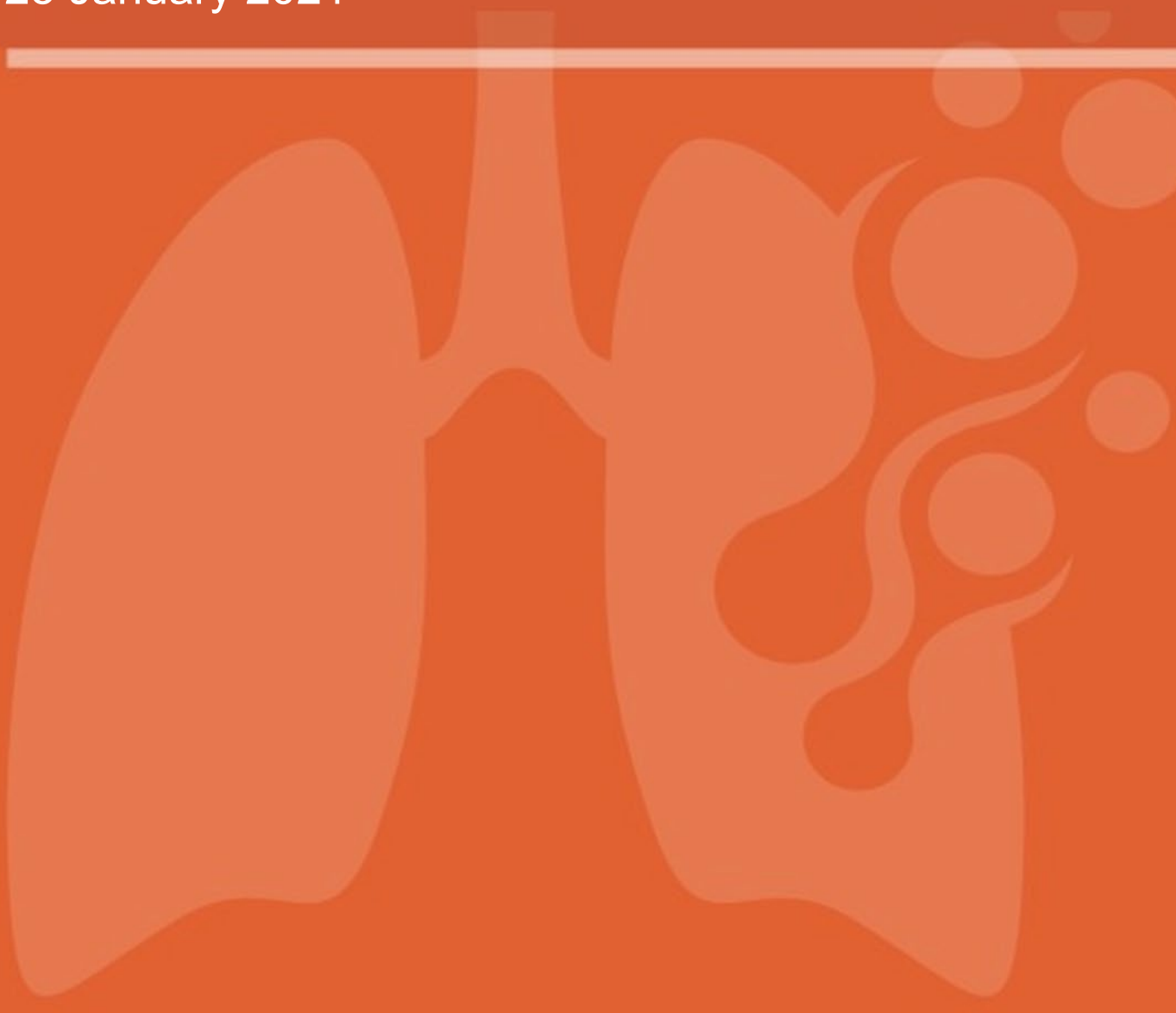
# COVID-19
# Clinical management

Living guidance

25 January 2021

World Health Organization



# COVID-19
# Clinical management

## Living guidance
## 25 January 2021

World Health Organization

This document is the update of an interim guidance originally published under the title “Clinical management of COVID-19: interim guidance, 27 May 2020".

WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.



WHO reference number: WHO/2019-nCoV/clinical/2021.1

# Contents

# Foreword and summary

The *Strategic preparedness and response plan* outlines the World Health Organization (WHO) strategic objectives to end the COVID-19 pandemic and assists national stakeholders with developing a structured approach to their response. The WHO's main objectives for COVID-19 are to:

1) supress transmission;
2) provide optimized care for all patients; and save lives
3) minimize the impact of the epidemic on health systems, social services and economic activity.

To achieve these objectives, the WHO *Operational considerations for case management of COVID-19 in health facility and community* describes key actions that should be taken in different scenarios: no cases; sporadic cases; clusters of cases; and community transmission, in order to enable delivery of clinical and public health services in a timely fashion.

The guidance in this document is based on the above strategic priorities, and is intended for clinicians involved in the care of patients with suspected or confirmed COVID-19. It is not meant to replace clinical judgment or specialist consultation but rather to strengthen frontline clinical management and the public health response. Considerations for special and vulnerable populations, such as paediatric patients, older people and pregnant women, are highlighted throughout the text.

In this document we refer to the **COVID-19 care pathway (Annex 1).** This describes a coordinated and multidisciplinary care pathway that a patient enters after s/he is **screened for COVID-19 and becomes a suspect COVID-19 case,** and follows the continuum of their care until release from the pathway. The objective is to ensure delivery of safe and quality care while stopping onwards viral transmission. All others enter the health system in the non-COVID-19 pathway. For the most up-to-date technical guidance related to the COVID-19 response, visit WHO Country & Technical Guidance *(1).*

Basic psychosocial support skills are at the core of any clinical intervention for COVID-19. Such skills are indispensable for all involved in the COVID-19 clinical response, whether they identify as mental health and psychosocial providers or not. Basic psychosocial skills are essential for supporting the emotional well-being of people who have COVID-19, those who have lost someone to COVID-19, or are family members and carers who are caring for someone with COVID-19 or have recovered from COVID-19.

**Summary: what is this living guidance?**

**Clinical questions:** What is the clinical management of patients with COVID-19?

**Target audience:** The target audience is clinicians and health care decision-makers.

**Current practice:** Current practice to treat COVID-19 is variable reflecting large-scale uncertainty. Numerous clinical trials are underway looking at various interventions that will inform clinical practice. Providing trustworthy guidance that is comprehensive and holistic for the optimal care of COVID-19 patients, throughout their entire illness, is necessary. The previous version of the *Clinical management of COVID-19* provided recommendations that can be applied when caring for patients during the COVID-19 care pathway. This guideline now also includes information on caring for COVID-19 patients after their acute illness.

**Updates to this guidance:** The panel made the following new recommendations:

- A conditional recommendation to use clinical judgment, including consideration of patients' values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the intensive care unit (ICU), rather than currently available prediction models for prognosis when caring for patients with COVID-19 of any severity assessed in a clinic or hospital (very low certainty).

- A conditional recommendation for use of pulse oximetry monitoring at home as part of a package of care, including patient and provider education and appropriate follow-up, in symptomatic patients with COVID-19 and risk factors for progression to severe disease who are not hospitalized (very low certainty).
- A conditional recommendation for the use of awake prone positioning in patients with severe COVID-19 that are hospitalized requiring supplemental oxygen or non-invasive ventilation (low certainty).
- A conditional recommendation to use thromboprophylaxis dosing of anticoagulation rather than intermediate or therapeutic dosing in patients hospitalized with COVID-19, without an established indication for higher dose of anticoagulation (very low certainty).
- A conditional recommendation for the use of existing care bundles (defined as three or more evidence-informed practices delivered together and consistently to improve care) chosen locally by hospital or ICU and adapted as necessary for local circumstances in patients with critical COVID-19 (very low certainty).
- Best practice statement: patients who have had suspected or confirmed COVID-19 (of any disease severity) who have persistent, new or changing symptoms should have access to follow-up care (see the new Chapter 24. Care of COVID-19 patients after acute illness).

For chapters without new recommendations, each responsible technical unit (member of steering committee) reviewed the chapter and provided narrative updates to reflect new literature searches. Two technical units used expert panel reviews to review and update their chapters (neurological and mental manifestations [Chapter 17] and rehabilitation [Chapter 19]).

**How this guideline was created:** This living guideline is an innovation from WHO, driven by the urgent need for global collaboration to provide trustworthy and evolving COVID-19 guidance informing policy and practice worldwide. An international Guideline Development Group (GDG) of content experts, clinicians, patients, ethicists and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. No conflict of interest was identified for any panel member. WHO has partnered with the non-profit MAGIC (Making GRADE the Irresistible Choice) Evidence Ecosystem Foundation for support through their publication platform that facilitates continued updating.

**The latest evidence:** The evidence included in this guidance update includes six rapid reviews on specific topics that can be found in Annex 3. No conflict of interest was identified for any external contributors.

**Understanding the recommendations:** When moving from evidence to recommendations, the panel made five conditional recommendations based primarily on low to very low certainty evidence.

- For suggested use of clinical judgment rather than available prediction models, the panel considered the evidence in favour of prognostic models in patients with COVID-19 to be of very low certainty, lack validation studies, and lack evidence of the impact of using models on decision-making and patient outcomes.
- For suggested use of pulse oximetry monitoring at home, the panel felt the potential benefits would outweigh the potential harms, especially if used in patients that were symptomatic and at risk for severe disease; but only as part of a larger package of care including education and follow-up.
- For suggested use of awake prone positioning in hospitalized patients with severe COVID-19, the panel emphasized the low certainty evidence of reduction in mortality, downgraded from higher certainty evidence for mechanically ventilated critically ill patients with acute respiratory distress syndrome (ARDS) and the limited harm with the experience thus far from different resource settings.
- For suggested use of existing care bundles, the panel emphasized the low to very low certainty evidence of reduction in mortality and possible administrative burdens for implementation; but if the hospital or ICU selected among existing care bundles and adapted them to local circumstances that would take into account contextual factors of resource considerations and increase feasibility.

For these four recommendations the panel did not expect much variation in values and preferences.

- For suggested use of thromboprophylaxis dosing rather than intermediate or therapeutic dosing, the panel emphasized the very low certainty evidence of reduction in mortality or pulmonary embolism with higher anticoagulant dosing but also an increased risk of major bleeding; the possible harm indicated by studies of therapeutic anticoagulation rather than intermediate dosing.

For this last recommendation, some panellists anticipated variability in patient values and preferences.

**Update 1.4 Clinical Management of COVID-19: Living Guidance**

This updated version of the *Clinical management of COVID-19* guidance includes five new recommendations and a new chapter on care for patients after acute illness with COVID-19, adding to the interim guidance published 27 May 2020. Please view section text for a summary of these new recommendations, also available within each section of the guidelines, labelled as new. Other recommendations remain unchanged although underlying content and references have been updated in this version. Concerning therapeutics for COVID-19, please see the linked WHO living guidelines also published as BMJ Rapid Recommendations, which replace the initial guidance (e.g. for corticosteroids).

As described in Methods (Chapter 2), the first interim guidance applied a simplified approach to produce rapid guidance. In this 4th updated version the GDG applied GRADE and standards for trustworthy guidelines. To reflect these two different approaches, the recommendations are therefore marked with different labels and colour codings.

This is a living guidance, so the recommendations included here will be updated, and new recommendations will be added as evidence emerges. The guideline is therefore written, disseminated and updated in MAGICapp, with a format and structure aiming to make it user friendly and easy to navigate while accommodating for dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations within the guideline.

# Abbreviations

| | |
|---|---|
| ADL | activities of daily living |
| ARDS | acute respiratory distress syndrome |
| AWaRe | Access, Watch or Reserve (antibiotics) |
| BiPAP | bilevel positive airway pressure |
| BMI | body mass index |
| BP | blood pressure |
| bpm | beats per minute |
| COPD | chronic obstructive pulmonary disease |
| CPAP | continuous positive airway pressure |
| CRF | case record form |
| CT | computed tomography |
| DIC | disseminated intravascular coagulation |
| DVT | deep vein thrombosis |
| ECMO | extracorporeal membrane oxygenation |
| $FiO_2$ | fraction of inspired oxygen |
| GDG | Guideline Development Group |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HFNO | high-flow nasal oxygen |
| HIV | human immunodeficiency virus |
| ICU | intensive care unit |
| IFRC | International Federation of Red Cross and Red Crescent Societies |
| InFACT | International Forum for Acute Care Trialists |
| IPC | infection prevention and control |
| IQR | interquartile range |
| ISARIC | International Severe Acute Respiratory and emerging Infection Consortium |
| LRT | lower respiratory tract |
| LTCF | long-term care facility |
| MAGIC | Magic Evidence Ecosystem Foundation |
| MAP | mean arterial pressure |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| MHPSS | mental health and psychosocial support |
| MISC- C | multisystem inflammatory syndrome temporally associated with COVID-19 in children and adults |
| NAAT | nucleic acid amplification test |
| NCD | noncommunicable disease |
| NICU | neonatal intensive care unit |
| NIV | non-invasive ventilation |
| OI | Oxygenation Index |
| OSI | Oxygenation Index using $SpO_2$ |
| $PaO_2$ | partial pressure arterial oxygen |
| PBW | predicted body weight |
| PEEP | positive end-expiratory pressure |
| PICS | post-intensive care syndrome |
| PPE | personal protective equipment |
| PTSD | post-traumatic stress disorder |
| PUI | person/patient under investigation |
| RCT | randomized controlled trial |
| RDT | rapid diagnostic test |
| RM | recruitment manoeuvre |
| RT-PCR | reverse transcription polymerase chain reaction |
| SARS-CoV | severe acute respiratory syndrome coronavirus |
| SBP | systolic blood pressure |
| SIRS | systemic inflammatory response syndrome |

| | |
|---|---|
| SOFA | sequential organ failure assessment |
| $SpO_2$ | oxygen saturation |
| TB | tuberculosis |
| UNICEF | United Nations Children's Fund |
| URT | upper respiratory tract |
| VTE | venous thromboembolism |
| WHO | World Health Organization |

# 1. Background

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly emergent coronavirus, that was first recognized in Wuhan, Hubei province, China, in December 2019. SARS-CoV-2 is a positive-sense single-stranded RNA virus that is contagious in humans. It is the successor to SARS-CoV-1, the strain that caused the 2002–2004 SARS outbreak.

Epidemiology and virologic studies suggest that transmission mainly occurs from both symptomatic and asymptomatic people to others by close contact through respiratory droplets or by direct contact with infected persons, or by contact with contaminated objects and surfaces *(2,3,4,5,6)*, or by aerosols, i.e. in enclosed spaces indoors, crowded and inadequately ventilated spaces, where infected persons spend long periods of time with others, which may include restaurants, choir practices, fitness classes, nightclubs, offices and places of worship *(7)*, or during aerosol-generating procedures. Clinical and virologic studies that have collected repeated biological samples from confirmed patients demonstrate that shedding of SARS-CoV-2 is highest in the upper respiratory tract (URT) (nose and throat) early in the course of the disease *(8,9,10)*, within the first 3 days from onset of symptoms *(10,11,12,13)*. A study of 77 infector-infectee transmission pairs observed the highest viral load in throat swabs at the time of symptom onset, suggesting infectiousness peak on or before symptom onset with an estimated 44% (95% confidence interval, 30–57%) of onward infections happening during the pre-symptomatic phase of the index case *(14)*. The incubation period for COVID-19, which is the time between exposure to the virus (becoming infected) and symptom onset, is, on average, 5–7 days, but can be up to 14 days. During this period, also known as the “presymptomatic” period, some infected persons can be contagious, from 1–3 days before symptom onset *(12)*. It is important to recognize that presymptomatic transmission still requires the virus to be spread via infectious droplets or by direct or indirect contact with bodily fluids from an infected person. An asymptomatic case is a person infected with SARS-CoV-2 who does not develop symptoms *(15,16)*. Among symptomatic patients, the duration of infectious virus shedding has been estimated at 8 days from the onset of any symptoms *(17,18,19)*.

The proportion of persons who become infected with SARS-CoV-2 and remain asymptomatic remains to be better understood, recent meta-analysis reported an overall estimate of 31%, from seven studies with predefined screened populations, prediction interval ranging between 26–37% *(20)*. One systematic review of 79 studies found that 20% (17–25%) of people remained asymptomatic throughout the course of infection *(20)*. Another systematic review, which included 13 studies considered to be at low risk of bias, estimated that 17% of cases remain asymptomatic (14–20%) *(21)*. A further meta-analysis included 28 studies. There was wide variance between two general population studies with the proportion of asymptomatic infections at the time of testing being 20% and 75% respectively, in contacts the proportion was 8.2–50% and 59% (49–68%) of obstetric patients remained asymptomatic throughout whilst 54% (42%-65%) of nursing home residents were asymptomatic at testing of which 28% (13–50%) remained asymptomatic through follow-up *(22)*. Whole cohort testing such as in the Diamond Princess cruise ship found an asymptomatic proportion (among all infected cases) of 17.9% (95% CI: 15.5–20.2%) *(23)* and in a cohort of 356 dialysis patients, 52 (40.3%) had asymptomatic disease or disease which was not detected using RT-PCR when serological testing for antibodies were done *(24)*. In those patients that do become symptomatic, most people with COVID-19 develop only mild (40%) or moderate (40%) disease (see Table 6.3), approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury *(25)*. Older age, smoking *(26,27)* and underlying noncommunicable diseases (NCDs), such as diabetes, hypertension, cardiac disease, chronic lung disease and cancer, have been reported as risk factors for severe disease and death, and multivariable analyses have confirmed older age, higher sequential organ failure assessment (SOFA) score and D-dimer > 1 µg/L on admission were associated with higher mortality *(28,29)* (see Table 6.3). This study also observed a median duration of viral RNA detection of 20.0 days (IQR 17–24 days) in survivors, but COVID-19 viral RNA was detectable until death in non-survivors. In a study of 20 immunocompromised haemoncology patients viral RNA was detected for up to 78 days after the onset of symptoms (IQR 24–64 days). Viable virus was detected up to 61 days after the onset of symptoms *(30)*.

COVID-19 is associated with mental and neurological manifestations, including anxiety, depression, sleep problems, headache, dizziness, impaired sense of smell or taste *(31)*, myalgias, delirium/encephalopathy, agitation, stroke, hypoxic ischaemic brain injury, seizures, coma, meningo-encephalitis and Guillain-Barré syndrome *(32,33,34,35)*. Anxiety and depression appear to be common amongst people hospitalized for COVID-19, with one hospitalized cohort from Wuhan, China, revealing over 34% of people experiencing symptoms of anxiety and 28% experiencing symptoms of depression *(36)*. Preliminary findings from retrospective cohort studies of over 60 000 COVID-19 cases in the United States of America indicate an 18.1% incidence of psychiatric diagnoses (including anxiety disorders and insomnia) in the first 2 weeks to 3 months after COVID-19 diagnosis, 5.8% of which were new diagnoses *(37)*.

In many cases, neurological manifestations have been reported even without respiratory symptoms. Over 80% of COVID-19 patients in a hospitalized United States' cohort experienced neurological symptoms during the course of their illness and these manifestations were associated with a four-fold higher risk of severe COVID-19 in this cohort *(38)*. An observational case series from France found that 65% of people with COVID-19 in ICUs showed signs of confusion (or delirium) and 69% experienced agitation *(39)*. Delirium, in particular, has been associated with increased mortality risk in the context of COVID-19 *(40)*. Moreover COVID-19 has been associated with acute cerebrovascular disease (including ischaemic and haemorrhagic stroke) with reports from multiple case series and/or cohort series from China, France, the Netherlands, the United Kingdom and the United States of America *(36,39,41,42,43)*. Case reports of Guillain-Barré syndrome and meningo-encephalitis among people with COVID-19 have also been reported *(44,45,46)*.

Clinical manifestations of COVID-19 are generally milder in children compared with adults *(47,48,49)*. Relatively few cases of infants confirmed with COVID-19 have been reported; infants also experience mild illness *(49,50)*. However, an acute presentation with a hyperinflammatory syndrome leading to multiorgan failure and shock has been reported *(51,52)*, described as multisystem inflammatory syndrome temporally associated with COVID-19 in children and adolescents. Underlying conditions with severe illness in children appear to be similar to adults. Among 655 children with laboratory-confirmed COVID-19 and complete information about underlying conditions, 23% had an underlying condition, with obesity, chronic lung disease (including asthma), cardiovascular disease and immunosuppression most commonly reported *(52)*.

