contact with patients' blood, body fluids, secretions and non-intact skin, safe injection measures, safe medical waste management, cleaning and disinfection of the environment and equipment. Please refer to Taiwan CDC "Infection Prevention and Control (IPC) Guidelines for Healthcare Facilities in Response to COVID-19" for IPC measures when treating suspected patients with COVID-19.

V. Give supportive treatment as early as possible and monitor clinical conditions

✔Give supplemental oxygen therapy immediately to patients with respiratory distress, hypoxaemia or shock and target SpO2 ≥ 94%.

Remarks: Adults with red flag signs (absent of breathing, severe respiratory distress, central cyanosis, shock, coma, or convulsions) should receive immediate airway management and oxygen therapy to target SpO2 ≥ 94%. Initiate oxygen therapy at 5 L/min and titrate flow rate accordingly. Once the patient is stable, the target is ≥ 90% SpO2 for non-pregnant and ≥ 92–95% for pregnant patients. Children with red flag signs should receive oxygen therapy during resuscitation to target SpO2 ≥ 94%, while the target for children without emergency signs is SpO2 ≥ 90%. Meanwhile, all areas where patients with COVID-19 are cared for should be equipped with pulse oximeters, functioning oxygen systems and single-use oxygen-delivering interfaces (nasal cannula/prongs, simple face mask and non-rebreathing mask).

✔Employ conservative fluid management in patients with COVID-19 when there is no evidence of shock.

Remarks: Patients should be treated cautiously with intravenous fluids since aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation.

✔Give empiric antimicrobials/antivirals to treat all possible bacterial/viral infections for patients with severe manifestations. For patients with sepsis, administering appropriate empiric antimicrobials after initial patient assessment is suggested. Please refer to Taiwan Guidelines for the Management of Pneumonia (2018) for empiric treatment of pneumonia.

Remark: Although the patient may be suspected to have COVID-19, according to the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock, administering appropriate empiric antimicrobials within 1 hour of identification of sepsis is suggested. Empiric antibiotic treatment should be based on clinical diagnosis, including comprehensive evaluation of community-acquired

pneumonia, local epidemiology, antimicrobial susceptibility testing (AST) results, and treatment guidelines.

When there is ongoing local circulation of seasonal influenza, or when risk factors for novel influenza A infection (e.g. travel or avian contact history) are present, empiric antiviral therapy may be considered. Empiric antibacterial/antiviral therapy should nonetheless be de-escalated according to microbiological results and clinical assessments.

X Do not routinely give systemic corticosteroids for treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) except under special conditions.

Remark 1: Systemic corticosteroids and viral pneumonia

A systematic review of observational studies on SARS patients reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance) after corticosteroid administration. A systematic review of observational studies on influenza patients found higher risks of mortality and secondary infections related with corticosteroid use; however, the evidence was judged as very low to low quality due to confounding indications for corticosteroid. A subsequent study which addressed this limitation by adjusting for time-varying confounders found no effect on mortality. Finally, a recent study of MERS patients receiving corticosteroids employed a similar statistical approach and found no effect of corticosteroids on mortality while significantly delaying lower respiratory tract (LRT) MERS-CoV clearance. Given the lack of effectiveness and possible adverse effects, routine corticosteroids should be avoided unless they are indicated for another reason.

Remark 2: Systemic corticosteroids and sepsis

The Surviving Sepsis Campaign and several meta-analyses suggest that systemic corticosteroids can be considered for selected patients, such as those who are unable to restore hemodynamic stability despite adequate fluid resuscitation and vasopressor therapy; however, this recommendation is based on low-quality evidence. Therefore, if corticosteroids are administered for sepsis in patients with COVID-19, the potential downside of prolonged viral shedding time would require special attention. Potential complication of electrolyte imbalance should be closely monitored as well.

V Closely monitor patients with COVID-19 for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and respond immediately with supportive care interventions.

Remarks: For patients who develop severe manifestations of COVID-19, application of timely, effective, and safe supportive therapies is the cornerstone of treatment.

! Aerosol treatments such as Nebulizer should be avoided for treating patients with suspected or confirmed COVID-19. Dry-powder inhaler or Metered-dose inhaler can be utilized instead.

