

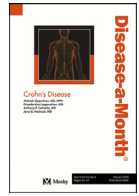


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Disease-a-Month

journal homepage: www.elsevier.com/locate/disamonth

COVID-19 medical management including World Health Organization (WHO) suggested management strategies

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Intro thoughts

We recognize that ongoing research, regional variation in treatment experiences, evolving information on new therapeutics, or more optimal approaches to utilizing current interventions continues to be part of the COVID-19 response. It is not a static knowledge base. Additionally, owing to differences in infrastructure, population density, and resources, medical responses to COVID-19, as with other public health threats reflects regional variability in medical care, the following section is an excerpt from the 05/20 World Health Organization Interim Medical Guidance <https://www.who.int/publications/i/item/clinical-management-of-covid-19> as general guidance for the purpose of providing basic foundation of approaches to COVID-19.

Of note insights and comments from *Disease a Month* authors are preceded by (**).

Please note: References listed at the end of this section are based upon the original WHO document, and pertain to information abstracted from their guidance document. The reference list is truncated to reflect only those information sources referred to in the WHO document, and that are noted in the following portions of the guidance document included in this review. For the entire document, and complete reference list which applies to sections omitted from the WHO document please visit <https://www.who.int/publications/i/item/clinical-management-of-covid-19>

Interim medical guidance/World Health Organization WHO – COVID-19

From <https://www.who.int/publications/i/item/clinical-management-of-covid-19>

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<https://doi.org/10.1016/j.disamonth.2020.101068>

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The following is abstracted from World Health Organization Interim Medical Guidance 05/27/20. The reader is referred to www.who.int for updates on COVID-19

Case identification COVID – 19 (World Health Organization)

Anyone suspected of COVID – 19 based upon exposure to persons with known infection, or symptoms consistent with infection, should undergo careful screening, including laboratory testing.

WHO guidance recommendation

“We recommend screening all persons at the first point of contact with the health system in order to identify individuals that have suspected or confirmed COVID-19.” These screening protocols should be at all health access points and during contact tracing activities.

Screening

**In review of WHO guidance it is important to recognize screening may need to be adapted to younger or older populations, as well as those for whom English is not a first language. Clinicians should be aware of the underlying physiological, medical, psychiatric, and pharmacological history of patients presenting for COVID-19 screening and adjust accordingly. This includes their cognitive capacity. Not always easy in overcrowded, shorthanded clinical situations, but essential nevertheless.

Symptoms

According to WHO guidance, persons with symptoms that meet the case definition for *suspected* COVID-19 enter into the COVID-19 care pathway and should immediately be given a medical mask and directed to a single room. If a single room is not possible, then group patients with similar clinical diagnosis and based on epidemiological risk factors, with a spatial separation. Suspected cases should not be cohorted together with confirmed cases.

**Clinicians should be alert to variations in clinical presentation depending upon patient age, and underlying comorbid conditions previous to suspected COVID-19 infection. The physiologic, pathophysiologic, and cognitive-psych response and capacity can vary significantly across patients.

**Special populations to consider include the elderly, children, women who are pregnant, persons with disabling mental or physical illnesses, and communications impaired persons.

**Elderly physiology – depending upon a variety of host factors, may have suppressed immune systems compared with younger patients. Also this demographic may present with varying levels of hearing, or cognitive loss, as well as delirium. This can be confounding since some older patients may have Alzheimer’s or other cognitive limiting disease process, or have medications prescribed to them for various comorbid conditions, which can cause some loss of intellectual function. Moreover physiologically it is well known that aging can blunt the febrile response, such that the absence of fever^{16–18} should not automatically dissuade the clinician from considering COVID-19 or other pathogen mediated infection.

Consider also persons who are immunosuppressed – by disease process or through medical intervention such as biologic disease modifiers for various inflammatory illnesses. These persons may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, GI complaints, including diarrhea and/or loss of appetite.

**As discussed earlier, the presenting symptoms of children may or may not fully align with the robust clinical data describing the adult experience with COVID-19. And, depending upon the age of the child, cognitive limitations, as well as underlying comorbidities and medications can add to the challenge of identifying potential COVID-19 cases in this population. It is best to err on the side of caution, and utilize COVID-19 laboratory testing.

****Important Consideration in initial identification/management**

Although many health care facilities (HCF) are imposing significant contact restrictions on who can accompany a patient suspected of COVID-19, or any other illness/injury upon presentation to HCF, special accommodation should be given to caregivers, especially those who have created a sense of routine and calm in patients who may not be capable of understanding the medical environment and change in routine they find themselves. In spite of COVID-19, we as health care professionals must treat the patient with the utmost care and caring, mindful of infection control, but adaptable to best serve the needs of those we treat. Summarily excluding potential sources of assistance – to us as well as the patient – may not serve the best interest of our patient. A case by case approach should be considered in special circumstances. An example of this is the elderly patient with dementia accompanied by a spouse and highly engaged children. With proper infection control precautions the needs of the patient, and protecting the HCF can be accommodated.

WHO Questionnaires –

Utilize readily understood screening questions based on the WHO case definition.

Co-infection

WHO suggests as part of screening, especially in areas with other endemic infections that cause fever, such as malaria, dengue, tuberculosis (TB), and other pathogen mediated illness, febrile patients should be tested as per routine protocols,¹⁹⁻²¹ irrespective of the presence of respiratory signs and symptoms. Co-infection with COVID-19 may coexist.