The results of a living systematic review (as of 6 October 2020) show that pregnant and recently pregnant women with COVID-19 appear to be less likely to be symptomatic (0.28, 95% CI 0.13–0.62; 4 studies; 462 051 women), or manifest common symptoms such as fever, dyspnoea and myalgia, compared with non-pregnant women of reproductive age *(53)*. These findings are largely influenced by studies of pregnant women who were managed in hospitals for any reason, with limited data on women during early pregnancy or postpartum. Pregnant or recently pregnant women with severe COVID-19 are at higher risk of requiring admission to an ICU (OR=2.13, 95% CI 1.53–2.95; 7 studies, 601 108 women), invasive ventilation (OR=2.59, 95% CI 2.28–2.94; 6 studies, 601 044 women) or extra corporeal membrane oxygenation (ECMO) (OR=2.02, 95% CI 1.22–3.34; 2 studies, 461 936 women). Older maternal age, high body mass index (BMI), non-white ethnicity, pre-existing comorbidities, chronic hypertension, pre-existing diabetes, are risk factors for developing severe COVID-19. Complications related to COVID-19 did not seem to be increased in women presenting in the third trimester compared with earlier trimester of pregnancy or in multiparous compared with primiparous women, but the existing sample sizes for these comparisons are not large.

The understanding of the mid- and long-term sequelae of COVID-19 is emerging. This new condition which has been described as post-COVID syndrome or long COVID *(54)* still lacks a consensus worldwide on terminology and clinical definition. The post-intensive care syndrome (PICS) has been well described in other critically ill patients and it seems is also being observed in COVID-19 patients. However, non-hospitalized patients (or those with mild and moderate COVID-19) and children are also reporting persisting clustering of symptoms and mid- and long-term sequalae, and children. Recent data (in press at *The Lancet* by Bin Cao et al.) on the long-term consequences of COVID-19 for patients in Wuhan, warned that dysfunctions and complications could persist in some discharged patients for at least 6 months *(55)*.

# 2. Methods

**The original version (v1.1)** of this document was developed in consultation with the International Forum for Acute Care Trialists (InFACT), the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the Surviving Sepsis Campaign. This is the fourth edition of this document, which was originally adapted from *Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected* (WHO, 2019).

**For the development of the third version (v1.3)** of the COVID-19 clinical guidance, a formal Guideline Development Group (GDG) comprising individuals with broad expertise spanning multiple specialties and all regions was convened. Confidentiality and declarations of interest were collected and reviewed and no conflict of interest was identified (see Acknowledgements). Because of the accelerated timeline and very broad scope of the third version of the guideline, it was not feasible to undertake a formal GRADE process (PICO questions; systematic reviews; formal documentation of values and preferences and incorporation of considerations of costs, resources, and feasibility). The topics for consideration originated in the WHO interim guidance for MERS, but for COVID-19 were greatly expanded to reflect the full spectrum of illness, from screening to rehabilitation. Published evidence was synthesized under the coordination of the Science Division in rapid systematic reviews, which were pre-circulated to the GDG. The WHO Steering Committee initially drafted the recommendations about interventions based on these reviews and input from expert clinicians participating in twice-weekly clinical network teleconferences. The GDG held four virtual meetings via teleconference (total of 12 hours) to discuss all previous and new recommendations. Suggested revisions were incorporated into the guidance. Consensus was achieved for all recommendations presented in the final version. The direction and strength of recommendations are presented using symbols rather than formal GRADE terminology (strong and conditional recommendations with grading of certainty of evidence, or best practice statements).

The GREEN symbol denotes a strong recommendation or a best practice statement in favour of an intervention.

The RED symbol denotes a recommendation or a best practice statement against an intervention.

The YELLOW symbol denotes a conditional recommendation in favour of an intervention, or a recommendation where special care is required in implementation.

**For this fourth version (v1.4)** of the guidance, new recommendations have been developed according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations. The methods are aligned with the *WHO Handbook for guideline development (56)*.

**Related guidelines**

This living WHO guidance for the clinical management of COVID-19 is related to the Living Guideline for therapeutics and COVID-19, also published in the BMJ and available in MAGICapp.

**Timing**

This guidance aims to be trustworthy and living; dynamically updated and globally disseminated once new evidence warrants a change in recommendations for COVID-19. We aim for an ambitious timeframe from trials that trigger guideline development process to WHO publication, within 1 month, while maintaining standards and methods for trustworthy guidelines (*WHO Handbook of guideline development*) *(56)*.

**Stepwise approach**

Here we outline the stepwise approach we take to improve efficiency and timeliness of the living, trustworthy guidance, in the development and dissemination of the recommendations. To do so, various processes occurred simultaneously.

Step 1: Evidence monitoring and mapping and triggering of evidence synthesis

Regular monitoring of evidence around key topics occurs with support from the WHO rapid review team and their network of collaborators. In September 2020, the WHO Steering Committee triggered this guidance update process, including PICO development. The trigger for producing or updating specific recommendations is based on the following:

- likelihood to change practice;
- relevance to a global audience.

Step 2: Convening the GDG

The pre-selected expert panel (see Acknowledgments) convened on four occasions. At each meeting, a review of the GRADE methodology was done, including how to make best practice statements.

The first meeting, held on 1 December 2020 reviewed the basics of GRADE methodology; including formulating PICO questions and subgroups of interests, assessment of certainty of evidence, incorporating patients' values and preferences, and prioritization of patient-important outcomes. Important questions in the clinical management of patients with COVID-19 focused on the prevention of complications by the use anticoagulation for thromboprophylaxis and the use of care bundles in ICU. The second meeting on 4 December 2020 addressed the use of pulse oximetry at home and awake prone positioning as well as further clarification around the use of care bundles in ICU. The third meeting on 11 December 2020 addressed the longer-term effects of COVID-19 and additional clarification around the use of care bundles in ICU. The fourth meeting on 11 December 2020 addressed risk factors as well as prognostic/prediction models in COVID-19 and completed recommendations for the use of care bundles in ICU.

Step 3: Evidence synthesis

The WHO Steering Committee requested the WHO methods support team to conduct rapid systematic reviews on the six PICOs. Two of the PICOs were conducted by the WHO rapid review team made up of systematic review experts, clinical experts and a librarian. The other four PICOs were addressed by collaborators, that were already engaged in conducting systematic reviews on these topics. This includes: National Institute of Health and Care Excellence (NICE, United Kingdom), the American Society of Haematology guideline/McMaster University GRADE Centre systematic review, COVIDPRECISE; and the Cochrane Library (see Acknowledgements).

Step 4: Final recommendations

The GDG panel members are responsible for the following critical activities:

- To advise on the priority questions and scope of guidance.
- To advise on the choice of important outcomes for decision-making.
- To comment on the evidence used to inform the guideline.
- To advise on the interpretation of the evidence, with explicit consideration of overall balance or risks and benefits.
- To formulate recommendations, taking into account diverse values and preferences according to GRADE.

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations *(57,58)*. Good practice statements can be made in addition to, or instead of a recommendation when a large body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly supports the net benefit of the recommended action, if deemed that it will be an onerous and unproductive exercise to collect the linked evidence supporting the recommendations. However, it still requires transparency and explicitness, with a clear rationale for the approach. Although a priori voting procedures were established at the outset, in case consensus was not reached, these procedures were not necessary for this recommendation which reached consensus amongst the panel.

The following key factors were used to formulate transparent and trustworthy recommendations:

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables);
- quality/certainty of the evidence *(57,59)*;
- values and preferences of patients *(60)*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *(60)*;
- each outcome will have an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in summary of findings tables. If such data are not available narrative summaries will be provided;

- recommendations will be rated as either conditional or strong, as defined by GRADE. If the panel members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established methods.

Step 5: External and internal review
The WHO guideline was then reviewed by pre-specified external reviewers (see Acknowledgements) and then approved by the WHO Publication Review Committee.

# 3. The latest evidence

Based on information needs from the GDG, six rapid reviews informed development of recommendations in this update. Whereas evidence summaries are provided for each updated recommendation, details about the literature search, identified studies and references can be found in the Annex 3 of this document.

**Table 3.1 Panel outcome rating from a patient perspective**

| Outcome | Mean | SD | Range |
|---|---|---|---|
| Death at 28 days | 9.0 | 0.0 | 9-9 |
| Need for invasive mechanical ventilation | 8.4 | 0.8 | 7-9 |
| Duration of invasive mechanical ventilation | 7.7 | 1.0 | 5-9 |
| Time to clinical improvement | 7.2 | 1.5 | 4-9 |
| Serious adverse effect leading to drug discontinuation | 7.1 | 1.4 | 4-9 |
| Time to symptom resolution | 6.6 | 1.5 | 3-9 |
| Duration of oxygen support | 6.6 | 1.3 | 5-9 |
| Duration of hospitalization | 6.4 | 1.3 | 3-8 |
| Hepatitis (increased liver enzymes) | 5.3 | 1.8 | 2-9 |
| Duration of viral shedding | 4.9 | 2.4 | 2-9 |
| Nausea/vomiting | 4.5 | 1.7 | 2-9 |
| Diarrhea | 4.3 | 1.5 | 2-8 |

**Note:** 1: not important, 9: critically important.

**Values and preferences**
There were insufficient published data to provide the GDG with an informative systematic review of studies describing patients' experiences or values and preferences on treatment decisions for COVID-19 drug treatments. The GDG therefore relied on their own judgments of what well-informed patients would value after carefully balancing the benefits, harms and burdens of treatment and their subsequent treatment preferences. The GDG included four patient-representatives who had lived experience with COVID-19. The WHO is currently conducting a survey of patients to expand the values and preferences statements for the next version update of the guidance.

The GDG agreed that the following values and preferences would be representative of those of typical well-informed patients:

- Mortality would be the outcome most important to patients, followed by need and duration of mechanical ventilation, time to clinical improvement, and serious intervention-related adverse events.
- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on the outcomes listed above. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

The GDG acknowledged, however, that values and preferences are likely to vary. There will be patients inclined to use a treatment in which evidence has not excluded important benefit, particularly when the underlying condition is potentially fatal. On the other hand, there will be those who have a high threshold of likely benefit before they will choose the intervention. Although the GDG focused on an individual patient perspective, they also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations.

# 4. Who the recommendations apply to

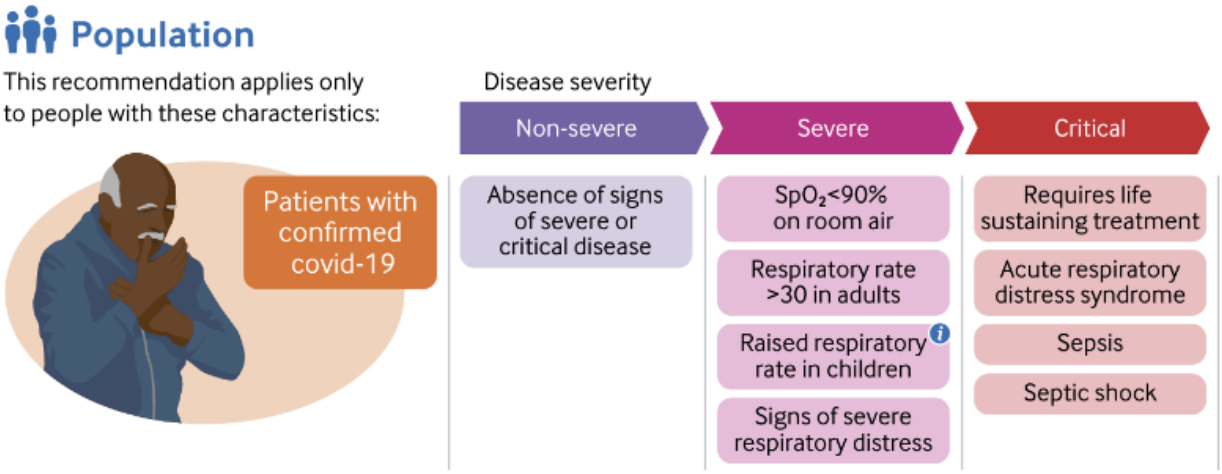
The GDG elected to use the WHO severity definitions based on clinical indicators, adapted from WHO COVID-19 disease severity categorization (see Table 6.3). These definitions avoid reliance on access to health care to define patient subgroups.

**WHO Severity definitions**

- Critical COVID-19: Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- Severe COVID-19: Defined by any of:
  - Oxygen saturation < 90% on room air.
  - Respiratory rate > 30 breaths/min in adults and children > 5 years old; ≥ 60 breaths/min in children < 2 months old; ≥ 50 in children 2–11 months old; and ≥ 40 in children 1–5 years old.
  - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
- Non-severe COVID-19: Defined as absence of any criteria for severe or critical COVID-19.

**Caution:** The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation > 90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.

The infographic illustrates these three disease severity groups and key characteristics to apply in practice, for a recommendation within this guideline.




Infographic co-produced by BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ Rapid Recommendations).

# 5. COVID-19 care pathway (see Annex 1)

**We recommend that COVID-19 care pathways be established at local, regional and national levels. COVID-19 care pathways are for persons with suspected or confirmed COVID-19.**

**Remarks:**

1. A person enters the COVID-19 care pathway after s/he is *screened*, based on a standardized case definition, including assessment of symptoms, and meets criteria for a suspect case.
   - Suspect cases may be 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 infection with SARS-CoV-2.
2. All persons with suspected, probable or confirmed infection with SARS-CoV-2 should be immediately isolated to contain virus transmission. Refer to Chapter on IPC considerations in cohorting suspect, probable and confirmed cases separately.
3. Considerations for co-infections (i.e. influenza, malaria, TB) and/or chronic diseases must be made within the COVID-19 care pathway. Ensuring that these other conditions can management according to national or local protocols.
4. 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.

**Discontinue transmission-based precautions (including isolation) and release from COVID-19 care pathway as follows.**

**Remarks:**

1. Criteria for discharging patients from isolation (i.e. discontinuing transmission-based precautions) without requiring retesting:
   - For symptomatic patients: 10 days after symptom onset, plus at least 3 additional days without symptoms (including without fever and without respiratory symptoms).
   - For asymptomatic cases: 10 days after positive test for SARS-CoV-2.
2. For example, if patient had symptoms for 2 days, then the patient could be released from isolation after 10 days + 3 = 13 days from date of symptom onset; for a patient with symptoms for 14 days, then the patient can be discharged 14 days + 3 days = 17 days from date of symptom onset; for a patient with symptoms for 30 days, the patient can be discharged 30 days + 3 days = 33 days after symptom onset.
3. Countries may choose to continue to use testing as part of the release criteria. If so, the initial recommendation of two negative PCR tests at least 24 hours apart can be used.
4. Some patients may experience symptoms beyond the period of infectivity. See Chapter 24. Care of COVID-19 patients after acute illness.
5. Please note that the clinical pathway needs to be clearly outlined by countries to follow 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.
6. 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.
7. See scientific brief *Criteria for releasing COVID-19 patients from isolation* for more details *(13)*.

# 6. Screening, triage and clinical assessment: early recognition of patients with COVID-19

The primary objective of the COVID-19 global response is to slow and stop transmission, find, isolate and test every suspect case, and provide timely appropriate care of patients with COVID-19. The recommended location of care will depend on the epidemiologic scenario and be either at a designated COVID-19 health facility, community facility or, where not possible, at home. Refer to the WHO *Operational considerations for case management of COVID-19 in health facility and community (61).*

**Please find new recommendation on methods for clinical decision-making in COVID-19 as the third 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.**

**Remarks:**

1. Screening can be performed in areas such as the emergency unit, outpatient department/primary care clinic, in the community by a community health worker or by telemedicine. In the context of this outbreak, this should be done at a distance (> 1 m). Use a simple set of questions based on the WHO case definition (see Table 6.1). This is best done by establishing screening protocols at all health access points and during contact tracing activities. Older people and those immunosuppressed may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium and absence of fever *(62,63,64)*. Thus, screening questions may need to be adjusted for certain settings and guided by epidemiologic considerations.
2. Persons with symptoms (see Table 6.1) 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 (at least 1 m between patients). Suspected cases should not be cohorted together with confirmed cases (see Chapter 7 on infection prevention and control (IPC)).
3. In areas with other endemic infections that cause fever, such as malaria, dengue, tuberculosis (TB) etc., as part of screening, febrile patients should be tested as per routine protocols *(65,66,67,68,69)*, irrespective of the presence of respiratory signs and symptoms. Coinfection with COVID-19 may coexist.
4. When influenza virus is known or suspected to be circulating, ensure that is also considered as part of screening of patients with fever and influenza-like-illness; and that testing is per local routine protocols. Coinfection with COVID-19 may exist.
5. Large outbreaks have been observed in long-term care facilities (LTCFs) *(63)*. The COVID-19 care pathway should be activated for all residents of LTCFs who are contacts of a confirmed case in that LTCF, including immediate isolation, testing and treatment as needed. The priority focus in these settings should be to ensure the well-being of residents and protect health workers, and implementation of clinical management and IPC that considers the individual's condition and prognosis (such as screening visitors for COVID-19) *(70)*.

**In community settings, community health workers should continue to follow usual protocols for recognition and treatment of other common illnesses and danger signs while activating the COVID-19 care pathway (including for referral as needed) for suspect cases. Refer to WHO/IFRC/UNICEF guidance on community-based health care, including outreach and campaigns, in the context of the COVID-19 pandemic *(71)*.**

**At a health facility, after screening and isolation, triage patients with suspected COVID-19 using a standardized triage tool (such as the WHO/IFRC Interagency Integrated Triage Tool); and evaluate the patient to determine disease severity (see Table 6.3).**

- **Initiate timely care for the acutely ill using a systematic approach, as described in WHO/ICRC Basic emergency care *(72,73)*.**
- **After initial assessment, management and stabilization, refer patient to appropriate COVID-19 care destination: within the health facility (critical care unit or ward); to a different health facility; community facility; or home, according to patient medical needs and established COVID-19 care pathways.**

**Remarks:**

1. Patients with mild and moderate illness may not require emergency interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases to contain virus transmission. The decision to monitor a suspect case in a health facility, community facility or home should be made on a case-by-case basis. This decision will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease (see Table 6.2), and conditions at home, including the presence of vulnerable persons in the household. In situations where TB may co-exist, specific measures may be necessary in addition to the above *(67)*.
2. Early identification of patients at risk for and with severe disease allows for rapid initiation of optimized supportive care treatments and safe, rapid referral to a designated destination in the COVID-19 care pathway (with access to oxygen and respiratory support).
3. Known risk factors for rapid deterioration, severe disease, and/or increased mortality are: older age (> 60 years) and NCDs such as cardiovascular disease, diabetes mellitus, chronic lung disease, cancer and cerebrovascular disease *(28)* (see Table 6.2). Patients with one or more of these risk factors should be monitored closely for deterioration, preferably in a health facility. As described above, the decision to monitor in a health facility, community facility or home should be made on a case-by-case basis. This decision will depend on the clinical presentation, requirement for supportive care, risk factors and conditions at home, including the presence of additional vulnerable persons in the household. Risk factors for severe disease in pregnancy include increasing maternal age, high BMI, non-white ethnicity, pre-existing comorbidities and pregnancy-specific conditions such as gestational diabetes and pre-eclampsia *(53)*.
4. Some patients develop severe pneumonia and require oxygen therapy, and a minority progress to critical disease with complications such as respiratory failure or septic shock (see Table 6.3) *(74,75)*.
5. COVID-19 confirmation needs to be made prior to determining severity; particularly in children, for whom the differential diagnosis for respiratory distress is particularly important.
6. Children with suspected or confirmed COVID-19 infection should be kept together with caregivers wherever possible (if caregivers also have suspected or confirmed COVID-19 infection), and cared for in child-friendly spaces, taking into account specific medical, nursing, nutritional, and mental health and psychosocial support needs of children.

**Methods for clinical decision-making in COVID-19**

Conditional recommendation for

For patients COVID-19 of any severity assessed in a clinic or hospital, we suggest clinical judgment, including consideration of patients' values and preferences and local and national policy if available, to guide management decisions including admission to hospital and to the ICU, rather than currently available prediction models for prognosis (conditional recommendation, very low certainty).

**Evidence to decision**

**Benefits and harms** Important harms

Clinical judgment and policy developed locally or nationally are typically used to make decisions regarding admission of patients with COVID-19 to hospital and to the ICU. Judgment and policy may include ethical considerations regarding allocation of resources. Over the course of the pandemic, many models have been developed for patients with COVID-19 to predict hospital admission, ICU admission, need for

mechanical ventilation, mortality, or other outcomes. All existing models are at unclear or high risk of bias using the multiple domain PROBAST assessment tool *(76)*, and there are as yet no studies of whether the use and implementation of these models improves (shared) decision-making and subsequent patient outcomes. With respect to their effects on patient outcomes, the certainty of evidence for any of these prognostic models is very low.

| **Certainty of the evidence** | Very low |
|---|---|

The GDG considered the evidence in favour of prognostic models in patients with COVID-19 to be of very low certainty, due to risk of bias, insufficient predictive accuracy with many models (range of C-statistics for prognosis models 0.54 to 0.99), lack of validation studies, and lack of evidence of the impact of using models on decision-making and patient outcomes. A review and assessment of existing models on their applicability and risks of bias is available (https://www.covprecise.org/living-review/). These prediction models for patient prognosis are distinct from triage models that have been developed to decide which patients are offered admission (typically to an ICU); triage models were not reviewed.