V Individualize treatment and assess prognosis for each patient after evaluating their comorbidities. Communicate effectively with the patient and family members regarding the management.

Remarks: During the treatment course of COVID-19 patients with severe illness, determine which chronic therapies should be continued or discontinued temporarily. Proactively communicate with the patient and family members and provide information on treatment and prognosis. Evaluate the patient's opinion and preference towards life-sustaining supportive treatments.

Reference

1. Chou CC, Shen CF, Chen SJ, Chen HM, Wang YC, Chang WS et al. Recommendations and guidelines for the treatment of pneumonia in Taiwan. J Microbiol Immunol Infect. 2019 Feb;52(1):172-199. doi: 10.1016/j.jmii.2018.11.004. PubMed PMID: 30612923

2. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017;43(3):304-77. Epub 2017/01/20. doi: 10.1007/s00134-017-4683-6. PubMed PMID: 28101605.

3. Lamontagne F, Rochwerg B, Lytvyn L, Guyatt GH, Moller MH, Annane D et al. Corticosteroid therapy for sepsis: a clinical practice guideline. BMJ. 2018;362:k3284. Epub 2018/08/12. doi: 10.1136/bmj.k3284. PubMed PMID: 30097460.

VI. Specimen collection for laboratory diagnosis

V Collect blood cultures for bacteria that cause pneumonia and sepsis before antimicrobial therapy, but antimicrobial therapy should not be delayed to collect blood cultures.

V Collect specimens from throat swab, expectorated sputum or lower respiratory tract aspirates, and serum following the Taiwan CDC "Recommendations for COVID-19 Case Definition, Specimen Collection, and Diagnostic Tests". Send the specimens to Taiwan CDC or designated laboratory facilities for SARS-CoV-2 testing, while packaging, handling, and shipment of the specimens should follow regulations regarding certifiable disease specimens.

Remarks: Specimen collection should be conducted under appropriate PPE use and within a negative pressure isolation room if feasible. Please refer to Taiwan CDC "Infection Prevention and Control (IPC) Guidelines for Healthcare Facilities in Response to COVID-19" for guidance on appropriate PPE use. When collecting upper respiratory tract (URT) specimens, do not sample the nostrils or tonsils. For patients with suspected COVID-19, especially those presenting with pneumonia or severe illness, a single URT specimen is insufficient to exclude SARS-CoV-2 infection. Lower respiratory tract (LRT) samples are more likely to be positive. Co-infections of other respiratory viruses have been found among SARS and MERS patients, and studies of COVID-19 patients have also demonstrated bacterial or fungal co-infections. Therefore, microbiological testing for other related pathogens is recommended for all patients with suspected SARS-CoV-2 infection.

V In hospitalized patients with confirmed COVID-19, repeat collection of URT (nasopharyngeal or throat swab) and LRT (expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage) samples to follow up on viral clearance. The frequency of specimen collection suggested by WHO is at least once every 2-4 days*. However, Taiwan's domestic experience and international studies have shown that URT samples can remain positive for over two weeks, and even longer for LRT samples, thus frequent sampling during early hospitalization is unnecessary. After the first negative result, collect specimens twice at an interval of 24 hours (waiting is unnecessary) until the release-from-isolation criteria are met*. As for antibody detection, acute-phase serum (within 1-5 days after symptom onset) should be obtained for confirmed cases. If a patient remains hospitalized 14-40 days after symptom onset, recovery-phase serum should be collected. Stool sampling should also be considered depending on clinical manifestations (e.g. diarrhea). Please refer to Table 2 for suggestions of other routine clinical examinations and follow-up frequencies.