Long-term care facilities (LTCF)

Large outbreaks have, and continue to be observed in long-term care facilities (LTCFs).¹⁷ The COVID-19 care pathway should be activated for all residents of LTCFs who are contacts of a confirmed case in that LTCF. Immediate isolation, testing and treatment should be provided as needed. The priority for these settings is to ensure the well-being of residents and protect health care workers. Rapid clinical management is essential. Screening visitors for COVID-19 should be a policy, and affording protections to these populations is critically important.^{22,23}

Based upon World Health Organization guidance the following are three categories of COVID-19 possible patients. These include:

- Suspect cases referred to as “persons or patients under investigation” (PUIs) in some contexts.
- Probable cases are suspect cases for whom testing for SARS-CoV-2 is inconclusive or not available.
- Confirmed cases are persons with laboratory confirmation of COVID-19.

WHO recommends the following Transmission Precaution management strategies:

- All persons with suspected, probable or confirmed COVID-19 should be immediately isolated to contain virus transmission. See for IPC considerations in cohorting suspect, probable and confirmed cases separately.
- Considerations for co-infections and/or chronic diseases must be made within the COVID-19 care pathway.

- All suspect cases should be tested to determine if they are a **confirmed** case. Until proven negative, all suspected cases should remain in the COVID-19 care pathway. If testing is not available, the person becomes a probable case (based on clinical suspicions) and should be cared for in the COVID-19 pathway.

WHO suggests discontinuation of transmission precaution containment strategies with the following criteria:

- Symptomatic patients
 - 10 days after symptom onset, plus at least 3 days without symptoms (without fever and respiratory symptoms). Of note other guidance suggests at least 14 days
- Asymptomatic patients
 - 10 days after test positive. (If patient remains asymptomatic. If symptoms develop, reevaluation and containment must be initiated).

Caveats

WHO cautions there are limited published and pre-published reports referable to estimates on viral shedding of up to 9 days for mild patients and up to 20 days in hospitalized patients. Moreover they note patients can remain consistently polymerase chain reaction (PCR) positive for many weeks, or even test PCR positive after days/weeks of a negative test.

Moreover their clinical pathway refers infers following each patient until outcome, including full recovery. Discharge criteria from clinical care need to take into account the patient's condition, disease experience and other factors.

WHO counsels *"release from the COVID-19 care pathway is not the same as clinical discharge from a facility or from one ward to another. For example, some patients may still require ongoing rehabilitation, or other aspects of care, beyond release from the COVID-19 care pathway, based on clinical needs in the COVID-19 care pathway. If release from the COVID-19 care pathway coincides with clinical discharge, then several clinical considerations, such as medication reconciliation, plan for follow up with clinical provider in place, review of routine immunization status, among others, should be taken into account."*

COVID – 19 clinical manifestations

General overview

**The signs and symptoms associated with COVID-19 can be multiple and varied depending upon host and viral influences. Although COVID-19 was identified as, and remains a highly pathogenic respiratory virus, causing a wide range of pulmonary illness – from mild symptoms to frank respiratory failure, extrapulmonary illness is possible, and present in a not insignificant proportion of advance stage, severe illness.

WHO guidance

Common symptoms reported at the onset of illness include **fatigue, cough, and fever**. As symptoms progress in more severely ill patients, dry cough, dyspnea, and fever progress, and these are consistent with chest CT findings of ground glass opacity, often bilateral, and other pulmonary findings, including progressive decline in oxygen saturation. The pathophysiology of progressive lung damage is complex, including alveolar damage, and inflammation.

**As discussed earlier, symptoms start to appear after the incubation period (average 5 – 6 days, range 2 – 14 with outliers possible), and the time from symptoms to death was between 6

– 41 days with a 14 day average, in patients with severe disease. This time may be shorter with patients over 70 years of age compared to younger patients.

Among the possible extrapulmonary systems involved in COVID-19, cardiovascular involvement seems well described. But it is worth noting COVID-19 is also associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningo-encephalitis, impaired sense of smell or taste anxiety, depression and sleep problems. These can occur during initial symptoms (loss of smell or taste), or in patients with moderate or more severe illness. Moreover, as noted earlier, underlying comorbidities may make the patient more susceptible to COVID-19 pulmonary and extrapulmonary effects.

Of note, according to World Health Organization guidance documents, neurological manifestations have been reported even without respiratory symptoms. Anxiety and depression appear to be common in persons hospitalized for COVID-19, with a report describing a hospitalized cohort from Wuhan, China, revealing 34% experienced symptoms consistent with anxiety and 28% with symptoms of depression.⁴ An observational case series from France revealed 65% of a cohort infected with COVID-19 in intensive care units (ICUs) demonstrated signs of confusion or delirium.⁵ Also in that report, 69% experienced agitation.⁵ Although some of these are associated with ICU medical care in general, and a response by some elderly hospitalized patients in general, nevertheless they may portend severe neurological infection and should be addressed. Of note, delirium has been associated with an increased risk of mortality persons infected with COVID-19.⁶ Moreover, there have been multiple cases series from multiple nations raising concern about acute cerebrovascular disease, which includes both ischemic and haemorrhagic type strokes, based on a variety of case series from China, France, the Netherlands, and the United States.^{4,5,7,8} Case reports of Guillain-Barré syndrome and meningo-encephalitis among people with COVID-19 have also been reported.^{9,10}

Special populations

According to WHO, and numerous other sources from the United States and internationally, compared with information relative to adult populations, there is significantly less available describing the clinical presentation of COVID-19 in more specific subpopulations, as well as children and women who are pregnant. There are few data available describing significant differences between the clinical manifestations of COVID-19 in women who are pregnant, and non-pregnant adults of reproductive age.