The GDG acknowledged that ongoing model development and validation, along with studies of predictive accuracy and impact on decision-making and patient outcomes of those selected models with sufficient predictive accuracy, may change the certainty of evidence in the future.

| **Values and preferences** | Substantial variability is expected or uncertain |
|---|---|

Applying the agreed values and preferences, the GDG inferred that the majority of well-informed physicians and patients would not want care decisions to be based on existing prognostic models, due to the very low certainty of evidence for benefit on patient outcomes. Given the lack of evidence of harm, some patients may choose to have their care informed by the use of such models.

| **Resources and other considerations** | Important considerations |
|---|---|

Commonly included predictors in these prognostic models include age, sex, comorbidities, vital signs (e.g. temperature, heart rate, respiratory rate, oxygen saturation, blood pressure), imaging features, lymphocyte count, and C reactive protein (https://www.covprecise.org/living-review/). Some laboratory tests and imaging modalities may not be available in resource-constrained settings, and existing models have not been validated such settings.

**Justification**

The GDG emphasized the very low certainty evidence supporting the use of prognostic models to enhance clinical-decision making and patient outcomes, and recognized the lack of studies and uncertain feasibility in resource-constrained settings and potential negative impact on health equity, depending on how prognostic models are used to inform clinical decisions. Accordingly, the GDG made a conditional recommendation in favour of usual practice to guide decision-making, consisting of clinical judgment, patients' values and preferences, and local and national policy, if available.

**Subgroup analyses**

The GDG did not find any evidence bearing on subgroup effects across patients with different levels of COVID-19 disease severity or between children and adults. In other words, the conditional recommendation is applicable across all these subgroups.

**Applicability**

*Special populations*

There is insufficient information on the performance and impact of prognostic models in pregnant women. Therefore, the GDG concluded that the recommendation applies to pregnant women.

**Practical info**

Existing prognostic models are reviewed in a living systematic review, available at https://www.covprecise.org/living-review/.

**Uncertainties**

Available prognostic models need to be validated in other populations.

**Table 6.1 Symptoms associated with COVID-19**

Presenting signs and symptoms of COVID-19 vary.

Most persons experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgias (11–35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported *(28,77,78,79)*. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported *(31,80,81)*.

Additional neurological manifestations reported include dizziness, agitation, weakness, seizures, or findings suggestive of stroke including trouble with speech or vision, sensory loss, or problems with balance in standing or walking *(32,33)*.

Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, confusion, and absence of fever *(62,63,64)*.

Symptoms such as dyspnoea, fever, gastrointestinal (GI) symptoms or fatigue due to physiologic adaptations in pregnant women, adverse pregnancy events, or other diseases such as malaria, may overlap with symptoms of COVID-19 *(82)*.

Children might not have reported fever or cough as frequently as adults *(83)*.

**Table 6.2 Risk factors associated with severe disease**

Age more than 60 years (increasing with age).

Underlying noncommunicable diseases (NCDs): diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, dementia, mental disorders, chronic kidney disease, immunosuppression, obesity and cancer have been associated with higher mortality *(84,85)*.

In pregnancy, increasing maternal age, high BMI, non-white ethnicity, chronic conditions and pregnancy specific conditions such as gestational diabetes and pre-eclampsia *(53)*.

Smoking.

**Table 6.3 COVID-19 disease severity**

| | | |
|---|---|---|
| **Mild disease** | | Symptomatic patients (Table 6.1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.<br><br>See the WHO website for most up-to-date case definitions *(1)*. |
| **Moderate disease** | **Pneumonia** | **Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including $SpO_2$ ≥ 90% on room air *(86)*.<br><br>**Child** with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia.<br>Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(87)*.<br><br>While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.<br><br>**Caution:** The oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously. For example, clinicians must use their judgment to determine whether a low oxygen |

| | | |
|---|---|---|
| | | saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation >90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe. |
| **Severe disease** | **Severe pneumonia** | **Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or $SpO_2$ < 90% on room air *(86,88)*.<br><br>**Child** with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following:<br>• Central cyanosis or $SpO_2$ < 90%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions *(87)*.<br>• Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(87)*.<br><br>While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications. |
| **Critical disease** | **Acute respiratory distress syndrome (ARDS)** *(89,90,91)* | **Onset:** within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms.<br><br>**Chest imaging:** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.<br><br>**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/oedema if no risk factor present.<br><br>**Oxygenation impairment in adults** *(89,91)*:<br>• Mild ARDS: 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O).b<br>• Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O).b<br>• Severe ARDS: $PaO_2/FiO_2$ ≤ 100 mmHg (with PEEP ≥ 5 $cmH_2O$).[b]<br><br>**Oxygenation impairment in children:** note OI and OSI.[c] Use OI when available. If $PaO_2$ not available, wean $FiO_2$ to maintain $SpO^2$ ≤ 97% to calculate OSI or $SpO_2/FiO_2$ ratio:<br>• Bilevel (NIV or CPAP) ≥ 5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264.<br>• Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5.<br>• Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3.<br>• Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3. |
| | **Sepsis** *(92,93)* | **Adults:** acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status (delirium), difficult or fast breathing, low oxygen saturation, reduced urine output *(92)*, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.<br><br>**Children:** suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria,[d] of which one must be abnormal temperature or white blood cell count. |
| | **Septic shock** *(92,93)* | **Adults:** persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L.<br><br>**Children:** any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; |

| | | |
|---|---|---|
| | | fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia *(94)*. |
| | **Acute thrombosis** | Acute venous thromboembolism (i.e. pulmonary embolism), acute coronary syndrome, acute stroke. |
| | **MIS-C** | **Preliminary case definition:** children and adolescents 0–19 years of age with fever ≥ 3 days **AND** two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated D-dimers), acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain); **AND** elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. **AND** no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. **AND e**vidence of COVID-19 **(**RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19. See scientific brief, 15 May 2020 WHO: Multisystemic inflammatory syndrome in children and adolescents temporally related to COVID-19 |

[a] If altitude is higher than 1000 m, then the correction factor should be calculated as follows: $PaO_2/FiO_2$ x barometric pressure/760.
[b] When $PaO_2$ is not available, $SpO_2/FiO_2 \leq 315$ suggests ARDS (including in non-ventilated patients).
[c] Oxygenation Index (OI) is an invasive measurement of the severity of hypoxaemic respiratory failure and may be used to predict outcomes in paediatric patients. It is calculated as follows: percentage of fraction of inhaled oxygen multiplied by the mean airway pressure (in mmHg), divided by the partial pressure of arterial oxygen (in mmHg). Oxygen Saturation Index (OSI) is a non-invasive measurement and has been shown to be a reliable surrogate marker of OI in children and adults with respiratory failure. OSI replaces $PaO_2$ with oxygen saturation as measured by pulse oximetry ($SpO_2$) in the OI equation.
[d] SIRS criteria: abnormal temperature (> 38.5 °C or < 36 °C); tachycardia for age or bradycardia for age if < 1 year; tachypnoea for age or need for mechanical ventilation; abnormal white blood cell count for age or > 10% bands.
Abbreviations: BP blood pressure; bpm beats per minute; CPAP continuous positive airway pressure; CT computed tomography; $FiO_2$ fraction of inspired oxygen; MAP mean arterial pressure; NIV non-invasive ventilation; OI Oxygenation Index; OSI Oxygenation Index using $SpO_2$; $PaO_2$ partial pressure arterial oxygen; PEEP positive end-expiratory pressure; SBP systolic blood pressure; SD standard deviation; SIRS systemic inflammatory response syndrome; SOFA sequential organ failure assessment; $SpO_2$ oxygen saturation.

# 7. Immediate implementation of appropriate infection prevention and control measures

Infection prevention and control (IPC) is a critical and integral part of clinical management of patients, health workers' safety and hospital-acquired infections. In addition to screening, triage, and rapid source control, WHO guidance emphasizes the importance of administrative, environmental and engineering controls in health care settings *(95)*. Universal masking in health facilities (wearing a mask at all times except when eating or drinking) is required for all persons (staff, patients, visitors, service providers and others) in areas of known or suspected community or cluster SARS-CoV-2 transmission *(96)*, as well as rational and appropriate use of all personal protective equipment (PPE) *(101)*.

For the most up-to-date, comprehensive WHO guidance see *Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed (95)* and *Transmission of SARS-CoV- 2: implications for infection prevention precautions*, 9 July 2020 *(102)*.

**How to implement IPC measures for patients with suspected or confirmed** ***(95)***

**Screening and triage for early recognition of suspected COVID-19 patients and rapid implementation of source control measures.** Screen all persons at first point of contact in health facility to allow for early recognition followed by their immediate isolation/separation.

**Remarks:**
Ask the suspected or confirmed COVID-19 patient to wear a medical mask and direct the patient to a separate, well-ventilated area, ideally an isolation room/area if available. Keep at least 1 m distance between patients. Instruct all patients to cover nose and mouth during coughing or sneezing with tissue or flexed elbow, dispose of tissues safely immediately after use in a closed bin and perform hand hygiene

after contact with respiratory secretions. In areas with COVID-19 community transmission, restrict visitors to those that are essential such as the parents of paediatric patients and caregivers and ask them to wear a mask.

**Apply standard precautions for all patients.**

**Remarks:**
Apply standard precautions according to risk assessment for all patients, at all times, when providing any diagnostic and care services. Standard precautions include but are not limited to, hand and respiratory hygiene and the appropriate use of PPE; universal masking is required for all persons in areas of known or suspected community or cluster SARS-CoV-2 transmission *(96)*. Standard precautions also include appropriate patient placement; environmental cleaning; prevention of needle-stick or sharps injury and safe waste management.

Carefully practise hand hygiene using an alcohol-based hand rub if hands are not visibly dirty or soap and water and disposable towels, before PPE use and after PPE removal, and when indicated while providing care, according to the WHO Five Moments for hand hygiene *(97)*.

If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs, pulse oximeters and thermometers). If equipment needs to be shared among patients, clean and disinfect between each patient use. Ensure that health care workers avoid contaminating environmental surfaces that are not directly related to patient care (e.g. door handles and light switches) and refrain from touching their eyes, nose and mouth with potentially contaminated gloved or ungloved hands. All surfaces should be routinely cleaned and disinfected, especially high touch surfaces, those surfaces touched by patients and whenever visibly soiled or if contaminated with blood and body fluids.

Best practices for safely managing health care waste, including waste related to surgeries and obstetric care, should be followed.

**Apply contact and droplet precautions for suspected or confirmed COVID-19 patients.**

**Remarks:**
For suspected and confirmed COVID-19 patients, contact and droplet or airborne precautions should be applied depending on activity to be undertaken. Where possible, designate a team of health workers to care for patients with suspected or confirmed COVID-19 and restrict their contact with COVID-19 patients.

Place all cases in well-ventilated single rooms if feasible. When single rooms are not available or bed occupancy rate is anticipated to be 100% or more, suspected, probable or confirmed COVID-19 patients should be grouped together (cohorted) in adequately ventilated areas with bed space at least 1 m apart.

Limit patient movement within the institution and ensure that patients wear medical masks when outside of their care area (e.g. when being transported).

Health workers should use gloves, a clean, long sleeved gown, medical mask and eye protection (goggles or face shield). Remove PPE when leaving the patient care area, following instructions how to remove PPE safely *(98)*.

**Apply airborne precautions when performing aerosol-generating procedures.**

**Remarks:**
Perform procedure in adequately ventilated rooms.

When performing aerosol-generating procedures (tracheal intubation, non-invasive ventilation [CPAP and BiPAP], tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy and sputum induction induced by using nebulized hypertonic saline) or in settings where aerosol-generating procedures are performed, airborne in combination with contact precautions should be used. Use the appropriate PPE, including fit-tested particulate respirators (N95 or equivalent, or higher level of protection), gloves, long-sleeved gowns, eye protection (goggles or face shield). In areas of community transmission, in ICUs where aerosol-generating procedures are frequently performed, the health worker may choose to wear a particulate respirator throughout their shift. There is insufficient evidence to classify

high-flow nasal oxygen (HFNO) and nebulizer therapy as an aerosol-generating procedure that is associated with transmission of COVID-19; thus airborne in combination with contact precautions should be used.

*Note:* In situations where TB may co-exist, specific measures may be necessary in addition to the above *(67)*.

# 8. Laboratory diagnosis

For more details, we refer to published WHO guidance *Diagnostic testing for SARS-CoV-2* regarding specimen collection, processing and laboratory testing and the diagnostic algorithm *(99)*.

**We recommend, for all suspect COVID-19 cases, at minimum the collection of respiratory specimens for nucleic acid amplification testing (NAAT), for example reverse transcription polymerase chain reaction (RT-PCR). Repetitive testing of upper respiratory tract (URT) and/or lower respiratory tract (LRT) might be needed to establish a diagnosis *(100)*. Additional samples that might aid the diagnosis of COVID-19 can be faecal specimens (if appropriately validated by the receiving laboratory). If deceased consider the collection of postmortem specimens *(99)*. In addition, testing for other respiratory viruses and bacteria should be considered when clinically indicated according to local guidelines.**

**SARS-CoV-2 antibody tests are not recommended for diagnosis of current infection with COVID-19.**

**Remarks:**

1. Use appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens). See IPC guidelines for the most up-to-date guidance *(101,102)*.
2. In the first week of symptom onset relatively high viral loads are generally observed in the upper respiratory tract (URT) specimens. For the collection of URT samples, we recommend the collection of nasopharyngeal and oropharyngeal specimens. When collecting URT samples, use viral swabs (sterile Dacron or rayon, not cotton), for nasopharyngeal swabbing use a swab with a long flexible shaft designed for nasopharyngeal sampling. For instructions on appropriate URT sampling see *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (73)*. Unless specified differently by the receiving laboratory, transport sample in viral transport media.
3. LRT (vs URT) samples are more likely to be positive after the first week of illness. Thus if URT are negative and clinical suspicion remains, also collect specimens from the LRT when readily available (expectorated sputum, or endotracheal aspirate/bronchoalveolar lavage in ventilated patient). 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 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 *(99)*. 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 *(13)*.
4. NAAT testing is the recommended for the diagnosis of COVID-19. However in cases where NAAT is unavailable or where prolonged turnaround times preclude clinical utility, antigen testing can be included in the diagnostic algorithm under the right circumstances. For details on appropriate utilization of antigen testing see interim guidance *Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays (103)*. If antigen testing is used, assure that sample collection and testing is performed according to the instructions for use of the antigen tests, staff are appropriately trained and testing quality is embedded in a diagnostic quality system and assessed regularly.
5. If repetitive negative NAAT/RT-PCR results are obtained from a patient in whom COVID-19 is strongly suspected, a paired serum specimen could be collected. One specimen taken in the acute phase and one in the convalescent phase 2–4 weeks later. This is only useful if validated (semi) quantitative

serology assays and trained staff for the interpretations are available in the receiving laboratory. With these paired samples it can be retrospectively evaluated whether there is seroconversion or a rise in antibody titres, further supporting the suspicion that this individual indeed had recent COVID-19 despite negative NAATs.

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

**Remarks:**

1. Patients should also be tested for other respiratory pathogens, as recommended in local clinical management guidelines. Examples, but not excluding others as this depends on epidemiological or clinical parameters, are the viral respiratory pathogens influenza A and B (including zoonotic influenza A), respiratory syncytial virus, parainfluenza viruses, rhinoviruses, adenoviruses, enteroviruses (e.g. EVD68), human metapneumovirus and endemic human coronaviruses (i.e. HKU1, OC43, NL63, and 229E). Examples of bacterial pathogens include *Streptococcus pneumoniae, Haemophilus influenzae*, atypical respiratory pathogens (e.g. *Legionella pneumophila, Coxiella burnetii, Chlamydia psittaci or pneumoniae, Mycoplasma pneumoniae*). URT and LRT specimens are generally suitable for viral respiratory pathogens. For bacterial culture sputum or other LRT specimens are required.
2. Dual infections with other respiratory infections (viral, bacterial and fungal) have been found in COVID-19 patients *(104)*. As a result, a positive test for a non-COVID-19 pathogen does not rule out COVID-19, or vice versa. Some microbes found in respiratory culture can be either be a pathogen or be part of normal mouth/respiratory flora, thus evaluation on whether a found micro-organism is a coinfection or part of the normal flora needs to be weighted for each individual patient.
3. In malaria-endemic areas, patients with fever should be tested for the presence of malaria or other co-infections with validated rapid diagnostic tests (RDTs) or thick and thin blood films and treated as appropriate *(105)*. In endemic settings, arbovirus infection (dengue/chikungunya) should also be considered in the differential diagnosis of undifferentiated febrile illness, particularly when thrombocytopenia is present *(65)*. Coinfection with COVID-19 virus may also occur and a positive diagnostic test for dengue (e.g. dengue RDTs) does not exclude the testing for COVID-19 *(106)*. If TB is also suspected, collect sputum with specific instructions (e.g. to be done in open area outside the home and away from others) or in an open, well-ventilated space – preferably outside of the health facility *(67)*. Staff should not stand near the patient during sample collection.
4. When influenza virus is known or suspected to be circulating, test patients with severe or complicated disease and those with risk factors for severe influenza (note, this includes younger children and pregnant women up to two weeks postpartum) for influenza virus with a rapid molecular testing when results can be made available within 24 hours preferably. The longer the time lag between sampling and test results, the less the test will benefit clinical management (see policy brief) *(107)*. Empiric treatment, when indicated, should not be delayed while waiting for results (see Chapter 16. Treatment of other acute and chronic infections in patients with COVID-19).

**For COVID-19 patients with severe or critical disease, also collect blood cultures, ideally prior to initiation of antimicrobial therapy *(92)*.**

**Remark:**

If blood cultures cannot be taken timely before the administration of antimicrobial therapies, indicate the details of administered antibiotics on the laboratory request.

# 9. 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.

**Please find new recommendation on the use of pulse oximetry at home in Chapter 10 (Management of moderate COVID-19: pneumonia treatment).**

**We 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:**

1. 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 *(65,66,69)* irrespective of the presence of respiratory signs and symptoms. Coinfection with COVID-19 may occur.
2. 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.
3. 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 *(108)*.

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

**Remark:**
At present, there is no evidence to indicate that there are severe adverse events in patients with COVID-19 as a result of the use of non-steroidal anti-inflammatory drugs *(109)*.

**Counsel patients with mild COVID-19 about signs and symptoms of complications that should prompt urgent care.**

**Remark:**
Patients with risk factors for severe illness should be monitored closely, given the possible risk of deterioration. If they develop any worsening symptoms (such as light headedness, difficulty breathing, chest pain, dehydration, etc.), they should seek urgent care through the established COVID-19 care pathway. 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 *(110)*. See new recommendation in Chapter 10 on use of home pulse oximetry.

**We recommend that antibiotic therapy or prophylaxis should not be used in patients with mild COVID-19.**

**Remark:**
Widespread use of antibiotics should be discouraged, as their use may lead to higher bacterial resistance rates, which will impact the burden of disease and deaths in a population during the COVID-19 pandemic and beyond *(111,112,113)*.

# 10. Management of moderate COVID-19: 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 Table 6.3 for definition of non-severe pneumonia.

**Please find new recommendation on the use of pulse oximetry at home in this chapter as the second recommendation.**

**We recommend that patients with suspected or confirmed moderate COVID-19 (pneumonia) be isolated to contain virus transmission. Patients with moderate illness may not require emergency interventions or hospitalization; 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 on 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 (see Table 6.2), isolation in hospital is preferred.**

**Remark:**
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 *(65,66,105)*, irrespective of the presence of respiratory signs and symptoms. Coinfection with COVID-19 may occur.

Conditional recommendation for

**For symptomatic patients with COVID-19 and risk factors for progression to severe disease who are not hospitalized, we suggest the use of pulse oximetry monitoring at home as part of a package of care, including patient and provider education and appropriate follow-up (conditional recommendation, very low certainty evidence).**

**Evidence to decision**

| **Benefits and harms** | Uncertain benefits or harms |
|---|---|

Possible theoretical benefits of home oximetry monitoring include earlier detection of and intervention for severe disease (such as more intense monitoring for deterioration or starting corticosteroid therapy), patient reassurance in case of normal values, limiting hospital strain due to prevented admission of patients who may not need acute care, and increased opportunities for patient-provider educational conversations (very low certainty).

Possible harms of home oximetry monitoring include the possibility of increased patient anxiety and stress, the possibility of increased hospital visits for patients who would otherwise not seek out hospital care, and the possibility of false reassurance with misinterpretation of the data. Low quality or inaccurate pulse oximeters, particularly with pulse oximeters not validated in different skin colours, may provide false reassurance or false alarms (very low certainty).