***On February 24th, 2020, Taiwan's Expert Advisory Council revised the release-from-isolation criteria as "hospitalization in isolation until clinically recovered for at least 24 hours, with 3 consecutive negative tests of SARS-CoV-2 for respiratory tract samples (each at least 24 hours apart)."**

Table 2: Suggestion of routine examinations and follow-up frequencies for patients with COVID-19

	Upon admission	Once every four days, and recheck when necessary	Remarks
CBC/DC	V	V	
PT/aPTT	V		
D-dimer	V		
BUN	V	V	
Creatinine	V	V	
Na	V	V	
K	V	V	
AST	V	V	
ALT	V	V	
ALP	V	V	
Total bilirubin	V	V	
Albumin	V	V	
LDH	V	V	
Creatine kinase	V	V	
Myoglobin	V		If available
Glucose	V		
CRP	V	V	
ESR	V		
IL-6	V		If available
Serum Ferritin	V		
Procalcitonin	V		If available
Urine routine	V		
CXR	V	V	

VII. Management of acute respiratory distress syndrome (ARDS) in patients with COVID-19

V Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy, and provide timely advanced oxygen/ventilatory support.

Remarks: Patients may develop increased respiratory rate or hypoxemia even when oxygen is delivered via a simple face mask or non-rebreathing mask (flow rates of 10–15 L/min; FiO2 0.60–0.95). Hypoxemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation.

! High-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV) should only be used in selected patients and routine use is NOT recommended for both adult and pediatric patients. Experience from MERS-CoV cases suggests a high failure rate in patients who received NIV. Patients treated with either HFNO or NIV should be closely monitored for clinical deterioration.

Remarks: Patients receiving HFNO should be closely monitored and cared for by experienced personnel capable of endotracheal intubation, in case the patient does not improve or acutely deteriorates after a short period of time (about 1 hour). NIV is not recommended in hypoxemic respiratory failure (apart from cardiogenic pulmonary edema and post-operative respiratory failure) or pandemic viral illness (please refer to studies of SARS and pandemic influenza for further details). Risks associated with NIV use include delayed intubation, large tidal volume, and injurious transpulmonary pressure. Patients with hemodynamic instability, multiorgan failure, or altered level of consciousness should not receive NIV**.**

V Endotracheal intubation should be performed by a trained and experienced provider. Adopt infection control and safety precautions to avoid airborne or droplet transmission.

Massive viral droplets are generated during endotracheal intubation for patients with COVID-19. Close contact during the procedure exposes medical staff to very high risks of infection. Therefore, conduct the procedure with complete personal protective equipment (PPE). Endotracheal intubation should be performed by a well-trained, experienced provider and should be conducted in a negative pressure isolation room. Evaluate the risks of difficult intubation and notify the difficult airway response team beforehand. The team should prepare appropriate PPE and standby outside the isolation room, ready to assist in case of any difficult intubation.

Immediate endotracheal intubation is suggested when a patient develops respiratory failure due to desaturation or unstable vital signs. Appropriate medication should be administered to carry out rapid sequence intubation. Use a high flow oxygen delivery

system (non-rebreathing mask, NRM) for 5 minutes to perform pre-oxygenation for patients with spontaneous breathing, while Ambu-bagging is not suggested. Use video-assisted laryngoscope to assist endotracheal intubation. A closed system suction should be employed during mechanical ventilation after intubation is completed. If intra-hospital transport is required, plan the route well beforehand. Before transport, complete sputum and saliva suction and check for sufficient oxygen storage. Ensure the safety of pipelines and do NOT delay the transport.

Remarks: Patients with ARDS, especially young children or obese, pregnant individuals may desaturate quickly during intubation. Pre-oxygenate with 100% FiO2 for 5 minutes via a face mask with reservoir bag or bag-valve mask. Rapid sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation.

The following recommendations pertain to mechanically ventilated adult and pediatric patients with ARDS.

V Implement mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight, PBW) and lower inspiratory pressures (plateau pressure < 30 cmH2O).

Remarks for adults: This is a strong recommendation from a clinical guideline for patients with ARDS, and is suggested for patients with respiratory failure resulting from sepsis-induced indirect lung injury. The initial tidal volume is 6 mL/kg PBW; tidal volume up to 8 mL/kg PBW is allowed if unwanted side-effects occur (e.g. dyssynchrony, pH < 7.15). Permissive hypercapnia is acceptable. The use of deep sedatives may be required to control respiratory drive and achieve tidal volume targets.

Remarks for children: In children, the targeted plateau pressure is < 28 cmH2O and the targeted pH is 7.15–7.30. Tidal volumes should be adjusted based on disease severity: 3–6 mL/kg PBW if respiratory system compliance is poor, and 5–8 mL/kg PBW for preserved compliance.