**Certain signs and symptoms, including fatigue, may be due to physiologic adaptations associated with pregnancy, medications, or underlying comorbidities, as well as to COVID-19. Also adverse events associated with pregnancy or other underlying NCDs or infectious diseases such as malaria, may overlap with symptoms of COVID-19, and confound treatment.²⁶

Children infected with COVID-19 do not seem to have reported fever or cough with the same frequency as adults based on the still limited information available.¹⁵ In general the clinical manifestations have been reported as milder in children when compared with what adults experience.^{11–13} Identifying trends in subpopulations, such as infants has been confounded by the relatively few cases reported, but from the available evidence infants also seem to experience more mild illness than adults.¹² Nevertheless, the astute clinician should be vigilant with any infant or child suspected of COVID-19 infection. This is supported by a recent report describing a hyperinflammatory syndrome, currently termed *multisystem inflammatory syndrome temporally associated with COVID-19 in children and adolescents*, which is appearing in children infected with COVID-19. This inflammatory syndrome has led to multisystem organ failure and shock.¹⁴

Of note, among 345 children with laboratory-confirmed COVID-19 and complete information about their underlying conditions, 23% had a preexisting comorbid condition, with chronic lung disease (including asthma), cardiovascular disease and immunosuppression most commonly reported.¹⁵ With children also receiving various immune modulating treatments for various comorbidities, and the prevalence of respiratory disease in both the general population, and among

persons living in environmentally challenged areas, these influencers of health need to be considered in children infected with COVID-19.

Clinical testing COVID-19

In the last several months various testing strategies, and laboratory tests have been developed.

The following guidance from the World Health Organization (WHO), followed in another section by recommendations by the Centers for Disease Control and Prevention (CDC) are provided for information, and is current at the time of publication. However we recommend the clinician refer to the respective websites of WHO and CDC, as well as their hospital laboratorian, state or regional public health departments for real time guidance for the testing of COVID-19.

WHO guidance – laboratory specimens

WHO guidance referable to specimen collection, processing and laboratory testing can be found in the document *WHO Laboratory testing strategy recommendations for COVID-19*.²⁷

The reader is also referred to the **CDC Testing Section** in this article.

For all suspected cases:

- Collect upper respiratory tract (URT) specimens (nasopharyngeal and oropharyngeal) for testing by reverse transcription polymerase chain reaction (RT-PCR)
- Where clinical suspicion remains and URT specimens are negative, collect specimens from the lower respiratory tract (LRT) when readily available (expectorated sputum, or endotracheal aspirate/bronchoalveolar lavage in ventilated patient).
- In addition, testing for other respiratory viruses and bacteria should be considered when clinically indicated.

Guidance:

- Appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens).
- For URT samples –
 - use viral swabs (sterile Dacron or rayon, not cotton) and viral transport media.
 - Do not sample the nostrils or tonsils.
 - In a patient with suspected COVID-19, especially with pneumonia or severe illness, a single negative URT sample does not exclude the diagnosis, and additional URT and LRT samples are recommended.
- LRT (vs URT)
 - samples are more likely to be positive and for a longer period.
 - Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients).
 - Sputum induction should be avoided owing to increased risk of aerosol transmission.
- In hospitalized patients with confirmed COVID-19, repeated URT and LRT samples can be collected, as clinically indicated, but are no longer indicated for release from COVID-19 precautions. The frequency of specimen collection will depend on local epidemic characteristics and resources.

Thoughts to consider - WHO

- Depending on local epidemiology and clinical symptoms, test for other potential etiologies (e.g. malaria, dengue fever, typhoid fever) as appropriate.

- Tickborne illnesses and other vector borne disease should be considered, especially as the emergence of other seasonal illnesses are possible
- Dual infections with other respiratory infections (viral, bacterial and fungal) have been found in COVID-19 patients.
- A positive test for a non-COVID-19 pathogen **does not rule out** COVID-19, or vice versa.
 - At this stage, detailed microbiologic studies are needed in all suspected cases.
 - Both URT and LRT specimens can be tested for other respiratory viruses
 - These include influenza A and B (including zoonotic influenza A), respiratory syncytial virus, para-influenza viruses, rhinoviruses, adenoviruses, enteroviruses (e.g. EVD68), human metapneumovirus and endemic human coronaviruses (i.e. HKU1, OC43, NL63, and 229E).
- LRT specimens can also be tested for bacterial pathogens, including *Legionella pneumophila*.

Medical management general considerations (WHO)

The rapidity with which COVID-19 spread, the variation in presentations from mild illness to severe pulmonary disease and extrapulmonary multisystem organ dysfunction, in the context of no specific antiviral therapies against coronaviruses, led to multiple treatment approaches attempted, in addition to aggressive symptomatic and supportive care.