The GDG suggested that the possible benefits would outweigh the possible harms, and this may be most likely in specific subgroups of patients, i.e. those with symptoms and those with risk factors for severe disease. The GDG also suggested that the intervention would only have benefit in symptomatic patients with COVID-19, and that asymptomatic patients would have no benefit.

| **Certainty of the evidence** | Very low |
|---|---|

For key outcomes of hospitalization, mortality, mechanical ventilation, and ICU admission the panel considered the evidence to be of very low certainty.

| **Values and preferences** | No substantial variability expected |
|---|---|

Applying the agreed values and preferences, the GDG inferred that well-informed patients would consider the minimal possible harms associated with home oximetry monitoring to not outweigh the possible, theoretical benefits on the outcomes of hospitalization and patient satisfaction. Patient members of the panel agreed with this standard.

| **Resources and other considerations** | Important considerations |
|---|---|

Home oximetry monitoring is not accessible to many patients, due to lack of available equipment, lack of relevant personnel to monitor it, lack of ability to interpret the results at home, or lack of knowledge about implementation. Home pulse oximetry may be useful in certain settings, including low-resource settings, particularly when hospitals are strained and where it may be necessary to effectively monitor patients in a home-based setting. However, home oximetry monitoring will only be of value if the users are adequately informed on how to interpret the readings and have ready access to providers who can advise on the response to readings. Considerations for education and training of patients and providers, as well as adequate staffing, to implement care pathways with available access to acute care, will need to be integrated.

**Justification**

When moving from evidence to the conditional recommendation for the use of home pulse oximetry monitoring for patients with COVID-19, the panel emphasized the lack of evidence in either direction and the need for high-quality clinical trials examining both patient symptoms of stress, as well as other clinical outcomes listed above. The panel also emphasized contextual factors, such as resource considerations, accessibility, feasibility, and impact on health equity as important considerations. Ultimately, the panel thought that the theoretical benefit targeted to symptomatic and high-risk populations was notable only as part of a larger package of care including education and follow-up. Important caveats raised by the panel included the importance of integrating any intervention with education between providers and patients about the meaning of relevant output from the pulse oximeter and ability to act on results.

**Subgroup analyses**

There were insufficient data based on the presented data to perform any subgroup analyses.

**Applicability**

*Special populations*

There is no evidence for home pulse oximetry monitoring for patients with COVID-19 in special populations. Considerations for implementation and applicability centred around focusing on higher-risk populations, where benefits would be most notable. Please see Table 6.2 for information on definitions of who would be considered high risk for this implementation.

**Practical info**

The GDG made a conditional recommendation for the use of home pulse oximetry monitoring. This recommendation is predicated on the availability and accessibility of high-quality and reliable pulse oximeters for home use; the integration of home pulse oximetry into a health system, from a training and human resources perspective; and targeting the intervention to patients who would likely get the most benefit, namely those at high risk and those who are symptomatic. Also, no recommendation was made on the frequency or duration of pulse oximetry monitoring. *Note:* training on appropriate IPC (cleaning and disinfection) should be included.

**Uncertainties**

The panel encourage further research to clarify uncertainties, especially in low-resource settings. Research gaps remain as to ensuring standards of quality across pulse oximeter devices.

**PICO (12.1)**
Population: Patients treated at home with confirmed or suspected COVID-19 disease
Intervention: $SpO_2$ < 92% (Pulse oximetry use at home)
Comparator: $SpO_2$ ≥ 92% (Pulse oximetry use at home)

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** $SpO_2$ ≥ 92% (Pulse oximetry use at home) | $SpO_2$ < 92% (Pulse oximetry use at home) | **Certainty of the evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| Hospitalization | Relative risk: 7.0 (CI 95% 3.4–14.5) Based on data from 77 patients in 1 study | **103** per 1000 | **840** per 1000 Difference: **737 more per 1000** (CI 95% 453 more – 1597 more) | **Very low** Due to serious risk of bias. Due to serious imprecision[a] | $SpO_2$ < 92% possibly increases need for hospitalization. |
| ICU admission | Relative risk: 9.8 (CI 95% 2.2–44.6) Based on data from 77 patients in 1 study | per 1000 | per 1000 Difference: **fewer per 1000** | **Very low** Due to serious risk of bias. Due to serious imprecision[b] | $SpO_2$ < 92% possibly increases need for ICU admission. |
| ARDS | Relative risk: 8.2 (CI 95% 1.7–38.7) Based on data from 77 patients in 1 study | per 1000 | per 1000 Difference: **fewer per 1000** | **Very low** Due to serious risk of bias. Due to serious imprecision[c] | $SpO_2$ < 92% possibly increases the risk of ARDS. |
| Septic shock | Relative risk: 6.6 (CI 95% 1.3–32.9) Based on data from 77 patients in 1 study | per 1000 | per 1000 Difference: **fewer per 1000** | **Very low** Due to serious risk of bias. Due to serious imprecision[d] | $SpO_2$ < 92% possibly increases the risk of septic shock. |
| Hospitalization | Based on data from patients in 2 studies | Two small single arm (no comparator group) studies that offered home monitoring to patients discharged from emergency department. 3/20 (150 per 1000) and 6/52 (115 per 1000) of patients using home $SpO_2$ monitors required hospitalization. | | **Very low** Due to serious risk of bias. Due to serious imprecision[e] | No data re whether home $SpO_2$ monitoring vs no monitoring affects hospitalization rates. |

[a] **Risk of bias: serious. Imprecision: serious.**
[b] **Risk of bias: serious. Imprecision: serious.**
[c] **Risk of bias: serious. Imprecision: serious.**
[d] **Risk of bias: serious. Imprecision: serious.**
[e] **Risk of bias: serious. Imprecision: serious.**

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

**Remarks:**

1. 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 *(104)*.
2. Consider in older people, particularly those in LTCFs, and children < 5 years of age, to provide empiric antibiotic treatment for possible pneumonia *(111,112)*. 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) *(113)*.

**We 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:**

1. For patients being treated at home, counselling regarding signs and symptoms of complications (such as difficulty breathing, chest pain, etc.) should be provided to patients and their caregivers. If they develop any of these symptoms, they should seek urgent care through the established COVID-19 care pathway. Consider alternative delivery platforms such as home-based, phone, telemedicine or community outreach teams to assist with monitoring.
2. 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 *(114)*.

# 11. Management of severe COVID-19: severe pneumonia treatment

**Please find new recommendation on awake prone positioning in this chapter as the fourth recommendation.**

**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).**

**Remark:**
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 (115)*.

**We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target $SpO_2$ ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxaemic patient) to target $SpO_2$ > 90% or ≥ 92–95% in pregnant women.**

**Remarks for adults:**

1. 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 $SpO_2$ ≥ 94% *(72,116)*.
2. Once the patient is stable, target > 90% $SpO_2$ in non-pregnant adults and ≥ 92–95% in pregnant women.
3. Deliver oxygen flow rates using appropriate delivery devices (e.g. use nasal cannula for rates up to 5 L/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 (73)*.
4. In adults, techniques such as positioning, e.g. high supported sitting, may help to optimize oxygenation, ease breathlessness and reduce energy expenditure *(117)*.
5. In 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 cycle of breathing technique. 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 *(117)*.

**Remarks for children:**

1. 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 $SpO_2 \geq 94\%$ *(72,116,118)*.
2. Once patient is stable, the target is > 90% $SpO_2$ *(118)*.
3. Use of nasal prongs or nasal cannula is preferred in young children, as they may be better tolerated.

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

**Remarks:**

1. 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 *(114)*.
2. Haematology and biochemistry laboratory testing and electrocardiogram and chest imaging should be performed at admission and as clinically indicated to monitor for complications, such as 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.
3. 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 coronary syndrome, and proceed according to hospital protocols for diagnosis (such as laboratory tests and/or imaging) and further management.
4. 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.

Conditional recommendation for

**We suggest awake prone positioning of severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes high-flow nasal oxygen) or non-invasive ventilation (conditional, low certainty evidence).**

**Evidence to decision**

**Benefits and harms** — Uncertain benefits or harms

There have been no randomized controlled trials (RCTs) completed for awake prone positioning for patients with COVID-19 requiring supplemental oxygen or non-invasive ventilation. Observational studies of awake prone position in patients with COVID-19 suggest benefits on patient-important outcomes of mortality and the need for intubation COVID-19 (very low certainty). Evidence from RCTs of prone positioning for intubated, critically ill patients with ARDS (non-COVID-19) have demonstrated benefits in mortality. The effect on less important outcomes is uncertain.
The harms of awake prone positioning are possibly patient discomfort and pain (very low certainty). The indirect evidence on harms of prone positioning from the randomized evidence on sedated, intubated patients are pressure sores, nerve injury, and haemodynamic instability, which were not considered relevant for this less severely ill population.

**Certainty of the evidence** — Low

For patient-important outcomes of mortality and the need for mechanical ventilation, the panel considered the direct evidence to be of very low certainty. For the patient-important outcomes of mortality, indirect evidence from intubated, sedated patients with ARDS was downgraded for indirectness, from high to low, with key considerations including the different physiology of critical disease, data from a non-COVID-19 period, and the different sedation strategies employed.

**Values and preferences** — No substantial variability expected

Applying the agreed values and preferences, the GDG inferred that almost all well-informed patients would want to undergo prone positioning if awake, requiring oxygen or non-invasive respiratory support, given the lack of harm from the observational studies and panel experience. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention. Patient discomfort for prone position could limit time spent in individual circumstances.

**Resources and other considerations** — Important considerations

Patients who are able to follow instructions can self-prone, without assistance from health care workers. Proning patients who require assistance is associated with human resource requirements regarding training, particularly with monitoring of respiratory status. The panel felt that that this intervention should be feasible in all settings, but implementation requires dedicated training and monitoring.

**Justification**

When moving from evidence to the conditional recommendation for the use of awake prone positioning in severely ill hospitalized patients with COVID-19, the panel emphasized the low certainty evidence of reduction in mortality, downgraded from higher certainty evidence in critically ill patients with ARDS. It also noted the limited harm with the experience thus far with awake prone positioning across different resource settings.

**Subgroup analyses**

The panel commented on the need for data in specific populations, namely paediatrics, older people, and pregnant women in the first two trimesters.

**Practical info**

The GDG made a conditional recommendation for awake prone positioning in severely ill patients with COVID-19 requiring supplemental oxygen (including HFNO) or non-invasive ventilation.

In light of the uncertain benefits of awake prone positioning, a high level of vigilance should be maintained, and patients should be monitored closely for signs of clinical deterioration.

Monitoring of patients and training of providers in caring for patients who are awake and prone is an important part of implementation, as part of multi-faceted training for acute care management, which includes medical device training.

As for duration, some suggest regimens that target being in awake prone position for 8–12 hours/day, broken into shorter periods over the day.

**Uncertainties**

Further RCTs are recommended to better define benefits and harms, as well as specific populations of interest.

**PICO (13.1)**

Population: Patients hospitalized with severe COVID-19 infection
Intervention: Awake prone positioning + usual care
Comparator: Usual care

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Usual care | Awake prone positioning + usual care | **Certainty of the evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| Mortality | Based on data from 334 patients in 17 studies | 17 single arm (no comparator group) studies that enrolled a total of 334 participants. 37/334 (110 per 1000) patients positioned prone while receiving oxygen supplementation or NIV dead. | | **Very low** Due to serious risk of bias. Due to very serious imprecision[a] | There are no comparative data assessing the effect of awake proning in COVID-19 patients with regards to mortality. |

| | | | | |
|---|---|---|---|---|
| Intubation | Based on data from 450 patients in 25 studies | 25 single arm (no comparator group) studies that enrolled a total of 450 participants. 130/450 (289 per 1000) patients positioned prone while receiving oxygen supplementation or NIV required intubation. | **Very low** Due to serious risk of bias. Due to very serious imprecision[b] | There are no comparative data assessing the effect of awake proning in COVID-19 patients with regards to intubation rates. |
| Adverse effect (pain or discomfort) | Based on data from 151 patients in 6 studies | 6 single arm (no comparator group) studies that enrolled a total of 151 participants. 29/151 (192 per 1000) patients positioned prone while receiving oxygen supplementation or NIV reported pain or discomfort. | **Very low** Due to serious risk of bias. Due to very serious imprecision[c] | There are no comparative data assessing the effect of awake proning in COVID-19 patients with regards to adverse events. |

[a] **Risk of bias: serious. Imprecision: very serious.**
[b] **Risk of bias: serious. Imprecision: very serious.**
[c] **Risk of bias: serious. Imprecision: very serious.**

**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 *(119)*. This applies to both children and adults.

# 12. Management of critical COVID-19: acute respiratory distress syndrome (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 *(92)*.

**Please find new recommendation on the use of existing care bundles in Chapter 14 (Prevention of complications in hospitalized and critically ill patients with COVID-19).**

The following recommendations pertain to adult and paediatric patients with mild ARDS who are treated with non-invasive or 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 Table 6.3 for definitions of mild, moderate and severe ARDS.**

**Remarks:**

1. Patients with hypoxaemic respiratory failure and haemodynamic instability, multiorgan failure or abnormal mental status should not receive HFNO or NIV in place of other options such as invasive ventilation.
2. 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 hour). Intubation should not be delayed if the patient acutely deteriorates or does not improve after a short trial.
3. Adult HFNO systems can deliver 60 L/min of gas flow and $FiO_2$ 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 (115)*.

4. 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.
5. Compared with standard oxygen therapy, HFNO may reduce the need for intubation *(121)*. Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary oedema), haemodynamic instability, multiorgan 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 *(121)*. Evidence-based guidelines on HFNO do not exist, and reports on HFNO in patients infected with other coronaviruses are limited *(122,123)*.
6. NIV guidelines make no recommendation on use in hypoxaemic respiratory failure (apart from cardiogenic pulmonary oedema, postoperative respiratory failure and early NIV for immunocompromised patients) or pandemic viral illness (referring to studies of SARS and pandemic influenza) *(120)*. 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 *(123)*.
7. 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 hypoxaemia *(124)*.

The following recommendations pertain to adult and paediatric 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; $FiO_2$ 0.60–0.95). Hypoxaemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation *(92)*.

**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% $FiO_2$ for 5 minutes, 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 *(125,126,127)*.

The following recommendations pertain to mechanically ventilated adult and paediatric patients with ARDS *(92,128)*.

**We recommend implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 $cmH_2O$).**

**Remark 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 *(92)*, and is also suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria *(92)*. 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 *(129)*. 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 $cmH_2O$) 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 *(128)*.

**In adult patients with severe ARDS ($PaO_2/FiO_2$ < 150) prone ventilation for 12–16 hours per day is recommended.**

**Remarks:**
Application of prone ventilation is recommended for adult patients, preferably for 16 hours 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 *(130,131)*.
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 guideline *(92)*. The main effect is to shorten the duration of ventilation. A sample protocol for implementation of this recommendation is available *(132)*.

**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) vs 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 $SpO_2$ *(133)*. In younger children, maximal PEEP pressures are 15 $cmH_2O$. Although high driving pressure (plateau pressure − PEEP) may more accurately predict increased mortality in ARDS compared with high tidal volume or plateau pressure *(134)*; data from RCTs of ventilation strategies that target driving pressure are not currently available.
A related intervention of recruitment manoeuvres (RMs) is delivered as episodic periods of high CPAP (30–40 $cmH_2O$), 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-analysis *(135)* 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 *(136)*. 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 *(137)*.

**In patients with moderate-severe ARDS ($PaO_2/FiO_2$ < 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 ($PaO_2/FiO_2$ < 150) without causing significant weakness *(138)*, 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 *(139)*. 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 *(117)*.

**In patients with excessive secretions, or difficulty clearing secretions, consider application of airway clearance techniques. These should be performed only if deemed medically appropriate *(117)* and appropriate IPC measures are in place.**

**Remarks:**

Active cycle of breathing techniques and positioning techniques can be used to optimize oxygenation *(140,141)*. Techniques for airway clearance and secretion management include positioning with gravity-assisted drainage, active cycle of breathing techniques, positive expiratory pressure therapy, and assisted or stimulated cough manoeuvres *(141)*. These techniques are only indicated for patients with mucous hypersecretion and difficulties clearing secretions, and for patients with co-existing respiratory or neuromuscular comorbidities *(141)*.
All interventions inducing cough for airway clearance are potentially aerosol-generating procedures, and airborne precautions should be in place (see Chapter 7 on IPC) *(95)*; and single-patient-use disposable options are recommended (such as positive expiratory pressure device).
Consider use respiratory muscle training in patients recovering from critical illness with suspected respiratory muscle weakness *(141)*.
Especially for critically ill patients, the early involvement of the multidisciplinary rehabilitation team is paramount to improve short- and long-term outcomes. This may include physiotherapists, occupational therapists, speech and language therapists, mental health and psychosocial providers, dieticians and in complex cases, physical and rehabilitation medicine doctors. However, rehabilitation workforce composition may vary by context and availability in different parts of the world.

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 ECMO, consider referral of patients who have refractory hypoxaemia (e.g. including a ratio of partial pressure of arterial oxygen [$PaO_2$] to the fraction of inspired oxygen [$FiO_2$] of < 50 mmHg for 3 hours, a $PaO_2$:$FiO_2$ of < 80 mmHg for > 6 hours) 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) *(142)*. However, ECMO was associated with a reduced risk of the composite outcome that consisted of mortality and crossover to ECMO treatment *(142)*, and a post-hoc Bayesian analysis of this RCT showed that ECMO is very likely to reduce mortality across a range of prior assumptions *(143)*. In patients with MERS, ECMO vs conventional treatment was associated with reduced mortality in a cohort study *(123)*. 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 *(144,145)*. In children, ECMO can also be considered in those with severe ARDS, although high-quality evidence for benefit is lacking *(128)*.

# 13. Management of critical COVID-19: septic shock

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 sepsis *(92)*.

**Please find new recommendation on the use of existing care bundles in Chapter 14 (Prevention of complications in hospitalized and critically ill patients with COVID-19).**

**Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) ≥ 65 mmHg AND lactate is ≥ 2 mmol/L, in the absence of hypovolaemia (see Table 6.3).**

**Recognize septic shock in children with any hypotension (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 and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnoea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia (see Table 6.3).**

**Remarks:**

1. In the absence of a lactate measurement, use blood pressure (i.e. MAP) and clinical signs of perfusion to define shock.
2. Standard care includes early recognition and the following treatments to be done immediately, within 1 hour of recognition: antimicrobial therapy, and initiation of fluid bolus and vasopressors for hypotension *(92)*. 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 adults *(92)* and children *(87,93)*. Alternate fluid regimens are suggested when caring for adults and children in resource-limited settings *(146,147)*.

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:**

1. Crystalloids include normal saline and Ringer's lactate.
2. 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.
3. Consider dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation based on local resources and experience *(92)*. 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.

4. 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 *(148)*.
5. Clinical trials conducted in resource-limited settings comparing aggressive versus conservative fluid regimens suggest higher mortality in patients treated with aggressive fluid regimens *(146,147)*. Refer to the WHO-ICRC *Basic emergency care* (Shock module) for an initial approach and management of shock in resource-limited settings *(72)*.

**Do not use hypotonic crystalloids, starches or gelatins for resuscitation.**

**Remark:**

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 *(92,149)*. 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 *(92)*.

**In adults, administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥ 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 and HR < 70 bpm or > 150 bpm in children);**
- **prolonged capillary refill (> 2 seconds) or feeble pulses;**
- **tachypnoea; 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 *(93)*.**

**Remarks:**

1. 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 vein *(150)* 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 ≥ 65 mmHg *(151)*.
2. 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.
3. In children, epinephrine is considered the first-line treatment, while norepinephrine can be added if shock persists despite optimal dose of epinephrine *(93)*.

**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.**

**Remark:**
No RCTs have compared dobutamine with placebo for clinical outcomes.

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

**Please find new recommendation on the use of existing care bundles in this chapter as the first recommendation, and new recommendation on anticoagulation for thromboprophylaxis in this chapter as the third recommendation.**

Conditional recommendation for

For patients with COVID-19 who are critically ill, with or without invasive mechanical ventilation, we suggest the use of existing care bundles (defined as three or more evidence informed practices delivered together and consistently to improve care; (see Evidence to decision for examples), chosen locally by the hospital or ICU and adapted as necessary for local circumstances (conditional recommendation, very low certainty).

**Evidence to decision**

| **Benefits and harms** | Some benefits |
|---|---|

Indirect evidence in patients without COVID-19 suggest that some care bundles may improve patient-important outcomes, such as mortality, but the effects vary depending on the specific bundle, and the population targeted. The certainty of evidence is generally low to very low. Examples of care bundles in the critically ill include those for reducing delirium and improving cognition and sleep (reviewed in *(152)*; other information available at https://www.icudelirium.org/medical-professionals/overview), preventing VAP *(153)*, treating sepsis (reviewed in http://links.lww.com/CCM/C326), preventing central venous catheter infection *(154)*, and preventing pressure ulcers (https://www.nice.org.uk/guidance/cg179). Details of selected other bundles reviewed by the Cochrane Collaboration in their review of the literature are in Annex 3. The effect on other outcomes is uncertain.