V In adult patients with severe ARDS, prone ventilation for at least 12–16 hours per day is recommended.

Remarks: Application of prone ventilation is strongly recommended for adult patients and may be considered for pediatric patients. Human resources and expertise are required to perform the treatment safely.

V Employ conservative fluid management strategy in ARDS patients without tissue hypoperfusion.

Remarks: This is a strong advice. Its main effect is to shorten the duration of ventilator usage.

! For patients with moderate or severe ARDS, higher PEEP is suggested.

Remark 1: Advantages (reduce atelectrauma and improve alveolar recruitment) and relative risks (end-inspiration hyperinflation may lead to lung injury and higher pulmonary vascular resistance) should be taken into consideration when titrating PEEP. Please refer to other related instructions or guidelines for the adjustment strategy of PEEP based on the FiO2 required to keep SpO2. PEEP for children should not exceed 15 cm H2O.

Remarks 2: Measurements of recruitment maneuvers include: episodic high positive airway pressure (30–40 cm H2O), progressive increase in PEEP with fixed or high driving pressure. However, the benefits and risks should be evaluated with care. In a related clinical guideline based on meta-analysis of patient data from 3 randomized controlled trials, employing higher PEEP and recruitment maneuvers are conditionally recommended. However, another randomized controlled trial concluded that high PEEP combined with prolonged high-pressure recruitment maneuvers led to an inferior prognosis. Therefore, the authors advised against employing such ventilation strategy. Close monitoring of patients starting on higher PEEP or other recruitment maneuvers is advised in order to timely identify responsive cases and to discontinue the strategy in patients without significant improvement.

! For patients with moderate or severe ARDS (PaO2 / FiO2 < 150), continuous infusion of neuromuscular blocking agents should not be routinely used.

Remarks: An earlier trial found that this strategy improved survival of patients with severe ARDS (PaO2 / FiO2 < 150) without causing prominent muscle weakness. However, a larger trial recently revealed no significant difference in survival between the strategy of neuromuscular blocking agents with high PEEP and the strategy of mild sedation without neuromuscular blocking agents. In certain situations, continuous neuromuscular blocking agents for adult and pediatric patients with ARDS can still be considered. These include patients with ventilator dyssynchrony despite sedation, or refractory hypoxemia or hypercapnia.

! For patients with refractory hypoxemia despite lung-protective ventilation, the need for extracorporeal membrane oxygenation (ECMO) should be evaluated by an experienced medical team with relevant expertise.

Remarks: A randomized controlled trial of ECMO for patients with ARDS was discontinued because there was no significant difference in the 60-day survival rate between ECMO and standard medical managements (including prone position ventilation and usage of neuromuscular blocking agents). However, ECMO was associated with reduced risk of the composite outcome of mortality, and post hoc Bayesian analysis of the randomized controlled trial indicated that ECMO may reduce mortality rate under a series of antecedent hypotheses. In another cohort study of patients with MERS-CoV, ECMO resulted in reduced mortality rate when compared to conventional treatments. ECMO for suspected or confirmed cases of SARS-CoV-2 infection should be offered in healthcare facilities with sufficient ECMO expertise and experience which are capable of providing adequate IPC measures when treating patients with COVID-19.

X Avoid disconnecting the patient from the ventilator, which may lead to loss of PEEP and atelectasis.

V Closed suction system should be used when treating patients on invasive mechanical ventilation. To ensure intact connection between the endotracheal tube and filter, it is necessary to disconnect at the distal end between the high-efficiency filter (e.g., HEPA, HMEF) and the endotracheal tube when disconnecting (e.g., when transferring pipelines to a portable ventilator).

VIII Management of septic shock in patients with COVID-19

V Definition of septic shock in adults: when infection is suspected or confirmed AND vasopressors are required to maintain MAP ≥ 65 mmHg AND serum lactate ≥ 2 mmol / L, without hypovolemia.