For example, nebulized interferons, and a variety of repurposed antiviral medications, as well as broad spectrum antibiotics, and convalescent plasma were utilized. Among the various medications trialed, hydroxychloroquine, and remdesivir, as well as a limited number of other repurposed antiviral therapeutics showed varying degrees of promise, depending upon the clinical situation and patient populations. These are described in the **THERAPEUTICS Section.

Other interventions such as hyperbaric oxygen, extracorporeal membrane oxygenation (ECMO), nebulization of medications usually parenterally administered, and other approaches are being trialed, with varied results ranging from increased mortality to clinical improvement.

Convalescent plasma - the blood plasma isolated from COVID-19 survivors is processed and injected into patients - this therapy has been clinically beneficial with rapid recovery reported among recipients.

The FDA approved to treat COVID-19, under emergency use authorization, is the antiviral Remdesivir.

**As of this writing, in the absence of clinical trial participation, the mainstay of medical treatment is symptomatic and supportive care (which is discussed shortly). Recognizing tertiary care facilities may have more resources for the most severely affected COVID-19 patient, early collaboration, as well as patient transfer to these locations is encouraged.

Specific medical management based on severity – WHO recommendations

<https://www.who.int/publications/i/item/clinical-management-of-covid-19>

Management of mild COVID-19 – symptomatic treatment

Patients with mild disease may present to an emergency unit, primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine.

WHO recommend that patients with suspected or confirmed mild COVID-19 be isolated to contain virus transmission according to the established COVID-19 care pathway. This can be done at a designated COVID-19 health facility, community facility or at home (self-isolation).

Remarks:

In areas with other endemic infections that cause fever (such as malaria, dengue, etc.), febrile patients should be tested and treated for those endemic infections per routine protocols,^{19,20} irrespective of the presence of respiratory signs and symptoms. Co-infection with COVID-19 may occur.

The decision to monitor a suspect case with mild COVID-19 in a health facility, community facility or home should be made on a case-by-case basis based on the local COVID-19 care pathway. Additionally, this decision may depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and conditions at home, including the presence of vulnerable persons in the household.

If managed at home in self-isolation, refer to WHO guidance on *Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts*.

WHO recommend patients with mild COVID-19 be given symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration.

Counsel patients with mild COVID-19 about signs and symptoms of complications (examples include light headedness, difficulty breathing, chest pain, dehydration) that should prompt urgent care.

Remarks:

Patients with high risk factors for severe illness should be monitored closely, given the possible risk of deterioration.

If patients develop any worsening symptoms such as light headedness, difficulty breathing, chest pain, dehydration, etc., they should seek urgent care.

Children with mild symptoms

Caregivers of children with mild COVID-19 should monitor for signs and symptoms of clinical deterioration requiring urgent re-evaluation. These include

- Difficulty breathing/fast or shallow breathing
 - for infants: grunting, inability to breastfeed,
- Blue lips or face,
- Chest pain or pressure,
- New confusion,
- Inability to awaken/not interacting when awake,
- Inability to drink or keep down any liquids.

Consider alternative delivery platforms such as home-based, phone, telemedicine or community outreach teams to assist with monitoring.

Management of moderate COVID-19 disease – pneumonia treatment

Patients with moderate disease may present to an emergency unit or primary care/outpatient department, or be encountered during community outreach activities, such as home visits or by telemedicine. See for definition of pneumonia.

WHO recommend that patients with suspected or confirmed moderate COVID-19 (pneumonia) be isolated to contain virus transmission. Patients with moderate illness may or may not require emergency interventions or hospitalization (case by case, based also on underlying risk factors); however, isolation is necessary for all suspect or confirmed cases.

- The location of isolation will depend on the established COVID-19 care pathway and can be done at a health facility, community facility or at home.

- The decision of location should be made on a case-by-case basis and will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and conditions at home, including the presence of vulnerable persons in the household.
- For patients at high risk for deterioration, isolation in hospital is preferred.

Remarks:

In areas with other endemic infections that cause fever (such as malaria, dengue, etc.), febrile patients should be tested and treated for those endemic infections per routine protocols,^{19–21} irrespective of the presence of respiratory signs and symptoms. Co-infection with COVID-19 may occur.

WHO recommendation for patients with suspected or confirmed moderate COVID-19, that antibiotics should not be routinely prescribed unless there is clinical suspicion of a bacterial infection.

WHO Remarks:

Few patients with COVID-19 experience a secondary bacterial infection. A recent systematic review of patients hospitalized with COVID-19 reported only 8% were reported as experiencing bacterial/fungal co-infection during hospital admission.³⁰

Consider in older people, particularly those in LTCFs, and children < 5 years of age, to provide empiric antibiotic treatment for possible pneumonia.^{28,29} As these patients are not hospitalized, treatment with Access antibiotics (such as co-amoxicillin) is adequate, instead of broad-spectrum antibiotics (Watch and Reserve antibiotics).³¹

WHO recommend close monitoring of patients with moderate COVID-19 for signs or symptoms of disease progression. Provision of mechanisms for close follow up in case of need of escalation of medical care should be available.