Potential harms of bundles include the administrative burden of initial implementation, ongoing training, and monitoring of performance (very low certainty).

| **Certainty of the evidence** | Very low |
|---|---|

The evidence review consisted of a rapid review by the Cochrane Collaboration, supplemented by references provided by GDG members. The Cochrane review found very low certainty evidence in support of a mortality reduction with implementation of care bundles in critically ill patients. Supplementary references provided low to very low certainty evidence for important effects on mortality with bundles to reduce delirium *(152)*, prevent VAP *(153)*, treat sepsis (http://links.lww.com/CCM/C326), and prevent central venous catheter infection *(154)* and pressure ulcers (https://www.nice.org.uk/guidance/cg179). All evidence reviewed was indirect, from non-COVID-19 populations.

| **Values and preferences** | No substantial variability expected |
|---|---|

Applying the agreed values and preferences, the GDG inferred that the majority of well-informed patients would want to receive care bundles, locally adapted as necessary and applicable to their situation, given the low to very low certainty evidence suggesting a reduction in mortality and very low certainty of harm.

| **Resources and other considerations** | Important considerations |
|---|---|

Care bundles may contain practices that require adaptation to implement in all settings, depending on their contents. For example, early mobilization and rehabilitation as part of a care bundle to reduce delirium may require additional training, and central line insertion may require multiple sterile towels or a sterile gown placed on the patient, if large sterile drapes are not available.

**Justification**

When moving from evidence to the conditional recommendation in favour of care bundles for critically ill patients with COVID-19, the panel emphasized the low to very low certainty evidence of reduction in mortality and possible administrative burdens for implementation. The GDG recognized that hospital or ICUs may select among existing care bundles and adapt them to local circumstances as required, based on contextual factors of resource considerations and feasibility. The GDG judged that considerations of accessibility and impact on health equity would not alter the recommendation. The GDG was not aware of ongoing studies of care bundles in the critically ill COVID-19 population.

**Subgroup analyses**

The panel did not find any evidence bearing on the question of subgroup effects across patients with different levels of disease severity or between children and adults. In other words, the conditional recommendation is applicable across all these subgroups.

**Applicability**

*Special populations*

None of the reviewed studies of care bundles enrolled children, and therefore the applicability of this recommendation to children is uncertain. However, the panel thought that the implementation of relevant care bundles for children with COVID-19 would have similar effects to care bundles in adults. Similarly, the panel concluded that the recommendation applies to pregnant women.

**Practical info**

The GDG made a conditional recommendation in favour of care bundles for critically ill patients with COVID-19. Existing care bundles for critically ill patients include those for reducing delirium and improving cognition and sleep (reviewed in *(152)*; other information available at https://www.icudelirium.org/medical-professionals/overview), preventing VAP *(153)*, treating sepsis (reviewed in http://links.lww.com/CCM/C326), preventing central venous catheter infection *(154)*, and preventing pressure ulcers (https://www.nice.org.uk/guidance/cg179). For some bundles, observational data have shown variable association between the bundle components and patient important outcomes *(155)*. Even in currently accepted care bundles, the components may change as the evidence base evolves. Hospitals and ICUs should choose bundles for which adherence is likely to be high.

**Uncertainties**

Monitor multiple RCTs in process in patients with COVID-19.

**PICO (16.2)**

Population: Patients with COVID-19 and ARDS or viral pneumonia who are critically ill in ICU, with or without invasive ventilation. Populations of children (defined <18 years) and adult patients (≥18 years)
Intervention: Existing validated care bundles*, chosen locally by the hospital or ICU, adapted to local circumstances, and felt to be appropriate for patients with COVID-19 as specified above. *A care bundle is defined as three or more evidence informed practices delivered together and consistently to improve care.
Comparator: Not using existing care bundles

| Outcome<br>Timeframe | Study results and measurements | Absolute effect estimates<br>No care bundles | <br>Care bundles | Certainty of the evidence<br>(Quality of evidence) | Plain text summary |
|---|---|---|---|---|---|
| Mortality (randomized trials)<br>at 6 months | Relative risk: 0.75<br>(CI 95% 0.53–1.06)<br>Based on data from 180 patients in 1 study | **489**<br>per 1000 | **367**<br>per 1000<br><br>Difference: **122 fewer per 1000**<br>(CI 95% 259 fewer – 29 more) | **Very low**<br>Due to very serious indirectness. Due to very serious imprecision[a] | ICU care bundles possibly reduce mortality. |
| Mortality (observational studies)<br>28 days or to hospital discharge | Relative risk: 0.75<br>(CI 95% 0.65–0.86)<br>Based on data from 1258 patients in 7 studies | **359**<br>per 1000 | **269**<br>per 1000<br><br>Difference: **90 fewer per 1000**<br>(CI 95% 126 fewer – 50 fewer) | **Very low**<br>Due to very serious indirectness. Due to very serious imprecision[b] | ICU care bundles possibly reduce mortality. |
| Administrative burden | Based on data from 0 patients in 0 studies | | | **Very low** | Care bundles may be associated with an appreciable administrative burden. |
| Impingement on physician autonomy | Based on data from 0 patients in 0 studies | | | **Very low** | Care bundles may be associated with an impingement of physician autonomy. |

[a] **Indirectness: very serious. Imprecision: very serious.**
[b] **Indirectness: very serious. Imprecision: very serious.**

### Thromboembolism

Coagulopathy is common in patients with severe COVID-19, and both venous and arterial thromboembolism have been reported *(41,42,156,157,158)*.

**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.**

### Thromboprophylaxis

Conditional recommendation for

In hospitalized patients with COVID-19, without an established indication for higher dose anticoagulation, we suggest administering standard thromboprophylaxis dosing of anticoagulation rather than therapeutic or intermediate dosing (conditional recommendation, very low certainty).

**Evidence to decision**

**Benefits and harms** Important harms

Therapeutic or intermediate dosing of anticoagulation, compared with prophylactic dosing of anticoagulation, possibly reduces mortality (very low certainty) and pulmonary embolism and probably increases the risk of major bleeding (moderate certainty for therapeutic anticoagulation; low certainty for intermediate dosing of anticoagulation). The effects on other outcomes are uncertain.

The absolute reductions in risks of mortality and pulmonary embolism, and the absolute increase in risk of major bleeding, are likely to be higher in patients with severe or critical illness due to COVID-19, who may have a higher baseline risk of these outcomes compared with patients with mild or moderate illness.

**Certainty of the evidence** — Very low

For reduction in mortality and pulmonary embolism, the panel considered the evidence in favour of therapeutic or intermediate dosing of anticoagulation to be of very low certainty, due to serious imprecision (confidence intervals included both important benefit and important harm) and risk of bias (confounding in observational studies; no randomized trials).

For avoidance of major bleeding, the panel considered the evidence in favour of standard thromboprohylaxis dosing, compared with therapeutic anticoagulation, to be of moderate certainty. This judgment was based on low-certainty evidence in observational studies in COVID-19 that was upgraded to moderate certainty based on a large body of supportive indirect evidence at low risk of bias (randomized trials of therapeutic anticoagulation for other indications).

For the comparison of standard thromboprophylaxis dosing compared with intermediate dosing of anticoagulation, the evidence for avoidance of major bleeding was rated as low certainty.

The panel acknowledged that reporting of ongoing randomized trials of therapeutic and intermediate dosing of anticoagulation, compared with standard thromboprophylaxis dosing, over the next several months were highly likely to upgrade the certainty of evidence and may lead to changes in recommendations.

**Values and preferences** — Substantial variability is expected or uncertain

The majority of GDG members inferred that most well-informed patients would not want to receive therapeutic or intermediate dosing of anticoagulation given the very low certainty evidence suggesting a possible reduction in mortality and pulmonary embolism and the low certainty (for intermediate dosing of anticoagulation) or moderate certainty (for therapeutic anticoagulation) of increased risk of major bleeding. A minority of GDG members believed that some well-informed patients would choose to receive intermediate dosing of anticoagulation, given the very low certainty evidence suggesting a possible reduction in mortality and pulmonary embolism and the low certainty of increased risk of major bleeding.

**Resources and other considerations** — Important considerations

Unfractionated heparin sodium and low molecular weight heparins such as enoxaparin are relatively inexpensive and are listed on the WHO Model List of Essential Medicines; but availability is variable. Shortages may reduce the availability of low molecular weight heparins in some settings. In low-resource settings, management of bleeding complications in patients receiving anticoagulant dosing higher than that used for standard thromboprophylaxis may be challenging due to limited coagulation testing and transfusion capacity.

**Justification**

When moving from evidence to the conditional recommendation in favour of standard thromboprophylaxis anticoagulation for patients with moderate, severe, and critical COVID-19, the panel emphasized the very low certainty evidence of reduction in mortality or pulmonary embolism with higher anticoagulant dosing. The panel recognized that the evidence supporting an increased risk of major bleeding was dominated by studies of therapeutic anticoagulation rather than intermediate dosing. The GDG panellists anticipated variability in patient values and preferences, and judged that other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation. The panel acknowledged that ongoing randomized trials are expected to add substantially to the evidence base over the next several months.

**Subgroup analyses**

The panel did not find any evidence bearing on the question of subgroup effects across patients with different levels of disease severity, between children and adults, by different anticoagulant regimens (including agent, dose and duration), and therefore did not make any subgroup recommendations. In other words, the conditional recommendation is applicable across all these subgroups.

**Applicability**

*Special populations*

None of the studies enrolled children, and therefore the applicability of this recommendation to children is uncertain. However, the panel did not think that children with COVID-19 would respond any differently to therapeutic or intermediate intensity anticoagulation. One observational study enrolled pregnant women, with very low certainty evidence in this population for a possible reduction in mortality. The panel thought that pregnant women would have a similar risk of increased bleeding as non-pregnant individuals. Therefore, the panel concluded that the recommendation applies to pregnant women. Safe anticoagulants for the fetus in pregnancy include unfractionated heparin and low molecular weight heparin, which do not cross the placental barrier.

**Practical info**

Therapeutic dosing of anticoagulation refers to the dose used for treatment of acute venous thromboembolism; intermediate dosing is commonly interpreted as twice the standard thromboprophylaxis dose. The GDG made a conditional recommendation in favour of standard thromboprophylaxis dosing of anticoagulation in patients with COVID-19 who do not have an established indication for higher dose anticoagulation.

Patients on standard thromboprophylaxis dosing of anticoagulation do not require monitoring, except for platelet count monitoring after 5–7 days if unfractionated heparin is used. Dosing should be adjusted according to body weight/BMI and renal function according to local protocols. For example, if renal failure is present, patient should receive unfractionated heparin or reduced dose of low molecular weight heparin.

Suggested dosing of standard thromboprophylaxis is as follows:

Enoxaparin 40 mg by subcutaneous injection every 24h:
- Prophylactic dosages (non-weight adjusted) in low body weight (women < 45 kg, men < 57 kg) may lead to a higher risk of bleeding. Careful clinical observation is advised.
- If BMI > 40 kg/$m^2$ or weight > 120 kg: enoxaparin 40 mg by subcutaneous injection every 12h.

Unfractionated heparin (UFH) 5000 units by subcutaneous injection every 8 or 12h:
- If BMI > 40 kg/$m^2$ or weight > 120 kg: 7500 units q12h or 5000 units every 8h.

Tinzaparin 4500 units/day if BMI < 40 kg/$m^2$ or weight < 120 kg; 9000 units/day if BMI > 40 kg/$m^2$ or weight > 120 kg.

Dalteparin 5000 units/day BMI < 40 kg/$m^2$ or weight < 120 kg; 5000 units every 12h if BMI > 40 kg/$m^2$ or weight > 120 kg.

Fondaparinux 2.5 mg by subcutaneous injection every 24h.

Exoxaparin and unfractionated heparin are both on the WHO Model List of Essential Medicines; enoxaparin has the advantage of daily dosing. The suggested duration of standard thromboprophylaxis is until hospital discharge.

If therapeutic dosing is prescribed, clinicians should be aware of the increased risk of bleeding, including major bleeding requiring transfusion (e.g. gastrointestinal) or clinically significant bleeding even if transfusion is not required (e.g. intracranial). These increased risks may also occur with intermediate dosing of anticoagulants, especially in the presence of other risk factors for bleeding. Heparin-induced thrombocytopenia associated with thrombosis is also a risk of unfractionated heparin and, less commonly, low molecular weight heparin.

Potential agents for therapeutic and intermediate intensity anticoagulation include low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, or fondaparinux. Factors influencing the choice of agent include availability of laboratory monitoring (needed for unfractionated heparin), requirement for rapid reversibility (favours unfractionated heparin), presence of severe renal dysfunction (favours unfractionated heparin), interaction with other drugs used to treat COVID-19 (especially direct oral anticoagulants), convenience (least with unfractionated heparin, most with direct oral anticoagulants), and suspicion of heparin-induced thrombocytopenia (favours fondaparinux or direct oral anticoagulants).

For therapeutic or intermediate intensity anticoagulation, patients should have baseline creatinine, platelet count, prothrombin time or international normalized ratio, and partial thromboplastin time. Patients on therapeutic dosing of unfractionated heparin require monitoring of partial thromboplastin time or anti-factor Xa levels and ideally platelet count. Patients on warfarin require monitoring of international normalized ratio.

**PICO (16.1)**
Population: Hospitalized patients without an indication for therapeutic anticoagulation
Intervention: Anticoagulation at therapeutic or intermediate intensity
Comparator: Anticoagulation at prophylactic intensity

| **Outcome** Timeframe | **Study results and measurements** | **Absolute effect estimates** Anticoagulation at prophylactic intensity | Anticoagulation at therapeutic or intermediate intensity | **Certainty of the evidence** (Quality of evidence) | **Plain text summary** |
|---|---|---|---|---|---|
| Mortality at 14 days | Hazard Ratio: 0.86 (CI 95% 0.73–1.07) Based on data from 2626 patients in 1 studies | Difference: **19.0 fewer** (CI 95% 38.0 fewer – 3.0 more) | | **Very low** Due to very serious risk of bias. Due to very serious imprecision[a] | Therapeutic or intermediate intensity anticoagulation possibly reduces mortality. |
| Pulmonary embolism at 14–28 days | Odds Ratio: 0.09 (CI 95% 0.02–0.57) Based on data from 82 patients in 1 studies | Difference: **16.0 fewer** (CI 95% 15.0 fewer – 7.0 fewer) | | **Very low** Due to very serious risk of bias. Due to very serious imprecision[b] | Therapeutic or intermediate intensity anticoagulation possibly reduces pulmonary embolism. |
| Major bleeding at 4–12 days | | Effect estimates ranged from OR 1.42 (matched case control) to 3.89 (retrospective cohort). Risk differences ranged from: 7 fewer per 1000 to 46 more per 1000 | | **Moderate** Upgraded due to all plausible confounding would have reduced the effect[c] | Therapeutic or intermediate intensity anticoagulation probably increases major bleeding. |

[a] **Risk of bias: very serious. Imprecision: very serious.**
[b] **Risk of bias: very serious. Imprecision: very serious.**
[c] **Upgrade: All plausible confounding would have reduced the effect.** Upgraded from low certainty evidence due to large body of relevant indirect evidence.

This summary of findings table was generated from a living systematic review (www.hematology.org/COVIDguidelines) based on data accessed on 1 December 2020.

## Prevention of other complications

Table 14.1 shows interventions to prevent complications in hospitalized and critically ill patients with COVID-19. They are based on Surviving Sepsis *(92)* or other guidelines *(153,159,160,161)*, 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 *(162)*. See the WHO *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation* for practical tools to assist implementation *(73)*.

**Table 14.1 Interventions to prevent complications in hospitalized and critically ill patients with COVID-19**

| **Anticipated outcome** | **Interventions** |
|---|---|
| Reduce days of invasive mechanical ventilation | • Use weaning protocols that include daily assessment for readiness to breathe spontaneously<br>• Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions<br>• Early mobilization<br>• Implementation of the above as a bundle of care (may also reduce delirium); such as the **A**wakening and **B**reathing **C**oordination, **D**elirium assessment/management, and **E**arly mobility (ABCDE) |
| Reduce incidence of ventilator-associated pneumonia | • Oral intubation is preferable to nasal intubation in adolescents and adults<br>• Keep patient in semi-recumbent position (head of bed elevation 30–45º)<br>• Use a closed suctioning system; periodically drain and discard condensate in tubing<br>• Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged, but not routinely |

| | |
|---|---|
| | • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days |
| Reduce incidence of catheter-related bloodstream infection | • Use a checklist with completion verified by a real-time observer as a reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed |
| Reduce incidence of pressure ulcers | • Turn patient every 2 hours |
| Reduce incidence of stress ulcers and GI bleeding | • Give early enteral nutrition (within 24–48 hours of admission)<br>• Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for GI bleeding include mechanical ventilation for ≥ 48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score |
| Reduce the development of antimicrobial resistance | • Utilize de-escalation protocols as soon as patient is clinically stable and there is no evidence of bacterial infection |
| Reduce the development of adverse drug effects | • Expose patient to empiric antimicrobial therapy for the shortest time possible, to prevent nephrotoxicity, cardiac and other side-effects from unnecessary antimicrobial use |
| Promote appropriate antimicrobial prescribing and use during the COVID-19 pandemic *(163)* | • Do not prescribe antibiotics to suspected or confirmed COVID-19 patients with low suspicion of a bacterial infection, to avoid more short-term side-effects of antibiotics in patients and negative long-term consequences of increased antimicrobial resistance |

**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.**

**Remarks:**

1. 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.
2. Use medications that carry the least risk possible for drug-drug interactions with other medications the person may be receiving. Psychotropic medications with sedative proprieties, 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.

# 15. Therapeutics and COVID-19

For the most up to date clinical practice guideline on therapeutics and COVID-19 see WHO website and BMJ website and MAGICapp.

By 17 December 2020 this guideline contains the following recommendations:

- Strong recommendations against the use of hydroxychloroquine and lopinavir/ritonavir in patients with COVID-19, regardless of disease severity.
- A strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19.
- A conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19.
- A conditional recommendation against remdesivir in hospitalized patients with COVID-19.

**We recommend that the use of unproven drugs not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials.**

**Remarks:**

Outside of clinical trials, the following criteria should be met for access to investigational therapeutics: 1) no proven effective treatment exists; 2) it is not possible to initiate clinical studies immediately; 3) data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favourable risk–benefit analysis; 4) the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use; 5) adequate resources are available to ensure that risks can be minimized; 6) the patient's informed consent is obtained; and 7) the emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community *(164)*.

# 16. Treatment of other acute and chronic infections in patients with COVID-19

The prevalence of acute coinfections or secondary infections coinciding with COVID-19 has not been adequately described but appears to be low *(104)*, and will be based on local factors and endemic or other emerging infections *(77,111,112,163)*. Antibiotic overuse increases the risk of emergence and transmission of multidrug-resistant bacteria. Infections with multidrug-resistant bacteria are more difficult to treat, and associated with increased morbidity and mortality.

### Acute coinfections with bacteria

**We recommend for patients with suspected or confirmed mild COVID-19, against the use of antibiotic therapy or prophylaxis.**

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

**We recommend for patients with suspected or confirmed severe COVID-19, the use of empiric antimicrobials to treat all likely pathogens, based on clinical judgment, patient host factors and local epidemiology, and this should be done as soon as possible (within 1 hour of initial assessment if possible), ideally with blood cultures obtained first. Antimicrobial therapy should be assessed daily for de-escalation.**

**Remarks:**

1. For patients with severe disease, early and appropriate empiric antimicrobial therapy *(92)* can be administered in the emergency unit and/or pre-hospital setting. Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia (if infection was acquired in health care setting) or sepsis), local epidemiology and susceptibility data, and national treatment guidelines. Choose antibiotics with the least ecologic impact based on data and guidance from your own institution, region or country (e.g. of the Access group of the AWaRe classification) *(113)*. The AWaRe classification categorizes antibiotics into three different groups (Access, Watch and Reserve) based on their indication for common infectious syndromes, their spectrum of activity, and their potential for increasing antibiotic resistance. The AWaRe classification is a tool for antibiotic stewardship at local, national and global levels with the aim of optimizing antibiotic use and reducing antibiotic resistance.
2. Empiric antibiotic therapy should be de-escalated on the basis of microbiology results and clinical judgment. Regularly review the possibility of switching of intravenous to oral route of administration and provide targeted treatment based on microbiologic results.
3. Duration of empiric antibiotic treatment should be as short as possible; generally 5–7 days.
4. An increase in antibiotic use during the pandemic may cause adverse reactions such as *Clostridioides difficile* infections, with clinical disease ranging from diarrhoea and fever to colitis *(165)*. Antibiotic stewardship programmes should be put into place or continue among COVID-19 patients.

Acute coinfections with other pathogens (not bacteria)

**Treatment of other coinfections may be based on a laboratory-confirmed diagnosis or epidemiological and clinical criteria.**

**Remarks:**

1. In malaria endemic areas, when a malaria RDT is also positive, antimalarials should be initiated as soon as possible as per local protocol *(66)*.
2. When there is ongoing suspected or confirmed local circulation of seasonal influenza, empiric therapy with a neuraminidase inhibitor (i.e. oseltamivir) should be considered for patients with severe disease or at risk for severe influenza, and given as soon as possible.
3. If TB coinfection is suspected or confirmed, then follow local TB treatment protocols *(69)*.