V Definition of septic shock in children: any forms of hypotension (SBP< 5th percentile or > 2 standard deviations below average for age), or at least 2 of the following conditions: altered mental status; bradycardia or tachycardia (infant HR < 90 bpm or > 160 bpm, children HR < 70 bpm or > 150 bpm); prolonged capillary refill time (>2 seconds) or feeble pulses; tachypnea; skin mottling, petechiae, purpura or cold skin; elevated lactate; oliguria; hyperthermia or hypothermia. Please also refer to other guidelines of septic shock in adults or in children.

Remarks: When lactate level is unavailable, use blood pressure (eg. MAP) and clinical signs of perfusion to determine shock.

V During resuscitation for septic shock in adults, it is advised to give 250-500 mL isotonic crystalloid as rapid bolus within the first 15-30 minutes, and reassess signs of fluid overload after every bolus.

V During resuscitation for septic shock in children, it is advised to give 10-20 ml/ kg isotonic crystalloid as rapid bolus within the first 30-60 minutes, and reassess signs of fluid overload after every bolus.

! Fluid resuscitation may lead to volume overload, including respiratory failure. If a patient fails to respond to fluid resuscitation and develop signs of fluid overload (e.g., jugular vein engorgement, crackles on lung auscultation, pulmonary edema on imaging, or hepatomegaly in children), fluid administration should be reduced or discontinued.

Remark 1: Isotonic crystalloids include normal saline and Ringer's lactate

Remark 2: Reevaluate the need to repeat fluid resuscitation on the basis of improvements in clinical symptoms and perfusion targets (including adult MAP > 65 mmHg, adequate urine output, normal hemodynamics in extremities).

X DO NOT use hypotonic crystalloid, starches or gelatins for resuscitation

Remark: Starches may increase mortality rate and incidence of acute renal failure. Hypotonic crystalloid is not as effective as isotonic crystalloid for increasing blood volume.

V Timing of administering vasopressors in adults: If shock persists during or after fluid infusion, vasopressors should be given. Initial targets include MAP ≥ 65 mmHg and improvements in perfusion status.

V Timing of administering vasopressors in children:

1. **Clinical presentation of shock: altered mental status; bradycardia or tachycardia (infant HR < 90 bpm or > 160 bpm, children HR < 70 bpm or > 150 bpm); prolonged capillary refill time (>2 seconds) or feeble pulses; tachypnea; skin mottling, petechiae, purpura or cold skin; elevated lactate; oliguria persists after two repeated boluses; or**

2. **Blood pressure below age-appropriate standard values; or**

3. **Signs of fluid overload**

! Vasopressors should be administered through a central venous catheter with tightly controlled infusion rate.

! If signs of hypoperfusion and cardiac dysfunction persists despite reaching MAP ≥ 65 mmHg through fluid resuscitation and vasopressor, consider inotrope agents such as dobutamine.

Reference:

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Critical Care Medicine: March 2017 - Volume 45 - Issue 3 - p 486-552

IX Prevention of complications

V The following measures can be implemented to prevent complications related to severe illness (Table 3). These measures are based on relevant sepsis guidelines and feasible recommendations in other high-quality literature.

Table 3: Interventions to prevent complications

Expected effects	**Interventions**
Reduce duration of ventilator usage	● Daily assessment for readiness to breath spontaneously ● Minimize continuous sedation when feasible
Reduce incidence of ventilator-associated pneumonia (VAP)	● Oral intubation in adults and adolescent when feasible ● Elevate head-of-bed by 30-45 degrees ● Use closed suction system and routinely drain the condensate in catheter
Reduce incidence of catheter-related bloodstream infections (CRBSI)	● Daily assessment for catheter removal
Reduce incidence of pressure sore	● Turn the patients every 2 hours
Reduce incidence of stress ulcer and gastrointestinal bleeding	● Give early enteral nutrition (within 24-48 hours of admission) ● Administer H2 blocker or proton-pump inhibitors in patients with risk of gastrointestinal bleeding

X. Specific antiviral and other possible treatments for SARS-CoV-2

! There are currently no evidence from randomized controlled trials to recommend the use of any antiviral agents in treating patients with suspected/confirmed COVID-19.[1] Recommendations are largely based on previous clinical experiences and *in vitro/in vivo* trials on treating patients with SARS and MERS-CoV infections. Despite the lack of WHO-standardized treatment[2], multiple agents including antiviral agents (ribavirin, lopinavir/ritonavir, remdesivir), interferon(-α, -β), convalescent plasma ,and mono/polyclonal antibody were used[3,4]. Review of current evidence on the use of antiviral agents against SARS-CoV-2 is listed in Table 4.