Remarks:

For patients being treated at home, counsel regarding signs and symptoms of complications should be provided to patients and caregivers. These include:

- Difficulty breathing,
- Chest pain

If patient develops any of these symptoms, they should seek urgent care.

WHO Commentary - At this time, there is no evidence to guide the use of pulse oximeters in home settings. Consider alternative delivery platforms such as home-based, phone, telemedicine or community outreach teams to assist with monitoring.

For hospitalized patients, regularly monitor vital signs (including pulse oximetry) and, where possible, utilize medical early warning scores (e.g. NEWS2, PEWS) that facilitate early recognition and escalation of treatment of the deteriorating patient.³²

Management of severe COVID-19: severe pneumonia treatment

All areas where severe patients may be cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, Venturi mask, and mask with reservoir bag).

Remarks:

This includes areas in any part of health facilities, including emergency units, critical care units, primary care/outpatient clinics, as well as pre-hospital settings and ad hoc community facilities that may receive patients with severe COVID-19. See WHO *Oxygen sources and distribution for COVID-19 treatment centres*.³³

WHO recommend immediate administration of supplemental oxygen therapy to any patient with:

- Emergency signs
 - Obstructed or absent breathing
 - Severe respiratory distress
 - Central cyanosis
 - Shock
 - Coma
 - Convulsions
- Any patient without emergency signs but with $\text{SpO}_2 \leq 90\%$.

Remarks:

Adults with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target $\text{SpO}_2 \geq 94\%$.^{24,34}

Once the patient is stable

- Target $>90\%$ SpO_2 in non-pregnant adults
- $\geq 92\text{--}95\%$ in pregnant women.

Deliver oxygen flow rates using appropriate delivery devices (e.g. use nasal cannula for rates up to 5L/min; Venturi mask for flow rates 6–10 L/min; and face mask with reservoir bag for flow rates 10–15 L/min).

For more details about oxygen titration, refer to the WHO *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation*.²⁵

Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive emergency airway management and oxygen therapy during resuscitation to target $\text{SpO}_2 \geq 94\%$.^{24,34,35} Once patient is stable, **the target is $> 90\%$ SpO_2** .³⁵

Use of nasal prongs or nasal cannula is preferred in young children, as they may be better tolerated.

In adults, techniques such as positioning, e.g. high supported sitting, may help to optimize oxygenation, ease breathlessness and reduce energy expenditure.³⁶ Prone position for awake, spontaneously breathing patients may also improve oxygenation and the ventilation/perfusion ratio, but evidence is lacking and should be done under clinical trial protocol to assess efficacy and safety.

Adult patients with evidence of increased secretion production, secretion retention, and/or weak cough, airway clearance management may assist with secretion clearance. Techniques include gravity-assisted drainage and active cycles of breathing technique.

WHO Caveat: Devices including mechanical insufflation-exsufflation and inspiratory positive pressure breathing should be avoided where possible. Implementation of techniques should be tailored to the individual patient and follow available guidelines.³⁶

Closely monitor patients for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock, and respond immediately with supportive care interventions.

Remarks:

Patients hospitalized with COVID-19 require regular monitoring of vital signs (including pulse oximetry) and, where possible, utilization of medical early warning scores (e.g. NEWS2, PEWS) that facilitate early recognition and escalation of treatment of the deteriorating patient.³²

Hematology and biochemistry laboratory testing and electrocardiogram and chest imaging should be performed at admission and as clinically indicated to monitor for complications, such as acute respiratory distress syndrome (ARDS) and acute liver injury, acute kidney injury, acute cardiac injury, disseminated intravascular coagulation (DIC), and/or shock.

Application of timely, effective and safe supportive therapies is the cornerstone of therapy for patients who develop severe manifestations of COVID-19.

Monitor patients with COVID-19 for signs or symptoms suggestive of venous or arterial thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism or acute coro-

nary syndrome, and proceed according to hospital protocols for diagnosis (such as laboratory tests and/or imaging), and further management.

Special population – pregnant woman

After resuscitation and stabilization of the pregnant woman, fetal well-being should be monitored. The frequency of fetal heart rate observations should be individualized based on gestational age, maternal clinical status (e.g. hypoxia) and fetal conditions.

Use cautious fluid management in patients with COVID-19 without tissue hypoperfusion and fluid responsiveness.

Remark:

Patients with COVID-19 should be treated cautiously with intravenous fluids; aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation.³⁷ This applies to both children and adults.

ARDS

The mortality in hospitalized and critically ill patients has varied substantially in different case series throughout the pandemic. The following recommendations are aligned with current international standards for management of all cause ARDS.^{2,45,49,53}

The following recommendations pertain to adult and pediatric patients with mild ARDS who are treated with non-invasive or high-flow nasal oxygen (HFNO) systems.

In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) may be used. Refer to definitions of mild, moderate and severe ARDS.

Remarks:

Patients with hypoxemic respiratory failure and hemodynamic instability, multisystem organ failure or abnormal mental status should not receive HFNO or NIV in place of other options such as invasive ventilation.

Patients receiving a trial of HFNO or NIV should be in a monitored setting and cared for by personnel experienced with HFNO and/or NIV and capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 h). Intubation should not be delayed if the patient acutely deteriorates or does not improve after a short trial.