Chronic infections

It is currently unknown whether immunosuppression caused by chronic coinfections such as human immunodeficiency virus (HIV) puts persons at greater risk for severe COVID-19. However, people living with HIV with advanced disease have an increased risk of opportunistic infections (notably TB) *(166)* and related complications in general. Facility-based HIV testing services should continue and those newly diagnosed should start antiretroviral therapy as soon as possible. For people living with HIV already on treatment, continuity of antiretroviral therapy and prophylaxis for coinfections is essential, with multi-month prescribing.

# 17. Management of neurological and mental manifestations associated with COVID-19

People with COVID-19 are at increased risk for neurological, neuropsychiatric, and mental manifestations (see Chapter 1. Background). Neuropsychiatric manifestations such as delirium/encephalopathy and neurological manifestations such as stroke may be presenting features without respiratory symptoms (see Table 6.1). In addition to acute neurological manifestations, Guillain-Barré syndrome, acute disseminated encephalomyelitis, and acute haemorrhagic leukoencephalitis-like presentations may occur weeks after the acute stage of infection *(46)*. Moreover, there may be potential for longer term neurological consequences such as cognitive impairment *(167)* and/or post-intensive care syndrome (PICS). Further research is needed in order to fully characterize these complications.

Anxiety and depressive symptoms constitute common reactions for people in the context of COVID-19 diagnosis, especially for those who may be hospitalized, due to concerns for one's own health or the health of others, the need for physical isolation (which can lead to social isolation), potential risk of death, concerns over the risk of infecting others, and concerns over leaving family members alone who may need care. Stressors particular to COVID-19 include: fear of falling ill and dying, fear of being socially excluded/placed in quarantine, loss of livelihood and loss of loved ones, and feelings of helplessness, boredom and loneliness due to being isolated. These stressors may trigger new symptoms or exacerbate underlying mental or neurological conditions. Pre-existing mental, neurological or substance use disorders increase the risk of becoming severely ill or of death, or of having long-term complications due to COVID-19 *(84,85,168,169,170,171)*. People with COVID-19 are also at higher risk for sleep problems owing to acute stress responses, as well as additional reasons for those who are hospitalized such as environmental factors, invasive medical procedures (e.g. mechanical ventilation) and the frequent combination of multiple medications possibly disrupting sleep patterns *(172)*.

**Delirium**

**We recommend, in patients with COVID-19, that measures to prevent delirium, an acute neuropsychiatric emergency, be implemented; and patients be evaluated using standardized protocols, for the development of delirium. If detected, then immediate evaluation by a clinician is recommended to address any underlying cause of delirium and treat appropriately.**

**Remarks:**

1. Manage any underlying cause of delirium by monitoring oxygenation and fluid status, correcting metabolic or endocrine abnormalities, addressing coinfections, minimizing the use of medications that may cause or worsen delirium, treating withdrawal from substances, understanding and minimizing the effects of any harmful drug-drug interactions and maintaining normal sleep cycles as much as possible *(173)*.
2. In patients receiving invasive ventilation, minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions, to reduce delirium *(173)*.
3. In patients experiencing agitation (defined as marked restlessness or excessive motor activity, often accompanied by anxiety), use calming communication strategies and attempt to reorient the person. Acute pain due to physical illness or air hunger should be considered as triggers for agitation and need to be addressed immediately. If the person continues to be agitated despite the strategies described above and is experiencing severe distress, it may be necessary to use psychotropic medications *(174)*.
4. When using antipsychotic medications for agitation, consider side-effects that may worsen symptomatology, including sedation, respiratory or cardiac function, risk of fever or other immunological abnormalities, or coagulation abnormalities and any potential drug-drug interactions between these and other medications. Use minimum effective doses of antipsychotic medications at the lowest frequency and for the shortest duration possible, with doses adjusted according to age, medical co-morbidities and degree of distress *(174)*. For severe agitation, low doses of haloperidol (administered orally or by intramuscular injection) can be considered, while carefully monitoring for adverse effects such as QT prolongation and extrapyramidal symptoms *(174)*.
5. If haloperidol is contraindicated due to the patient's clinical condition (e.g. prolonged QT interval, recent myocardial infarction, Parkinson's Disease, Lewy-Body dementia, etc.), other antipsychotic medications with safer cardiovascular profiles may be used after careful consideration of other risks (such as respiratory suppression or sedation) and drug-drug interactions *(175)*.
6. If the patient remains severely agitated despite the strategies described above, benzodiazepines can be added, with preference given to those with shorter half-lives and lower risk of drug-drug interactions (such as lorazepam); lowest doses should be used and for the shortest duration possible. The intravenous route should be avoided *(175)*.

**Stroke**

**Patients presenting with rapidly developing neurological symptoms suggestive of stroke should be evaluated as soon as possible and standard stroke protocols should be followed including systemic thrombolysis and/or intra-arterial thrombectomy, if indicated. Signs and symptoms of stroke can include weakness of limbs or face, sensory loss, speech difficulties, impairment of vision, ataxia, confusion, or decreased consciousness. Standard IPC measures must be followed during the clinical evaluation, neuroimaging or procedures for patients with stroke.**

**Remark:**

Strokes can be missed in severely sick or unresponsive ICU patients and a low threshold for further evaluation (including neuroimaging) is recommended for acute neurological worsening.

### Mental health and psychosocial support

**We recommend providing basic mental health and psychosocial support (MHPSS) for all persons with suspected or confirmed COVID-19 by asking them about their needs and concerns, and addressing them *(176)*.**

**Remarks:**

1. Basic psychosocial support skills are essential for management of all patients and they represent an integral part of the care to be provided for different groups, including children, older adults, pregnant women and others affected by COVID-19 *(177)*.
2. This recommendation is consistent with the Inter-Agency Standing Committee briefing note about mental health and psychosocial aspects of COVID-19 *(176)*, and guidance on basic psychosocial skills for COVID-19 responders *(177)*, and WHO recommendations on providing access to support based on psychological first aid principles to people in acute distress exposed recently to a traumatic event *(178)*.
3. Ask people about their needs and concerns around diagnosis, prognosis, and other social, family or work-related issues. Listen carefully, try to understand what is most important to the person at this moment, and help them work out what their priorities are and link them with relevant resources and services.
4. Give accurate information on the person's condition and treatment plans in easily understood and non-technical language, as lack of information can be a major source of stress. Help people address urgent needs and concerns, and help with decision-making, as necessary. Help connect people with loved ones and social support, including through phone or internet as appropriate.
5. MHPSS and follow up should continue after the person is discharged from hospital to ensure their symptoms are not worsening and they are continuing to do well. This can be provided through telehealth, where available and appropriate.
6. Given the stress that COVID-19 may create at individual and family levels, the high prevalence of common mental health conditions among women in the antenatal and postpartum period, and the acceptability of programmes aimed at them, interventions for MHPSS targeted to mothers need to be more widely implemented. Prevention services should be available in addition to services that treat mental health conditions.
7. Parents and caregivers who may need to be separated from their children, and children who may need to be separated from their primary caregivers, should have access to appropriately trained health or non-health workers for MHPSS. MHPSS should be appropriately adapted for the needs of children, taking into consideration their social and emotional development, learning and behaviour *(176)*.

**We recommend prompt identification and assessment for anxiety and depressive symptoms in the context of COVID-19 and to initiate psychosocial support strategies and first-line interventions, for the management of new anxiety and depressive symptoms.**

**Remarks:**

1. For people who are experiencing symptoms of anxiety, basic psychological skills such as psychological first aid stress management, and brief psychological interventions based on the principles of cognitive behavioural therapy should be considered *(178,179)*.
2. For relieving anxiety causing severe distress that is not responsive to psychosocial support strategies, benzodiazepines can be considered, specifically in the hospital setting. Benzodiazepines should only be used with extreme caution with preference for those with shorter half-lives and lower risk of drug-drug interactions (such as lorazepam). Lowest doses should be used and for the shortest duration possible; high doses and longer term use should be avoided. Benzodiazepines carry the risks of confusion and respiratory suppression, may worsen traumatic stress reactions, can produce tolerance and dependence, and are known to be prescribed indiscriminately in many emergencies *(174)*.
3. For people who are experiencing symptoms of depression, brief psychological interventions based on the principles of cognitive behavioural therapy, problem-solving treatment and relaxation training can be considered *(180)*. Consider using remote mental health support (i.e. telephone therapy) when access to regular services is disrupted.

4. If a person's anxiety or depressive symptoms persist beyond recovery from COVID-19 and/or discharge from the hospital, then an underlying anxiety or depressive disorder may be suspected, and a mental health professional should be consulted and these conditions should be managed appropriately. Refer to the *mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings (181)*.
5. It is important to ask about thoughts or acts of self-harm, particularly during COVID-19, due to risk factors for self-harm and suicide such as sense of isolation, loss of a loved one, job, or financial loss and hopelessness. Remove possible means of self-harm, activate psychosocial support, follow up with the person, and consult a mental health professional as necessary. Refer to the *mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings (181)*.
6. To ensure comprehensive care and based on the initial assessment, following discharge, link the person to employment, education, social services (including housing) and other relevant sectors *(181)*.
7. Cognitive-behavioural therapy with a trauma focus, eye movement desensitization and reprocessing or stress management should be considered for adults with post-traumatic stress disorder (PTSD) *(182)*.

**We recommend psychosocial support strategies as the first-line interventions for management of sleep problems in the context of acute stress.**

**Remarks:**

1. Sleep hygiene advice (including avoiding the use of psychostimulants such as caffeine, nicotine or alcohol), and stress management (including relaxation techniques and mindfulness practices) are effective in reducing sleep problems and may be offered. Psychological interventions based on the principles of cognitive behavioural therapy may also be considered.
2. For people who are hospitalized for COVID-19, additional causes of insomnia may include environmental factors (e.g. excessive light and noise at night), anxiety, persistent cough, delirium, agitation, pain or air hunger. Identifying and promptly addressing underlying causes should be prioritized before using any pharmacological sleep aids.

## 18. Noncommunicable diseases and COVID-19

Pre-existing NCDs, including cardiovascular disease, diabetes, chronic respiratory disease, hypertension, obesity and cancer, have been identified as independent risk factors for death (see Table 6.1).

**We recommend when caring for patients with suspected and confirmed COVID-19 that have underlying NCDs to continue or modify previous medical therapy according to the patient's clinical condition.**

**Antihypertensive drugs should not routinely be stopped in patients with COVID-19, but therapy may need to be adjusted based on general considerations for patients with acute illness, with particular reference to maintaining normal blood pressure and renal function.**

**Remark:**

SARS-CoV-2 uses the ACE 2 receptor for entry into cells. It has been suggested that antihypertensive drugs that exert their effect by inhibiting ACE or blocking the ACE 2 receptor may either aggravate or ameliorate the clinical course of patients with COVID-19 *(183)*. To date, there are no studies that can substantiate this, and it is generally advised to continue these medications unless there are other reasons to stop these (e.g. hyperkalaemia, hypotension or acute deterioration in renal function) *(184)*.

# 19. Rehabilitation for patients with COVID-19

At the outset of the pandemic, the rehabilitation needs for patients recovering from COVID-19 were based on evidence from the critical care population and long-term sequelae in SARS-CoV-1 survivors *(185,186,187,188,189,190,191,192,193,194,195,196)*. Post-intensive care syndrome (PICS) refers to a range of impairments including physical deconditioning, and cognitive and mental health impairments. The COVID-19 patients who are at higher risk of ICU admission are also those at higher risk to develop PICS, i.e. older persons with underlying diseases such as diabetes, hypertension, increased frailty and other chronic disorders *(197)*. Intensive care unit-acquired weakness is ubiquitous in ARDS survivors, as it is in critically ill COVID-19 patients who required prolonged sedation *(198)*, and recovery may be incomplete at 5 years after ICU discharge *(199)*. Some studies suggest that cognitive impairment ranges from 70–100% at hospital discharge, 46–80% at 1 year, and 20% at 5 years. Mood disorders including depression and PTSD are also sustained and prevalent *(199)*. For ARDS survivors, a reduced exercise capacity persists in the context of relatively preserved pulmonary function at 1 year *(200)*. In SARS-CoV-1 survivors, pulmonary function at 1-year is reported to be normal in 63%, mildly reduced in 32% and moderately impaired in 5%, with abnormalities characterized by restrictive patterns and reduced carbon monoxide diffusing capacity *(201)*.

The following symptoms have been reported 4–8 weeks after discharge from the hospital in both ICU admitted COVID-19 patients and non-ICU admitted COVID-19 patients: new illness-related fatigue, breathlessness, PTSD symptoms, pain, voice change, cough, dysphagia, anxiety, depression, and problems with concentration, memory and continence. Patients admitted to ICU had greater prevalence of symptoms in almost all reported symptom domains than COVID-19 patients not admitted to ICU *(202)*. More than half of all COVID-19 patients who had been hospitalized, regardless of their clinical management, reported persistence of fatigue at 60 days since the onset of symptoms *(202,203)*.

With progression of the pandemic and the follow up of patients who have not been critically ill, new evidence is emerging about COVID-19 related persistent symptoms, which have parallels with other coronavirus diseases. Some patients with SARS-CoV-1 infection went on to develop a long-term illness with widespread pain, fatigue, depression and sleep disturbance *(204,205)*. PTSD has also been described after SARS-CoV- 1 infection *(205,205)*.

Early findings report, most commonly reported ongoing symptoms (regardless of hospitalization status) are fatigue, muscle ache, shortness of breath and headache at a follow up of 4 months *(205)*. Not returning to usual health within 2–3 weeks of testing was reported by approximately one third of symptomatic adults in an outpatient setting *(206)*. A study reported that at 3 months after the onset of symptoms, one third of non-hospitalized patients were to some degree dependent on others for personal care *(207)*.

In addition, several complications from COVID-19 have been reported in different clinical domains, resulting from a thrombotic event (such as ischaemic stroke and ischaemic heart disease), direct invasion (such as myocarditis, myositis, and meningitis) or an immune-mediated reaction (such as Guillain-Barré syndrome). While many of these complications are amenable for rehabilitation, they are not addressed in this chapter. Clinicians and rehabilitation professionals can refer to existing clinical practice guidelines for the appropriate management of these sequelae.

COVID-19 is a multisystem disease which, in certain cases, will require full multidisciplinary team rehabilitation to enable recovery *(208)*.

**In hospitalized patients, during the acute phase of illness, rehabilitation professionals may provide interventions that relieve respiratory distress, prevent complications and support communication.**

**Remarks:**

1. Decision on when to start rehabilitation should be determined by a multidisciplinary team taking into account the patient's medical status *(209)*. Ensure that appropriate IPC is available at designated rehabilitation areas caring for patients with COVID-19 that remain infectious. Make optimal use of digital and/or written information for the instruction of patients *(141)*. Telehealth may play a role in the acute and subacute phases, in which face-to-face rehabilitation is costly, risky, and impractical *(210)*. Consider strategies for communication with and engagement of families during physical distancing *(211)*.

2. Early mobilization is recommended for all patients with severe risk of functional limitations, resulting from frailty or ICU-acquired weakness *(117)*. In ICU, early mobilization should be part of a bundle of care (See Chapter 12 and 13 on management of critical COVID-19 for new recommendation on bundles), and appropriate levels of activity would be based on the Richmond Agitation-Sedation Scale *(141)*. Monitor oxygen saturation levels closely as desaturation may occur. To identify every next level of mobility the ICU mobility scale can be used.
3. See Chapter 12 (Management of critical COVID-19: ARDS) for examples of respiratory interventions that may be considered.
4. Communication challenges may result from voice and speech disorders that are often linked with intubation or a cognitive impairment. Augmented communication strategies may assist, and where available, refer for speech and language therapy.
5. COVID-19 patients with dysphagia are at risk of aspiration. Dysphagia is common post-extubation and the presumed aspiration prevalence for the general critical care population is 10–25% at ICU discharge *(185)*. Referral to an appropriately trained health professional such as a speech and language therapist, for additional breathing exercises, vocal exercises, and eating and drinking exercises where available *(212)*.
6. Patients with COVID-19 have demonstrated improved mobility at hospital discharge and higher probability of discharging home with increased frequency and longer mean duration of physical therapy visits *(213)*. Some reports have found that early aerobic exercises may not be well tolerated and result in rapid desaturation in COVID-19 inpatients. Exercise training may have to start with gradual functional exercises, using no or minimal equipment *(141)* including an active range of motion exercises, balance exercises, and walking with or without a walking aid. When (assisted) exercises are well tolerated while lying supine, the rehabilitation professional may proceed with exercises while sitting, and then standing *(141)*.

**Prior to hospital discharge, COVID-19 patients should be screened for rehabilitation needs in order to facilitate onward referral.**

**Remarks:**

1. Hospitalized COVID-19 patients may have ongoing rehabilitation needs which prevent safe discharge or require continued rehabilitation services. These needs can be based on physical deconditioning, and respiratory, swallow, cognitive and mental health impairments. Consider the context of the person's individual situation, including social support and home environment when making decisions about a course of intervention or support needs.
2. When indicated from screening, further assessment of rehabilitation needs can be based on a basic set of measures that cover potentially affected functioning domains. This includes, but is not limited to: respiratory function (such as respiratory rate and $SpO_2$), mobility (such as ICU mobility scale), muscle strength (such as Medical Research Council sumscore), balance (such as Berg balance scale), dysphagia (such as fluid and food trials), and activities of daily living (ADL) (such as Barthel index). Additional tests might be helpful based on a first screening for mental and cognitive impairment (such as Montreal Cognitive Assessment, Hospital Anxiety and Depression Scale, PTSD Checklist-5).
3. When the patient is ready for discharge, evaluate the need of an assistive device (such as a mobility aid) and oxygen requirements at rest and during exertion. Oxygen desaturation on exertion may happen during the recovery phase, even during physical exercise of moderate activity, and is unrelated to the oxygen saturation at rest and the degree of dyspnoea *(214)*. An example of a rapid exercise test to assess desaturation on exertion is the 1-minute sit-to-stand test *(215)*.
4. Where continued rehabilitation needs are identified, refer for inpatient, outpatient or community-based follow up as indicated and according to the type and severity of rehabilitation needs. When a patient does not require inpatient rehabilitation but would benefit from rehabilitation follow up post-discharge, refer to outpatient or community-based services according to local service availability. Consider which options have the least barriers to attendance/service utilization and, where available and appropriate, refer to services delivered through telehealth *(210)* particularly where IPC measures prevent in-person consultations.
5. Information, including documentation, should be communicated between hospitals and to other hospital-based or community rehabilitation services and primary care services *(209)*.
6. Ensure patients are provided with education and information resources for self-management management of COVID-19 symptoms, especially when barriers to accessing rehabilitation follow up are anticipated (patient leaflet https://www.who.int/publications/m/item/support-for-rehabilitation-self-management-after-covid-19-related-illness).

**Patients with COVID-19, should be provided with education and support for the self-management of breathlessness and resumption of activities, both in a hospitalized and a non-hospitalized setting caring for COVID-19.**

**Remarks:**

1. Education about control of breathing can support COVID-19 patients to those recovering from respiratory illness, especially those troubled by breathlessness. Patients may be advised to adopt positions, such as high side lying and forward lean sitting, and breathing techniques, such as pursed lip breathing and square box breathing, that help to manage breathlessness. Adequate walking pace regulation is recommended to reduce breathlessness and to prevent desaturation on exertion. Severe shortness of breath that is not relieved by positioning and breathing techniques requires medical investigation.
2. All rehabilitating patients should be educated about resuming everyday activities conservatively at an appropriate pace that is safe and manageable for energy levels within the limits of current symptoms and should not be pushed for post-exertional fatigue. A gradual increase in exercise should be based on symptoms.
3. For patients with COVID-19 that also have underlying cardiovascular or pulmonary conditions, resumption of exercise should be done after consultation with appropriate health professionals *(208,216,217)*. COVID-19 patients with confirmed cardiac involvement need a cardiac evaluation before resuming exercise.
4. Resuming sports gradually should also be guided by appropriate health professionals, an example is provided for return-to-play guideline for myocarditis *(208,216,217)*.

**For patients who have been discharged from the hospital or patients who have been managed at home and experience persistent symptoms and/or limitations in functioning, screen for physical, cognitive and mental impairments, and manage accordingly.**

**Remarks:**

1. Patients with COVID-19, regardless of the disease severity, might present with persistent symptoms and a functional decline which may not be obviously apparent (such as a cognitive impairment). Consult with family members or caregivers about health-related premorbid functional difficulties and compare with their current presentation.
2. Screening may include a full history, evaluation of pre-existing health conditions, observation of the patient performing functional tasks, and a symptom-based questionnaire or easily administered screening tool *(218)* (such as Timed Up and Go test for physical function, Whooley questions for depression, Generalized Anxiety Disorder 2-item for anxiety, and Mini-Cog for cognition). Rapid exercise tests for exertional desaturation should not be attempted outside a supervised care setting if resting oximeter reading is < 96% *(215)*.
3. When resources permit, define and clinically assess impairment types by functional domains, including respiratory function (such as spirometry, diffusing capacity of the lungs for carbon monoxide, Medical Research Council dyspnoea scale), cardiovascular function (such as 6 minutes walking distance), swallowing function (such as dysphagia severity scale), musculoskeletal function (such as hand grip strength, Medical Research Council sumscore), cognitive functioning (such as Montreal Cognitive Assessment, Mini-Mental State Examination), and mental functioning (such as Hospital Anxiety and Depression Scale, PTSD checklist-5, Impact of Event Scale-Revised). Additional tests may be indicated for pain, fatigue, and difficulties with ADL *(218)*.
4. Late deterioration of COVID-19 may still occur and late onset inflammatory, thromboembolic and autonomic complications including pulmonary embolism, heart attack, heart failure and stroke have been reported. Rehabilitation or health staff should be alerted and referred to specialist, as part of multidisciplinary, coordinated care pathway.