! There are several ongoing clinical trials evaluating direct treatments for SARS-CoV-2, which includes: lopinavir/ritonavir combined with interferon-α (ChiCTR2000029308), lopinavir/ritonavir with arbidol (umifenovir) (NCT04252885), corticosteroid (NCT04244591), remdesivir (NCT04257656,NCT04252664), hydroxychloroquine (NCT04261517), convalescent plasma (NCT04292340). Four

drugs or combinations (remdesivir, lopinavir/ritonavir, lopinavir/ritonavir with interferon-β , and chloroquine or hydroxychloroquine) are also being tested in the multinational WHO SOLIDARITY trial[5].

! After detailed review of the clinical severity and transmission potential of COVID-19 cases, as well as potential risks and benefits, ethical issues of off-label drug use, and pharmacokinetic parameters of hydroxychloroquine, early administration of hydroxychloroquine may be considered after doctors' evaluation and informed consent. A 7-day treatment course is recommended:

- Adults: hydroxychloroquine 400mg BID D1 followed by 200 mg BID D2-7
- Pediatric dosage: hydroxychloroquine 10 mg/kg/dose BID followed by 5 mg/kg/dose BID D2-7. **DO NOT** give over 400mg in a single dose.
- Not recommended for pregnant patients or those with known allergy to the agent
- Special considerations:
    - Adverse effects including retinopathy, QT prolongation have been reported and should be closely monitored.
    - Cautious evaluation is necessary for prolonged use or higher doses.

V As new evidence on management of SARS-CoV-2 continues to emerge, treatment recommendations in this guideline would be revised accordingly.

V Concomitant drug usage should be taken into consideration when administering any antiviral agents, as drug-drug interactions are not uncommon among these medications.

V All non-approved treatments should only be used in clinical studies approved by ethics committees and closely monitored.

Table 4: Current evidence on specific antiviral agents against SARS-CoV-2

Agent	**Current evidence**
Ritonavir/lopinavir	● Molecular modeling of binding abilities of Ritonavir and Lopinavir to viral protease demonstrated potential therapeutic effect on SARS-CoV-2.[6] ● A randomized controlled trial revealed no difference in time to clinical improvement or 28-day mortality among patients with severe COVID-19 (SpO2<94%) receiving Ritonavir/lopinavir (n=99) or standard care (n=100). 13.8% of patients in the ritonavir/lopinavir group dropped out due to adverse effects. [7]
Remdesivir	● Inhibitory effects against the virus were shown in *in vitro* studies.[8] ● A case report demonstrated improvements in clinical conditions one day after receiving intravenous Remdesivir on day 7 of hospitalization.[9]
(Hydroxy)chloroquine	● *In vitro* studies of both chloroquine and hydroxychloroquine demonstrated inhibitory effects on the virus and immune-modulation as well.[8,10,11] ● Effective inhibitory concentration can be acheived when using hydroxychloroquine for post-exposure prophylaxis. ● Small-scale, non-randomized trials have suggested accelerated clearance of SARS-CoV-2 in those receiving hydroxychloroquine. [12]

Reference:

1. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected—Interim guidance. Updated March 13,2020. WHO/2019-nCoV/clinical/2020.4

2. Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected—Interim guidance. Updated January 2019. WHO/MERS/Clinical/15.1 Revision 1.

3. Momattin, H., Mohammed, K., Zumla, A., Memish, Z. A., & Al-Tawfiq, J. A. (2013). Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)–possible lessons from a systematic review of SARS-CoV therapy. *International Journal of Infectious Diseases*, *17*(10), e792-e798.

4. Momattin, H., Al-Ali, A. Y., & Al-Tawfiq, J. A. (2019). A Systematic Review of therapeutic agents for the treatment of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). *Travel medicine and infectious disease*, *30*, 9-18.