Adult HFNO systems can deliver 60 L/min of gas flow and FiO₂ up to 1.0. Paediatric circuits generally only handle up to 25 L/min, and many children will require an adult circuit to deliver adequate flow. When considering delivering HFNO or NIV outside the usual care settings, evaluating oxygen capacity is important to ensure the higher flow rates required for these devices can be maintained. See WHO *Oxygen sources and distribution for COVID-19 treatment centres*.³³

Because of uncertainty around the potential for aerosolization, HFNO, NIV, including bubble CPAP, should be used with airborne precautions until further evaluation of safety can be completed. If these interventions are performed outside of private rooms in ICUs with appropriate ventilation systems installed, then cohorting of patients requiring these interventions in designated wards will facilitate the implementation of airborne precautions, ensuring all staff entering wear appropriate PPE and adequate environmental ventilation is ensured.

Compared with standard oxygen therapy, HFNO may reduce the need for intubation.³⁸ Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary edema), hemodynamic instability, multi-organ failure or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with

mild-moderate and non-worsening hypercapnia.^{38,39} Evidence-based guidelines on HFNO do not exist, and reports on HFNO in patients infected with other coronaviruses are limited.³⁹

NIV guidelines make no recommendation on use in hypoxemic respiratory failure (apart from cardiogenic pulmonary edema, postoperative respiratory failure and early NIV for immunocompromised patients) or pandemic viral illness (referring to studies of SARS and pandemic influenza).³⁸ Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate in patients with other viral infections such as MERS-CoV who receive NIV.⁴⁰

In situations where mechanical ventilation might not be available, bubble nasal CPAP may be a more readily available alternative for newborns and children with severe hypoxemia.⁴¹

The following recommendations pertain to adult and pediatric patients with ARDS who need intubation and invasive mechanical ventilation.

We recommend prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support.

Remark:

Patients may continue to have increased work of breathing or hypoxaemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10–15 L/min, which is typically the minimum flow required to maintain bag inflation; FiO₂ 0.60–0.95). Hypoxaemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation.²

We recommend that endotracheal intubation be performed by a trained and experienced provider using airborne precautions.

Remark:

Patients with ARDS, especially young children or those who are obese or pregnant, may desaturate quickly during intubation. Pre-oxygenation with 100% FiO₂ for 5 min, and use of a face mask with reservoir bag is preferred. When possible, avoid bag-valve mask ventilation to reduce exposure to aerosols. Rapid-sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation.^{42,43}

The following recommendations pertain to mechanically ventilated adult and paediatric patients with ARDS.^{2,45}

WHO recommend implementation of 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:

The implementation of mechanical ventilation using lower tidal volumes and lower inspiratory pressures is a strong recommendation from a clinical guideline for patients with ARDS,² and is also suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria.² The initial target tidal volume is 6 mL/kg PBW; tidal volume up to 8 mL/kg PBW is allowed if undesirable side-effects occur (e.g. dyssynchrony, pH < 7.15). Permissive hypercapnia is permitted. Ventilator protocols are available.⁴⁴ The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets.

Remarks for children:

In children, a lower level of plateau pressure (< 28 cmH₂O) is targeted, and a lower target of pH is permitted (7.15–7.30). Tidal volumes should be adapted to disease severity: 3–6 mL/kg PBW in the case of poor respiratory system compliance, and 5–8 mL/kg PBW with better preserved compliance.⁴⁵

In adult patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$) prone ventilation for 12–16 h per day is recommended.

Remarks:

Application of prone ventilation is recommended for adult patients, preferably for 16 per day, and may be considered for paediatric patients with severe ARDS but requires sufficient human resources and expertise to be performed safely; protocols (including videos) are available.^{46,47}

There is little evidence on prone positioning in pregnant women with ARDS; this could be considered in early pregnancy. Pregnant women in the third trimester may benefit from being placed in the lateral decubitus position.

Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion and fluid responsiveness.

Remarks for adults and children:

This has also been recommended in another international guideline². The main effect is to shorten the duration of ventilation. A sample protocol for implementation of this recommendation is available.⁴⁸

In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. In COVID-19, we suggest the individualization of PEEP where during titration the patient is monitored for effects (beneficial or harmful) and driving pressure.

Remarks:

PEEP titration requires consideration of benefits (reducing atelectrauma and improving alveolar recruitment) versus risks (end-inspiratory overdistension leading to lung injury and higher pulmonary vascular resistance). Tables are available to guide PEEP titration based on the FiO_2 required to maintain SpO_2 .⁴⁴ In younger children, maximal PEEP pressures are 15 cmH₂O. Although high driving pressure (plateau pressure – PEEP) may more accurately predict increased mortality in ARDS compared with high tidal volume or plateau pressure,⁴⁹ data from RCTs of ventilation strategies that target driving pressure are not currently available.

A related intervention of recruitment maneuvers (RMs) is delivered as episodic periods of high CPAP (30–40 cmH₂O), progressive incremental increases in PEEP with constant driving pressure, or high driving pressure; considerations of benefits vs risks are similar. Higher PEEP and RMs were both conditionally recommended in a clinical practice guideline. For PEEP, the guideline considered an individual patient data meta-analysis⁵⁰ of three RCTs. However, a subsequent RCT of high PEEP and prolonged high-pressure RMs showed harm, suggesting that the protocol in this RCT should be avoided.⁵¹ Monitoring of patients to identify those who respond to the initial application of higher PEEP or a different RM protocol and stopping these interventions in non-responders are suggested.⁵²

In patients with moderate-severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$), neuromuscular blockade by continuous infusion should not be routinely used.