**Provide individualized rehabilitation programmes from subacute to long term according to patient needs. The prescription and provision of rehabilitation programmes should be guided by persistent symptoms and functional limitations.**

**Remarks:**

1. COVID-19 related impairments, such as fatigue, muscle weakness and cognitive impairment, might impact the performance of ADLs. As patients regain strength and fitness, autonomy in ADLs will improve, but some will need to accept additional support from a caregiver for a time. Provide ADL training and consider home modifications (such as grab bars in the shower and toilet, handrails along stairs) and the provision of an assistive product (such as a mobility aid, shower chair, over-toilet frame), as needed.
2. The training principles of comprehensive pulmonary rehabilitation programmess apply for COVID-19 patients with persistent fatigue, reduced exercise capacity and breathlessness *(140,214,219)*. COVID-19 population needs patient-tailored supervised programmes that are flexible to adapt for patients with gas exchange abnormalities *(140,214,219,220)* guided by baseline oxygen needs at rest and during exercise.
3. Patients with physical deconditioning and muscle weakness should start with exercises that support recovery in daily functioning. Start with active range of motion exercises, and when tolerated, proceed with progressive muscle strengthening, typically offered with resistance training. Return to physical exercise should always be guided by symptoms *(216)*.
4. For patients having difficulties with memory, concentration and problem solving, education should be provided, and advice on strategies to help establish expectations (including from family members) and to alleviate stress and anxiety. Cognitive restorative rehabilitation may support with cognitive exercises (such as memory exercises, puzzles, games, reading) and compensation tools such as prompts (e.g. lists and notes) and breaking down activities. Encourage participation in daily activities that are meaningful for the patient.
5. For patients with anxiety, depression and PTSD, basic mental health and psychosocial support by appropriately trained health or non-health workers should be provided. See Chapter 17 on neurologic and mental manifestations *(218,221,222)*.
6. For patients with persistent pain, a multidisciplinary approach is recommended in order to provide pain management according to the principles of the biopsychosocial model.

# 20. Caring for women with COVID-19 during and after pregnancy

The results of a living systematic review (as of 6 October 2020) show that pregnant and recently pregnant women with COVID-19 appear to be less likely to be symptomatic (0.28, 95% CI 0.13 –0.62; 4 studies; 462 051 women), or manifest common symptoms such as fever, dyspnoea and myalgia, compared with non-pregnant women of reproductive age *(53)*. These findings are largely influenced by studies of pregnant women who were managed in hospitals for any reason, with limited data on women during early pregnancy or postpartum.

Pregnant women with COVID-19 are more likely to experience any type of preterm birth (OR=1.47, 95% CI 1.14–1.90; 18 studies; 8549 women) compared with pregnant women without the disease. Overall rates of spontaneous preterm birth in pregnant women with COVID-19 is broadly similar to those observed during the pre-pandemic period. A third of all neonates born to mothers with COVID-19 were admitted to the neonatal intensive care unit (NICU) (33%) and were at increased risk of NICU admission for any indication (OR=4.89, 95% CI 1.87–12.81; 10 studies, 5873 neonates) compared with those born to mothers without COVID-19.

Transmission of SARS-CoV-2 may be possible in utero or intrapartum, but most neonatal infections reported so far seem to have occurred in the postnatal period *(53)*. However, available studies varied in the rigor of ascertaining mother-to-child transmission of SARS-CoV-2, limiting interpretation of these results.

This section builds on existing recommendations from WHO on pregnancy and infectious diseases and provides additional remarks for the management of pregnant and recently pregnant women.

**We recommend all pregnant women with history of contact with a person with confirmed COVID-19 be carefully monitored considering asymptomatic transmission of COVID-19.**

**Pregnant or recently pregnant women with suspected or confirmed mild COVID-19 may not require acute care in hospital, unless there is concern for rapid deterioration or an inability to promptly return to hospital; but isolation to contain virus transmission is recommended, and can be done at a health facility, community facility or at home, according to established COVID-19 care pathways.**

**Pregnant or recently pregnant women with moderate or severe COVID-19 require acute care in the hospital, as there is concern for rapid deterioration that may warrant supportive care for severe respiratory morbidity; and/or interventions to improve maternal and fetal survival.**

**Remarks:**

1. Counsel pregnant and recently pregnant women about maternal and newborn signs, including COVID-19 danger signs and maternal perception of decreased fetal movements, and advise them to seek urgent care if they develop any worsening of illness or other danger signs, such as danger signs of pregnancy (including: bleeding or leaking fluid from the vagina, blurry vision, severe headaches, weakness or dizziness, severe abdominal pain, swelling of face, fingers, feet, inability to tolerate foods or liquids, convulsions, difficulty in breathing, decrease in fetal movements). Update birth preparedness and complication readiness plans so they know when and where to seek care.
2. In pregnant and postnatal women that are being cared for at home in self-isolation, self-care interventions should be encouraged. Routine antenatal or postnatal health visits in health facilities should be postponed, and delivery of antenatal and postnatal counselling and care, should instead be conducted via alternative platforms such as home-based, phone or telemedicine *(223,224)*. If postponed, health visits should be rescheduled until after the period of self-isolation following national guidelines and advice, and in consultation with the health care provider. For women requiring abortion services, consider alternative modes of service delivery, including self-management of medical abortion up to 12 weeks' gestation, where women have access to accurate information and to a health care provider at any stage of the process. Postponing abortion care may lead to increased morbidity and mortality where individuals resort to unsafe abortion practices as abortion service delivery is time-bound by gestational limits prescribed by the law *(225).* See the *WHO Consolidated guideline on self-care interventions for health (226).*
3. Counsel women about healthy diet, mobility and exercise, intake of micronutrients for herself and her infant, tobacco use and second-hand smoke exposure, use of alcohol and other substances, as per WHO guidelines on antenatal and postnatal care. Clinical enquiry about the possibility of gender-based violence should be strongly considered, where there is the capacity to provide a supportive response (including referral where appropriate) and where the WHO minimum requirements are met. See resource *(227)*.
4. When caring for pregnant and recently pregnant women with underlying NCDs or pregnancy-induced conditions (e.g. gestational diabetes, pregnancy-induced hypertension) continue or modify previous medical therapy according to the woman's clinical condition.

**Pregnant and recently pregnant women with suspected, probable or confirmed COVID-19, should have access to woman-centred, respectful skilled care, including midwifery, obstetric, fetal medicine and neonatal care, as well as mental health and psychosocial support, with readiness to care for maternal and neonatal complications.**

**Remarks:**

1. Woman-centred, respectful, skilled care refers to care organized for and provided to all women in a manner that maintains their dignity, privacy and confidentiality, ensures freedom from harm and mistreatment, and enables informed choice. During labour and childbirth this includes a companion of choice, pain relief, mobility during labour and birth position of choice.
2. Screen birth companions using the standardized case definition. If the companion has suspected or confirmed COVID-19, arrange for an alternative, healthy birth companion in consultation with the woman. Emphasize to any and all companions the importance of IPC measures during labour, childbirth and the mother's and newborn's postnatal stay in the health facility, including appropriate training on and use of PPE and movement restriction in the health care facility.

**Mode of birth should be individualized, based on obstetric indications and the woman's preferences. WHO recommends that induction of labour and caesarean section should only be undertaken when medically justified and based on maternal and fetal condition. COVID-19 positive status alone is not an indication for caesarean section. See *WHO recommendations for induction of labour (228)***

**Remarks:**

1. Emergency birth and pregnancy termination decisions are challenging and based on many factors such as gestational age, severity of maternal condition, and fetal viability and well-being.
2. Interventions to accelerate labour and childbirth (e.g. augmentation, episiotomy, operative vaginal birth) should only be undertaken if medically justified and based on maternal and fetal clinical condition. See *WHO recommendations: intrapartum care for a positive childbirth experience (229).*
3. Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes. The risk of transmission of COVID-19 through blood is likely to be minimal. There is no evidence that delaying cord clamping increases the possibility of viral transmission from the mother to the newborn. The proven benefits of a 1–3 minute delay, at least, in clamping the cord outweigh the theoretical, and unproven, harms.
4. Individualized decisions should be taken about postponing planned (elective) induction or caesarean section in pregnant women with suspected or confirmed mild COVID-19 *(227).*

**Pregnant and recently pregnant women who have recovered from COVID-19 and been released from the COVID-19 care pathway, should be enabled and encouraged to receive routine antenatal, postpartum, or postabortion care, as appropriate. Additional care should be provided if there are any complications.**

**Remarks:**

1. All pregnant women with or recovering from COVID-19 should be provided with counselling and information related to the potential risk of adverse pregnancy outcomes.
2. Women's choices and rights to sexual and reproductive health care should be respected regardless of COVID-19 status, including access to contraception and safe abortion to the full extent of the law *(225).*

# 21. Feeding and caring for infants and young children of mothers with COVID-19

Relatively few cases have been reported of infants confirmed with COVID-19; those that have been reported experienced mild illness. Of 115 mother-child pairs from 17 articles where the mother is confirmed to be infected with COVID-19, 13 children had COVID-19 (4 breastfed, 5 formula-fed, 2 mix-fed, 2 unreported feeding practice). Twenty mothers had breastmilk samples tested for the presence of SARS-CoV-2 RNA particles by RT-PCR; 7 of them had children with COVID-19 (2 breastfed,1 formula fed, 2 mix-fed, 2 unreported). Of the 20 with breastmilk tested, 18 had negative results and 2 had positive results. One of the two mothers whose breastmilk sample was positive for SARS-CoV-2, had a mix-fed child who was not infected with COVID-19; the other one had a child with COVID-19 (feeding practice was not reported) *(230,231,232,233,234,235,236,237,238,239,240)*.

Breastfeeding protects against morbidity and death in the post-neonatal period and throughout infancy and childhood. The protective effect is particularly strong against infectious diseases that are prevented through both direct transfer of antibodies and other anti-infective factors and long-lasting transfer of immunological competence and memory. See WHO *Essential newborn care and breastfeeding (241).* Therefore, standard infant feeding guidelines should be followed with appropriate precautions for IPC.

Recommendations on the care and feeding of infants whose mothers have suspected or confirmed COVID-19 promote the health and well-being of the mother and infant. Such recommendations must consider not only the risks of infection of the infant with the COVID-19 virus, but also the risks of serious morbidity and mortality associated with not breastfeeding or the inappropriate use of breastmilk substitutes as well as the protective effects of skin-to-skin contact and kangaroo mother care. In light of the current

evidence, WHO has concluded that mothers with suspected or confirmed COVID-19 should not be separated from their infants. Mother-infant contact and holding enhances thermoregulation and other physiological outcomes, significantly reduces mortality and morbidity, and improves child and parental attachment. Overall, the recommendation to keep mothers and their children together is based on several important benefits that outweigh the potential (and likely mild) harms of COVID-19 transmission to the child.

**We recommend that mothers with suspected or confirmed COVID-19 should be encouraged to initiate and continue breastfeeding. From the available evidence, mothers should be counselled that the benefits of breast-feeding substantially outweigh the potential risks of transmission.**

**Remarks:**

1. WHO recognizes that the recommendation for an infected mother to be in close contact with her baby may appear to contradict other IPC measures that include isolation of persons infected with COVID-19 virus *(53)*. However, the balance of risks is significantly different for infants than for adults. In infants, the risk of COVID-19 infection is low, the infection is typically mild or asymptomatic, and the consequences of not breastfeeding or separation of mother and child can be significant. At this point it appears that COVID-19 in infants and children represents a much lower risk to survival and health than the other infections and conditions that breastfeeding is protective against. This protection is especially important when health and other community services are themselves under pressure. In contrast, the risks associated with COVID-19 in adults are much higher and more severe. Improved communication is needed to address the uncertainties and confusion among programme managers, health workers and communities on this issue.
2. See Table 21.1 below for recommendations when mother with COVID-19 is caring for infant.

**Table 21.1. Summary of recommendations when mother with COVID-19 is caring for infant**

| | **Interventions** |
|---|---|
| **Mother infant contact at birth** | Mothers should not be separated from their infants unless the mother is too sick to care for her baby. If the mother is unable to care for the infant another competent family caregiver should be identified.<br><br>Mother and infant should be enabled to remain together while rooming-in throughout the day and night and practise skin-to-skin contact, including kangaroo mother care, especially immediately after birth and during establishment of breastfeeding, whether they or their infants have suspected or confirmed COVID-19 virus infection.<br><br>Neonates born to mothers with suspected or confirmed COVID-19 should be breastfed within 1 hour of birth. Mothers should apply appropriate IPC.<br><br>Early and uninterrupted skin-to-skin contact between mothers and infants should be facilitated and encouraged as soon as possible after birth, while applying necessary measures for IPC. This applies also to infants who are born preterm or low birth weight.<br><br>If the newborn or infant is ill and requires specialist care (such as neonatal unit), arrangements should be made to allow the mother free access to the unit, with appropriate IPC measures.<br><br>Earlier initiation of breastfeeding results in greater benefits. This may be relevant to mothers who give birth by caesarean section, after an anaesthetic, or those who have medical instability that precludes initiation of breastfeeding within the first hour after birth. |
| **During early childhood** | Infants should be breastfed exclusively during the first 6 months after birth, as breastmilk provides all the nutrients and fluids they need.<br><br>From 6 months of age, breastmilk should be complemented with a variety of adequate, safe and nutrient-dense foods. Breastfeeding should continue up to 2 years of age or beyond.<br><br>Breastfeeding counselling, basic psychosocial support and practical feeding support should be provided to all pregnant women and mothers with infants and young children if they or their infants and young children have suspected or confirmed COVID-19 infection. |

| | |
|---|---|
| **If feeding is interrupted** | In situations when severe illness in a mother prevents her from caring for her infant or prevents her from continuing direct breastfeeding, mothers should be encouraged and supported to express milk, and the breastmilk provided safely to the infant, while applying appropriate IPC measures.<br><br>In the event that the mother is too unwell to breastfeed or express breastmilk, explore the viability of feeding with donor human milk. If this is not possible, consider wet nursing (defined as another woman breastfeeds the child) or appropriate breastmilk substitutes, informed by feasibility, safety, sustainability, cultural context, acceptability to mother and service availability.<br><br>Mothers who are not able to initiate breastfeeding during the first hour after delivery should still be supported to breastfeed as soon as they are able. Assistance should be provided after recovery for relactation to re-establish a milk supply and continue breastfeeding. |
| **Practices the mother should perform during all infant and childcare** | Perform frequent hand hygiene with soap and water or alcohol-based hand rub, especially before contact with her child.<br><br>Perform respiratory hygiene: sneeze or cough into a tissue and immediately dispose of the tissue. Hands should immediately be washed with soap and water or alcohol-based hand rub.<br><br>Clean and disinfect surfaces with which the mother has been in contact.<br><br>Wear a medical mask until symptom resolution and criteria for release from isolation have been met.<br><br>Additionally, breastfeeding mothers should be helped to clean her chest with soap and water if she has been coughing on it before breastfeeding. She does not need to wash her breasts prior to every breastfeed.<br><br>While mothers are recommended to wear medical masks, if the mother does not have a medical mask, she should still be encouraged to continue breastfeeding as the benefits of breastfeeding outweigh the potential risks of transmission of the virus when breastfeeding while applying other IPC measures. |
| **Best practices for breast-feeding** | Health facilities providing maternity and newborn services should enable a mother to breastfeed for as often and for as long as she wishes. Minimizing disruption to breastfeeding will require health care practices that enable a mother to breastfeed.<br><br>All mothers should receive practical support to enable them to initiate and establish breastfeeding and manage common breastfeeding difficulties. This support should be provided by appropriately trained health care professionals and community-based lay and peer breastfeeding counsellors.<br><br>There should be no promotion of breastmilk substitutes, feeding bottles and teats, pacifiers or dummies in any part of facilities providing maternity and newborn services, or by any of the staff.<br><br>Health facilities and their staff should not give feeding bottles and teats or other products that are within the scope of the International Code of Marketing of Breast-milk Substitutes and its subsequent related WHA resolutions, to infants.<br><br>If the mother is too unwell to breastfeed or express breastmilk, explore the best alternatives to breastfeeding a newborn or young infant, in priority order, as follows: 1) donor human milk should be fed if available from a human milk bank; 2) if supplies are limited, prioritize donor human milk for preterm and low birth weight newborns; 3) wet nursing may be an option depending on acceptability to mothers and families, availability of wet nurses and services to support mothers and wet nurses. COVID-19 testing of a woman who is a potential wet nurse is not required. Prioritize wet nurses for the youngest infants. In settings where HIV is prevalent, prospective wet nurses should undergo HIV counselling and rapid testing where available. In the absence of testing, if feasible, undertake HIV risk assessment. If HIV risk assessment or counselling is not possible, facilitate and support wet nursing; 4) breastmilk substitutes may be used as a last resort. |

# 22. Caring for older people with COVID-19

Older age has been reported as a risk factor for increased mortality in those affected by COVID-19. Other risk factors that have been reported are: smoking, diabetes, hypertension, cardiovascular, cancer, chronic lung disease, and functional decline *(242,243,244)*. Since older people are often affected by these conditions, they are potentially at the highest risk for fatality. Furthermore, the majority of long-term care service users are older people with multiple underlying conditions and weak immune systems, which make them more susceptible to severe COVID-19 and poor outcomes *(245)*. Refer to the WHO policy brief *Preventing and managing COVID-19 across long-term care services (245)* and WHO guidance *Integrated care for older people (ICOPE) (246)* for person-centred and coordinated model of care.

**We recommend that older people be screened for COVID-19 at the first point of access to the health system, be recognized promptly if they are suspected to have COVID-19 and treated appropriately according to established COVID-19 care pathways. This should occur in all settings where older people may seek care; included but not limited to facility-based emergency units, primary care, prehospital care settings and LTCFs.**

**Remarks:**

1. Older patients may present with atypical symptoms (including delirium) of COVID-19, especially those with cognitive decline and dementia *(247,248)* (see Table 6.1); health workers should take this into account during the screening process.
2. Provide accessible information to older people and their caregivers on clinical manifestation of COVID-19 including atypical symptoms, how to monitor symptoms, as well as when and how to seek care.

**Identify if there is an advance care plan for patients with COVID-19 (such as desires for intensive care support) and respect their priorities and preferences. Tailor the care plan to be in line with patients' expressed wishes and provide the best care irrespective of treatment choice.**

**We recommend a review of medication prescriptions to reduce polypharmacy and prevent medicine interactions and adverse events for those being treated with COVID-19.**

**Remarks:**

1. Older people are at greater risk of polypharmacy, as a result of newly prescribed medications, inadequate medication reconciliation, and a lack of coordination of care, all of which increases the risk of negative health consequences. If medications are prescribed for mental and neurological manifestations of COVID-19 in older people, this should be done with extreme caution given the increased susceptibility to drug side-effects and drug interactions with other prescribed medications.
2. Over 20% of adults over 60 years have pre-existing mental or neurological conditions for which they may already be taking medications before infection *(249)*. If a person has a previously diagnosed mental or neurological condition and is already on medications, consider how these medications (or withdrawal from them) may affect their COVID-19 symptoms. Stopping or adjusting the dosage of medications in people with COVID-19 are decisions that require careful risk-benefit analyses and when possible, consultation with a specialist is advised.

**Ensure multidisciplinary collaboration among physicians, nurses, pharmacists, physiotherapists, occupational therapists, social workers, mental health and psychosocial providers, community workers and other health care professionals in the decision-making process to address multimorbidity and functional decline *(246,250,251)*.**

**Remarks:**

1. Physiological changes with age lead to declines in physical and mental capacities such as malnutrition, cognitive decline, depressive symptoms, and those conditions interact at several levels. These interactions require an integrated approach to the screening, assessment and management of older people *(246)*.