5. Thailand joins the WHO “Solidarity Trial”: global testing of effective treatments of COVID-19 across 8 countries – an aggressive effort to save lives from the pandemic. Who.int.

6. Lin, S., Shen, R., & Guo, X. (2020). Molecular Modeling Evaluation of the Binding Abilities of Ritonavir and Lopinavir to Wuhan Pneumonia Coronavirus Proteases. *bioRxiv*.

7. Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., ... & Li, X. (2020). A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine.*

8. Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., ... & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research*, *30*(3), 269-271.

9. Holshue, M. L., DeBolt, C., Lindquist, S., Lofy, K. H., Wiesman, J., Bruce, H., ... & Diaz, G. (2020). First case of 2019 novel coronavirus in the United States. *New England Journal of Medicine*.

10. Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., ... & Zhan, S. (2020). In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases*.

11. Zhou, D., Dai, S. M., & Tong, Q. (2020). COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *Journal of Antimicrobial Chemotherapy*.

12. Gautret, P., Lagier, J. C., Parola, P., Meddeb, L., Mailhe, M., Doudier, B., ... & Honoré, S. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-

19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*, 105949.

XI. Issues to consider among pregnant patients with COVID-19

V Pregnant patients with COVID-19 present with similar symptoms as other infected patients. Limited available data showed undetectable viral load in the amniotic fluid, cord blood, neonatal throat swab, or breast milk. Currently, no evidence exists to suggest the possibility of vertical transmission of SARS-CoV-2 if the mother is infected during the 3rd trimester.

V When treating pregnant patients with confirmed or suspected COVID-19 according to the aforementioned recommendations, physiological changes associated with pregnancy should be taken into consideration.

V For pregnant women who must to be isolated due to suspected or confirmed SARS-CoV-2 infection or positive contact history, comprehensive and multi-disciplinary care including obstetricians, neonatologists, and psychological support systems should be provided.

V There is currently no evidence of increased risk for pregnant patients with COVID-19 to develop severe complications or fetal distress. Once the patient recovers from COVID-19, routine prenatal and perinatal care should be provided.

V When adopting experimental treatment strategies outside of clinical trials, risk and benefit analysis on a case-by-case basis should be assessed in collaboration with obstetricians and ethics committees. Potential maternal benefit and fetal safety should be taken into consideration.

V For pregnant patients with confirmed COVID-19 at 24– 34 weeks of gestation and with risk of preterm delivery, systemic steroid for fetal lung maturation may be considered. Under such circumstances, fetal benefits may outweigh the maternal risks. Thorough discussion with the patient is warranted and decisions should be made on an individual basis.

V In the event of emergency delivery or abortion, the following factors should be taken into consideration: gestational week, maternal clinical condition, fetal stability. Consult obstetricians, neonatologists, and intensive care physicians (if needed).

Reference

1.Chen, H., Guo, J., Wang, C., Luo, F., Yu, X., Zhang, W., ... & Liao, J. (2020). Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *The Lancet*, *395*(10226), 809-815.

2. Rasmussen, S. A., Smulian, J. C., Lednicky, J. A., Wen, T. S., & Jamieson, D. J. (2020). Coronavirus Disease 2019 (COVID-19) and Pregnancy: What obstetricians need to know. *American journal of obstetrics and gynecology*.

3. Lu, Q., & Shi, Y. (2020). Coronavirus disease (COVID‐19) and neonate: What neonatologist need to know. *Journal of medical virology*.

XII. Issues to consider among mothers with COVID-19 and neonates

V Currently, no evidence exists to suggest the possibility of vertical transmission of SARS-CoV-2 if the mother is infected during the 3rd trimester. However, direct contact between confirmed cases and their newborn child could result in neonate SARS-CoV-2 infection.

! To reduce the risk of aforementioned SARS-CoV-2 transmission, temporary separation of the neonate from his/her mother with confirmed or suspected COVID-19 is advised, until the release-from-isolation criteria are met. Thorough discussion with the patient beforehand is necessary.

Reference

1.Interim Considerations for Infection Prevention and Control of Coronavirus Disease 2019 (COVID-19) in Inpatient Obstetric Healthcare Settings. *Centers for Disease Control and Prevention*