Remark:

A trial found that this strategy improved survival in adult patients with moderate-severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$) without causing significant weakness,⁵³ but results of a recent larger trial found that use of neuromuscular blockade with high PEEP strategy was not associated with a survival benefit when compared with a light sedation strategy without neuromuscular blockade.⁵⁴ Intermittent or continuous neuromuscular blockade may still be considered in patients with ARDS, both adults and children, in certain situations: ventilator dyssynchrony despite sedation, such that tidal volume limitation cannot be reliably achieved; or refractory hypoxaemia or hypercapnia.

Avoid disconnecting the patient from the ventilator, which results in loss of PEEP, atelectasis and increased risk of infection of health care workers.

Remarks:

Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).

Manual hyperinflation should be avoided and ventilator hyperinflation used instead, if indicated.³⁶

In patients with excessive secretions, or difficulty clearing secretions, consider application of airway clearance techniques. These should be performed only if deemed medically appropriate.³⁶

The following recommendations pertain to adult and paediatric patients with ARDS in whom lung protective ventilation strategy fails to achieve adequate oxygenation and ventilation.

In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxaemia (e.g. including a ratio of partial pressure of arterial oxygen [PaO₂] to the fraction of inspired oxygen [FiO₂FiO₂] of < 50 mmHg for 3 h, a PaO₂:FiO₂ of < 80 mmHg for > 6 h) despite lung protective ventilation.

Remarks for adults:

An RCT of ECMO for adult patients with ARDS was stopped early and found no statistically significant difference in the primary outcome of 60-day mortality between ECMO and standard medical management (including prone positioning and neuromuscular blockade).⁵⁵

However, ECMO was associated with a reduced risk of the composite outcome that consisted of mortality and crossover to ECMO treatment,⁵⁷ and a post-hoc Bayesian analysis of this RCT showed that ECMO is very likely to reduce mortality across a range of prior assumptions.⁵⁵ In patients with MERS, ECMO vs conventional treatment was associated with reduced mortality in a cohort study.¹ ECMO is a resource-intensive therapy and should be offered only in expert centres with a sufficient case volume to maintain expertise and staff volume and capacity to apply the IPC measures required.^{56,57} In children, ECMO can also be considered in those with severe ARDS, although high-quality evidence for benefit is lacking.⁴⁵

MANAGEMENT OF CRITICAL COVID-19 ** SEPTIC SHOCK **

Key points:

Recognize septic shock in adults when

- Infection is suspected or confirmed

AND

- Vasopressors are needed to maintain mean arterial pressure (MAP) \geq 65 mmHg

AND lactate is \geq 2 mmol/L, in the absence of hypovolemia

Recognize septic shock in children

- With any hypotension (systolic blood pressure [SBP] < 5th centile or > 2 SD below normal for age)

or

- Two or more of the following:
 - Altered mental status;
 - Bradycardia or tachycardia
 - HR < 90 bpm or > 160 bpm in infants
 - HR < 70 bpm or > 150 bpm in children;
- Prolonged capillary refill (> 2 sec) or feeble pulses;

- Tachypnea;
- Mottled or cold skin or petechial or purpuric rash;
- Increased lactate;
- Oliguria;
- Hyperthermia or hypothermia.

Remarks:

In the absence of a lactate measurement, use blood pressure (i.e. MAP) and clinical signs of perfusion to define shock.

Standard care includes early recognition and the following treatments to be done immediately, within 1 h of recognition: antimicrobial therapy, and initiation of fluid bolus and vasopressors for hypotension.² The use of central venous and arterial catheters should be based on resource availability and individual patient needs. Detailed guidelines from the Surviving Sepsis Campaign and WHO are available for the management of septic shock in adults² and children.⁵⁸ Alternate fluid regimens are suggested when caring for adults and children in resource-limited settings.^{59,60}

The following recommendations pertain to resuscitation strategies for adult and paediatric patients with septic shock.

In resuscitation for septic shock in adults, give 250–500 mL crystalloid fluid as rapid bolus in first 15–30 minutes.

In resuscitation for septic shock in children, give 10–20 mL/kg crystalloid fluid as a bolus in the first 30–60 minutes.

Fluid resuscitation may lead to volume overload, including respiratory failure, particularly with ARDS. If there is no response to fluid loading or signs of volume overload appear (e.g. jugular venous distension, crackles on lung auscultation, pulmonary oedema on imaging, or hepatomegaly), then reduce or discontinue fluid administration. This step is particularly important in patients with hypoxaemic respiratory failure.

Remarks:

Crystalloids include normal saline and Ringer's lactate.

Determine the need for additional fluid boluses (250–500 mL in adults; 10–20 mL/kg in children) based on clinical response and improvement of perfusion targets and reassess for signs of fluid overload after each bolus. Perfusion targets include MAP (> 65 mmHg or age-appropriate targets in children), urine output (> 0.5 mL/kg/hr in adults; 1 mL/kg/hr in children), and improvement of skin mottling and extremity perfusion, capillary refill, heart rate, level of consciousness, and lactate.

Consider dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation based on local resources and experience.² These indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation.

In pregnant women, compression of the inferior vena cava can cause a decrease in venous return and cardiac preload and may result in hypotension. For this reason, pregnant women with sepsis and or septic shock may need to be placed in the lateral decubitus position to off-load the inferior vena cava.⁶¹

Clinical trials conducted in resource-limited settings comparing aggressive versus conservative fluid regimens suggest higher mortality in patients treated with aggressive fluid regimens.^{59,60} Refer to the WHO/ICRC *Basic emergency care (Shock module)* for an initial approach and management of shock in resource limited settings.²⁴

WHO Caution: Do Not use hypotonic crystalloids, starches or gelatins for resuscitation.

Starches are associated with an increased risk of death and acute kidney injury compared with crystalloids. The effects of gelatins are less clear, but they are more expensive than crystalloids.^{2,62} Hypotonic (vs isotonic) solutions are less effective at increasing intravascular volume.

Surviving Sepsis guidelines also suggest albumin for resuscitation when patients require substantial amounts of crystalloids, but this conditional recommendation is based on low-quality evidence.²

Further guidance:

In adults, administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP \geq 65 mmHg in adults and improvement of markers of perfusion.

In children, administer vasopressors if signs of fluid overload are apparent or the following persist after two fluid bolus:

- signs of shock such as
 - altered mental state;
 - bradycardia or tachycardia;
 - HR < 90 bpm or > 160 bpm in infants
 - HR < 70 bpm or > 150 bpm in children
 - prolonged capillary refill (> 2 seconds) or feeble pulses;
 - tachypnea; mottled or cool skin or petechial or purpuric rash; increased lactate
 - oliguria persists after two repeat boluses;
 - or age-appropriate blood pressure targets are not achieved.⁵⁸

Remarks:

Vasopressors (i.e. norepinephrine, epinephrine, vasopressin and dopamine) are most safely given through a central venous catheter at a strictly controlled rate, but it is also possible to safely administer them via peripheral vein⁶³ and intraosseous needle. Monitor blood pressure frequently and titrate the vasopressor to the minimum dose necessary to maintain perfusion and prevent side-effects. A recent study suggests that in adults 65 years or older a MAP 60–65 mmHg target is equivalent to \geq 65 mmHg.⁶⁴

Norepinephrine is considered the first-line treatment in adult patients; epinephrine or vasopressin can be added to achieve the MAP target. Because of the risk of tachyarrhythmia, reserve dopamine for selected patients with low risk of tachyarrhythmia or those with bradycardia.

In children, epinephrine is considered the first-line treatment, while norepinephrine can be added if shock persists despite optimal dose of epinephrine.³

Further recommendations

If central venous catheters are not available, vasopressors can be given through a peripheral IV, but use a large vein and closely monitor for signs of extravasation and local tissue necrosis. If extravasation occurs, stop infusion. Vasopressors can also be administered through intraosseous needles.

If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors, consider an inotrope such as dobutamine.

Prevention of complications in hospitalized and critically ill patients with COVID-19.

Thromboembolism

Coagulopathy is common in patients with severe COVID-19, and both venous and arterial thromboembolism have been reported.^{7,8,65,66}

Further recommendations:

In patients (adults and adolescents) hospitalized with COVID-19, use pharmacological prophylaxis, such as low molecular weight heparin (such as enoxaparin), according to local and international standards, to prevent venous thromboembolism, when not contraindicated.⁶⁷ For

those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).

Monitor patients with COVID-19, for signs or symptoms suggestive of thromboembolism, such as stroke, deep venous thrombosis, pulmonary embolism or acute coronary syndrome. If these are clinically suspected, proceed immediately with appropriate diagnostic and management pathways.

Adverse effects of medications - Careful consideration should be given to the numerous, clinically significant side-effects of medications that may be used in the context of COVID-19, as well as drug-drug interactions between medications, both of which may affect COVID-19 symptomatology (including effects on respiratory, cardiac, immune and mental and neurological function). Both pharmacokinetic and pharmacodynamic effects should be considered in experimental and/or repurposed medications.

Remarks:

The risk of relevant side-effects and drug-drug interactions relating to COVID-19 symptomatology include sedation, cardiotoxicity via QTc-prolongation and respiratory suppression, and these may be dose-dependent (i.e. increase with escalating doses). For this reason, care should be taken that minimum effective doses of medications with dose-dependent negative effects are used and for the shortest durations possible.

Use medications that carry the least risk possible for drug-drug interactions with other medications the person may be receiving. Psychotropic medications with sedative properties, such as benzodiazepines, can worsen respiratory function. Some, psychotropic medications have QTc-prolonging activity (such as some antipsychotics and some antidepressants). Use medications that carry the least risk possible for side-effects that may worsen COVID-19 symptomatology, including sedation, respiratory or cardiac function, risk of fever or other immunological abnormalities, or coagulation abnormalities.

Other complications

These interventions are based on Surviving Sepsis² or other guidelines,^{68,69} and are generally limited to feasible recommendations based on high-quality evidence. Recent publications have encouraged best practices to continue during the COVID-19 outbreak (120). See the WHO *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation* for practical tools to assist implementation.²⁵

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