2. Person-centred care including geriatric, psychosocial, and palliative care by a multidisciplinary team, with a careful evaluation of baseline conditions and functions, and disease severity, followed by frequent reassessments, ensures the provision of the appropriate level of care *(252,253)*.
3. Hearing loss and vision impairments become more prevalent among older people and may pose a communication barrier, especially when masks prevent lip reading and decrease vocal clarity. Cognitive decline may also need to be considered when communicating with older patients. Such impairments should be identified early so that health workers involved in their care can adjust their communication accordingly *(254)*.
4. Older people who experience COVID-19, including those admitted to ICU and/or treated with protracted oxygen therapy and bed rest, are more likely to experience pronounced functional decline and require coordinated rehabilitation care after acute hospitalization (see Chapter 19. Rehabilitation for patients with COVID-19).
5. Ensure that chronic infections are diagnosed and treated appropriately in older people. Other infections such as TB may mimic or co-exist with COVID-19 and therefore pass unrecognized, causing increased mortality *(67,68,69)*.

# 23. Palliative care and COVID-19

Palliative care is a multifaceted, integrated approach to improving the quality of life of adults and paediatric patients and their families facing the problems associated with life-threatening illness such as COVID-19. Palliative care focuses on prevention and relief of suffering by means of early identification, assessment and treatment of physical, psychosocial and spiritual stressors. Palliative care includes but is not limited to end-of-life care *(255)*. Palliative interventions should be integrated with curative treatment *(255)*. Basic palliative care, including relief of dyspnoea or other symptoms and social support, should be practised by all doctors, nurses, social workers and others caring for persons affected by COVID-19, adult or child *(255,256)*. Refer to the WHO guide *Integrating palliative care and symptom relief into responses to humanitarian emergencies and crises (255)*.

**We recommend to identify, in all patients with COVID-19, if they have an advance care plan for COVID-19 (such as desires for intensive care support) and respect their priorities and preferences to tailor the care plan and provide the best care irrespective of treatment choice.**

**Palliative care interventions should be made accessible at each institution that provides care for persons with COVID-19.**

**Remarks:**

1. Appropriate interventions should be accessible at each institution that provides care for persons with COVID-19. Efforts should be made to assure accessibility of interventions at home *(255)*.
2. Palliative care includes but is not limited to end-of-life care. Palliative interventions should be integrated with curative treatment. Basic palliative care, including relief of dyspnoea or other symptoms and social support, should be practised by all doctors, nurses, social workers and others caring for persons affected by COVID-19.
3. In hospitals, palliative care does not require a separate ward or department. Palliative care can be provided in any setting.
4. Consider non-pharmacologic and pharmacologic interventions (such as opioids) for relief of dyspnoea that is refractory to treatment of the underlying cause (i.e. oxygen therapy, escalation of respiratory support, corticosteroids) and/or as part of end-of-life care *(257)*. The narrow therapeutic margin of opioids in the management of dyspnoea requires that opioids are prescribed in accordance with evidence-based treatment protocols and that patients are closely monitored to prevent negative unintended effects due to inappropriate use of opioids. Where opioids are used, preference should be given for compounds less likely to cause delirium in medically ill patients. Providers should reference their institutional standards regarding the potential use of opioids for dyspnoea in patients with COVID-19.

5. Relieving spiritual and psychological suffering is an important aspect of palliative care. Visits from relatives and spiritual counsellors should be facilitated, especially for patients near to the end of life. This may include employing a range of techniques such as voice/video calls.
6. Palliative care is a person-centred approach; therefore all patients and families should be actively included in the decision-making processes about escalation of care. Medical decisions, where possible, should respect the priorities and preferences of patients, and should always be clearly explained to patients and relatives.

# 24. Care of COVID-19 patients after acute illness (new chapter)

New evidence is emerging about COVID-19 related persistent symptoms, which have parallels with other coronavirus diseases *(204)*.

The clinical characterization of mid- and long-term effect of COVID-19 remain to be clearly described and understood. In hospitalized patients, ICU and non-ICU, there are reports of new illness-related fatigue, breathlessness, PTSD symptoms, pain, voice change, cough, dysphagia, anxiety, depression, and problems with concentration, memory and continence. Patients admitted to ICU had greater prevalence of symptoms in almost all reported symptom domains than COVID-19 patients not admitted to ICU *(202)*. As well, more than half of all COVID-19 patients who had been hospitalized, regardless of their clinical management, reported persistence of fatigue at 60 days since the onset of symptoms *(202,203)*.

Early findings report, most common ongoing symptoms (regardless of hospitalization status) are fatigue, muscle ache, shortness of breath and headache at a follow up of 4 months *(205)*. Not returning to usual health within 2–3 weeks of testing was reported by approximately one third of symptomatic adults in an outpatient setting *(206)*. A study reported that at 3 months after the onset of symptoms, one third of non-hospitalized patients were to some degree dependent on others for personal care *(207)*.

**Best Practice Statement**

Patients who have had suspected or confirmed COVID-19 (of any disease severity) who have persistent, new, or changing symptoms should have access to follow-up care.

**Remarks:**

*Recognition*

- All patients (and their caregivers) with COVID-19 should be counselled to monitor for resolution of signs and symptoms. If any one or more of these persist, or patient develops new or changing symptom, then to seek medical care according to national (local) care pathways.
- This includes counselling about acute life-threatening complications, such as pulmonary embolism, myocardial infarction, dysrhythmias, myopericarditis and heart failure, stroke, seizures and encephalitis *(54,258)* for which they should seek emergency care.
- Patients with severe and critical COVID-19 may develop post-intensive care syndrome (PICS), with a range of impairment including (but not limited to) physical deconditioning, cognitive, and mental health symptoms. See Chapter 19. Rehabilitation for patients with COVID-19 for more details on PICS.

*Management*

- National (local), coordinated care pathways should be established that can include primary care providers (i.e. general practitioners), relevant specialists, multidisciplinary rehabilitation professionals, mental health and psychosocial providers, and social care services.
- Management should be tailored according to patient needs and be coordinated.
- Management interventions include addressing promptly life-threatening complications. For non-life-threatening complications, management may entail education, advice on self-management strategies (i.e. breathing techniques, pacing), caregiver support and education, peer-to-peer groups, stress management, stigma mitigation and home modification; prescription of rehabilitation programmes, and/or specialty management.
- See Chapter 19. Rehabilitation for patients with COVID-19 for recommendations regarding screening, assessment and rehabilitation interventions to facilitate onward referrals for inpatient, outpatient, or community-based follow up, to ensure continuity during transitions of care.

**Evidence to decision**

| **Values and preferences** | No substantial variability expected |
|---|---|

Applying the agreed values and preferences, the GDG inferred that well-informed patients would consider the possible harms associated with COVID-19 follow-up to be negligible, and that ensuring access to care is an important value to consider.

| **Resources and other considerations** | Important considerations |
|---|---|

National (local), coordinated care pathways should be established that can include primary care providers (i.e. general practitioners), relevant specialists, multidisciplinary rehabilitation professionals, mental health and psychosocial providers, and social care services. Alternative delivery platforms such as home-based phone, telemedicine, or community outreach teams may be used.

**Justification**

**Applicability**

*Special populations*

Considerations should be made when following up special populations such as older persons (see Chapter 22. Caring for older people with COVID-19), and children and their caregivers.

**Practical info**

**Uncertainties**

Further research on mid- and long-term sequelae of COVID-19 is a priority. Some items identified include:

- A consensus case definition to facilitate global surveillance, diagnosis, management and research to be convened by WHO.
- Detailed clinical characterization of mid- and long-term sequelae, using standardized tools for data collection (see Chapter 27. Clinical research during the COVID-19 pandemic).
- Multidisciplinary approach to research which involves patients and communities affected with COVID-19.
- Impact of therapeutics on longer term outcomes.

# 25. Ethical principles for optimum care during the COVID-19 pandemic

Ethics are central to the clinical care of COVID-19 patients in the same way that ethics pertain to all patients. Clinical care involves using clinical expertise to do what is best for patients within a relationship of care. This section provides a brief introduction to some of the ethical considerations that are important to remember in the context of COVID-19 *(259,260)*.

Ethical considerations that impact all persons affected by COVID-19

**Equal moral respect:** Every person is equally valuable. Treatment and care decisions should be based on medical need and not on irrelevant or discriminatory features such as **ethnicity, religion, sex, age, disability or political affiliation**. Patients with similar health problems or symptoms must receive equal treatment and care. Showing moral respect means involving patients and their caregivers in decision-making to the greatest extent possible, explaining options and limitations in treatment.

**Duty of care:** Every patient is owed the best possible care and treatment available in the circumstances. Even when resources need to be rationed during a crisis, health care professionals and frontline workers have a duty of care to promote their patients' welfare within available resources. Health care professionals and frontline workers are also owed a duty of care. In this regard, appropriate PPE for health care professionals and frontline workers should be provided to promote their safety and well-being. This is a benefit to them but also to the whole of society by ensuring that they are available to support the clinical response for as long as possible.

**Non-abandonment:** It follows from consideration of equal moral respect and duty of care, that no person in need of medical care should ever be neglected or abandoned. Care will extend to families and friends of patients and options to maintain communication with them should be explored. Palliative care must be accessible for all patients with respiratory failure for whom ventilatory support will be withheld or withdrawn.

**Protection of the community:** Appropriate IPC should be in place, respected and enforced. Such actions protect patients, health care professionals and the community. During a pandemic the focus should be on both clinical care for patients and the promotion of public health.

**Confidentiality:** All communications between patient and clinician must remain confidential except in the case of compelling public health concerns (e.g. contact tracing and surveillance etc.) or other accepted justifications for breach of confidentiality. Private individual information must be kept secure unless it is a justified breach.

**We recommend that hospitals and health systems at local, regional, national and global level plan prepare and be ready to surge clinical care capacity (staff, structure, supplies and systems) in order to be able to provide appropriate care of all COVID-19 patients and maintain essential health services *(61,261)*.**

**Allocation of scarce resources: We recommend that each institution should establish a plan for what to do in situations of resource scarcity to cover the allocation or access to critical medical interventions (such as oxygen, intensive care beds and/or ventilators). Such a plan should establish a clear overall aim.**

**Decision-making regarding allocation: Part of planning for scarcity is ensuring that a fair system of decision-making for allocation is in place.**

**Remarks:**

1. Personnel familiar with the medical triage criteria and allocation protocols, who are distinct from the clinical treating team are one option. Allocation decisions should be done according to the established plan and regularly reviewed. If necessary, there should be a reallocation of a resource that was previously allocated where it is not proving beneficial.
2. For example, the aim might be to ensure the best possible use of limited resources based upon chosen medical criteria. Triage criteria should seek to balance medical utility and equity, and ease of implementation. The same criteria should be applied for all patients with similar levels of need, regardless of COVID-19 status.

**We recommend that it be clear when decision-making will move from routine allocation to pandemic allocation, so that institutions do not move too soon to restrict access in anticipation of possible future scarcity that might not arise.**

**Remarks:**

1. It should be clear what the “tipping point” is to change to pandemic allocation (e.g. a declaration by a ministry of health, or hospitals reaching ICU bed and ventilator capacity). This should take into account maximizing surge clinical capacity.
2. Whatever method is chosen should be subject to a fair process, such as using the following procedural principles:
    - **Inclusiveness:** Input should be obtained from the most affected population(s).
    - **Transparency:** The mechanism should be easily accessible and understandable at an elementary school level and in all major languages in the institution’s catchment area.
    - **Accountability:** A mechanism should be available to review the application of an approved triage protocol, or requests to review a particular decision, in light of novel or updated clinical information or other concerns.
    - **Consistency:** Allocation principles should be applied consistently.

**We recommend that caregivers should be:**

- **Given access to adequate training in caregiving, including IPC.**
- **Given access to appropriate and adequate PPE.**
- **Exempted from travel restrictions that would preclude caring for the patient.**
- **Be given access to psychological, social and spiritual care, and also to respite and bereavement support as needed.**

**Remark:**
Caregivers are at risk for the same types of psychological, social and spiritual distress as patients. They are also at risk for becoming infected. Basic mental health and psychosocial support should be provided for all caregivers by asking them about their needs and concerns, and addressing them *(262)*.

# 26. Reporting and coding during the COVID-19 pandemic (mortality and morbidity)

All coding advice is available in the official WHO languages and can be found together with more detail for classification purposes at https://www.who.int/standards/classifications/classification-of-diseases/emergency-use-icd-codes-for-covid-19-disease-outbreak. See Table 26.1 and 26.2 for details.

**Table 26.1 Morbidity and mortality coding for COVID-19 in ICD-10 and ICD-11**

| ICD**ICD** | **Description of codes** | |
|---|---|---|
| **ICD -10** | An emergency ICD-10 code of "U07.1 COVID-19, virus identified" is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing.<br>An emergency ICD-10 code of "U07.2 COVID-19, virus not identified" is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available.<br>Both U07.1 and U07.2 may be used for mortality coding and tabulation as cause of death. | |
| **ICD-11** | The code for the confirmed diagnosis of COVID-19 is RA01.0.<br>The code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. | |

A set of additional categories has been agreed to be able to document or flag conditions that occur in the context of COVID-19. Both, 3-character and 4-character codes have been defined to respond to the different levels of coding depth that is in place in different countries. The categories below will not be seen in primary tabulation of the single underlying cause of death. They may be used in multiple cause of death analysis and reporting.

**Table 26.2 Coding for conditions occurring in context of COVID-19 in ICD-10 and ICD-111**

| | |
|---|---|
| **ICD -10** | 1. U08 Personal history of COVID-19 U08.9 Personal history of COVID-19, unspecified<br><br>Note: This optional code is used to record an earlier episode of COVID-19, confirmed or probable that influences the person's health status, and the person no longer suffers of COVID-19. This code should not be used for primary mortality tabulation.<br><br>2. U09 Post COVID-19 condition U09.9 Post COVID-19 condition, unspecified<br><br>Note: This optional code serves to allow the establishment of a link with COVID-19. This code is not to be used in cases that still are presenting COVID-19.<br><br>3. U10 Multisystem inflammatory syndrome associated with COVID-19<br>U10.9 Multisystem inflammatory syndrome associated with COVID-19, unspecified |
| **ICD-11** | RA02 Post COVID-19 condition<br>RA03 Multisystem inflammatory syndrome associated with COVID-19<br>QC42/RA01 Personal history of COVID-19 |

**For mortality we recommend the use of emergency ICD codes as outlined in the *International guidance for certification and coding of COVID-19 as cause of death (263).***

**Remarks:**

1. The primary goal is to identify all deaths due to COVID-19. A death due to COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of pre-existing conditions that are suspected of triggering a severe course of COVID-19.
2. Specification of the causal sequence leading to death in Part 1 of the certificate is important. For example, in cases when COVID-19 causes pneumonia, sepsis and acute respiratory distress; then pneumonia, sepsis and acute respiratory distress should be included, along with COVID-19, in Part 1. Certifiers should include as much detail as possible based on their knowledge of the case, from medical records, or about laboratory testing *(263).*
3. The use of official terminology, COVID-19, should be used for all certification of this cause of death. COVID-19 should be recorded on the medical certificate as cause of death for all decedents where the disease caused, or is assumed to have caused, or contributed to death. This helps to reduce uncertainty for the classification or coding and to correctly monitor these deaths.

# 27. Clinical research during the COVID-19 pandemic

A living mapping and systematic review of COVID-19 studies are available *(264)*. For more information about the WHO research roadmap see https://www.who.int/teams/blueprint/covid-19.

**We recommend to collect standardized clinical data on all hospitalized patients to improve understanding of the natural history of the disease and contribute data to the WHO Global COVID-19 Clinical Data Platform (see website for details).**

**Remarks:**

1. Member States are invited to contribute anonymized clinical data to the WHO Global COVID-19 Clinical Data Platform; contact: COVID_ClinPlatform@who.int to get log-in credentials. This will serve to inform the public health and clinical response.
2. Four case record forms (CRFs) are now available: These can be accessed on the WHO website *(265)*.
   - Rapid CRF
   - Pregnancy CRF
   - Multisystem inflammatory syndrome temporally associated with COVID-19 CRF
   - Follow up CRF.
3. Clinical characterization research protocols are also available *(266).*

**The WHO Solidarity trial is a randomized clinical trial that is a currently enrolling. For more information see the WHO website *(267)*.**

**Remark:**
Older age is reported to be a predictor of mortality in patients with COVID-19. The systematic exclusion of older adults from research activities or from accessing investigational therapeutic agents is not justified *(260).*

# Acknowledgements

**Acknowledgements for *Clinical management of COVID-19: interim guidance* 25 January 2021**

**WHO Steering Committee members:** Janet V Diaz (Lead, Clinical Team for COVID-19 Response, Health Emergency Programme, Geneva); John Appiah (Lead, case management, WHO Regional Office for Africa); Lisa Askie (Quality Assurance of Norms and Standards Department); April Baller (Infection Prevention and Control); Anshu Banerjee (Department of Maternal, Newborn, Child and Adolescent Health and Ageing); Shannon Barkley (UHC, Primary Care Services); Silvia Bertagnolio (Communicable and Noncommunicable Diseases Division/Clinical Team for COVID-19 Response); Bianca Hemmingsen; Mercedes Bonet (Sexual and Reproductive Health and Research Department); Andrea Bosman (Global Malaria Programme); Marie-Charlotte Bousseau (Palliative Care); Maurice Bucagu (Department of Sexual and Reproductive Health and Research); Neerja Chowdhary (Department of Mental Health and Substance Use); Alarcos Cieza (Management of Noncommunicable Diseases, Disability, Violence and Injury); Jane Cunningham (Global Malaria Programme); Bernadette Daelmans; Meg Doherty (Treatment and Care, Department of HIV/AIDS); Wouter De Groute (Department for Management of Noncommunicable Diseases, Disability, Violence and Injury); Tarun Dua (Unit Head, Brain Health, Department of Mental Health and Substance Use); Nedret Emiroglu (Country Readiness Strengthening, Health Emergencies Department); Jill Farrington (Communicable and NCDs); Dennis Falzon (Global TB Programme); Nathan Ford (Department of HIV/AIDS and Global Hepatitis Programme); Gilles Forte; John Grove (Quality Assurance of Norms and Standards Department); Zee Han; Fahmy Hanna (Department of Mental Health and Substance Use); Licé Gonzalez Angulo (Global TB Programme); Laurence Grummer-Strawn (Department of Nutrition for Health and Development); Peter Hughes (Department of Mental Health and Substance Use); Benedikt Huttner (Infection Control Programme and Division of Infectious Diseases); Ernesto Jaramillo (Global TB Programme); Robert Jakob (Department of Health and Information Systems); Maria Van Kerkhove (Health Emergencies Programme); Chiori Kodama (Lead, case management, WHO Regional Office for Eastern Mediterranean), Kavita Kolappa (Department of Mental Health and Substance Use); (Caron Kim (Sexual and Reproductive Health and Research); Rok Ho Kim (Quality Assurance of Norms and Standards Department); Kavitha Kolappa (Department of Mental Health and Substance Abuse); Ornella Lincetto (Department of Reproductive Health and Research Sexual and Reproductive Health and Research Department); Lorenzo Moja (Health Products Policy and Standards Department); Allisyn Moran; Yasir Nisar; Olufemi Oladapo (Sexual and Reproductive Health and Research Department); Peter Olumese (Global Malaria Programme); Mark van Ommeren (Department of Mental Health and Substance Use); Mark Perkins (Lead, Laboratory Response COVID-19; Health Emergency Programme); Martina Penazzato (Paediatric Lead for HIV, Hepatitis and STI Programme); Dina Pfeifer (WHO Regional Office for Europe/Health Emergencies Programme); Anayda Portela (Department of Maternal, Newborn, Child and Adolescent Health); Jacobus Preller (Clinical Team for COVID-19 Response); Andreas Reis (Global Health Ethics); Pryanka Relan (Integrated Health Services Department/Clinical Team for COVID-19 Response); Ludovic Reveiz (Evidence and Intelligence for Action in Health Department, Incident Management Systems for COVID-19, Pan American Health Organization); Lisa Rogers (Department of Nutrition for Health and Development); Gojka Roglic; Nigel Rollins (Department of Maternal, Newborn, Child and Adolescent Health); Nicoline Schiess (Department of Mental Health and Substance Use); Katrin Seeher (Department of Mental Health and Substance Use); Ingrid Smith; Howard Sobel (WHO Regional Coordinator for Reproductive, Maternal, Newborn, Child and Adolescent Health); Maria Pura Solon (Methods and Standards, Quality Assurance of Norms and Standards Science Division); Yuka Sumi (Department of Maternal, Newborn, Child and Adolescent Health and Ageing); Soumya Swaminathan (Office of Chief Scientist); Anna Thorson (Sexual and Reproductive Health and Research); Nola Tomaska (Department of Health and Information Systems); Kavita TrivediMIS; Marco Vitoria (UHC, Communicable and NCDs); Cherian Varghese (Communicable and NCDs); Karin Von Eije (Health Emergency Programme); Prinzo Weise (Department of Healthier Population); Wilson Were (Maternal, Newborn, Child and Adolescent Health and Ageing); Pushpa Wijesinghe (Lead, case management, Regional Office for South East Asia); Matteo Zignol (UHC, Communicable and NCD).

**Supporting project officer:** Jacqueline Lee Endt (Health Care Readiness Unit, Health Emergencies Department).

**Observer**: Christine Halleux (Quality Assurance of Norms and Standards);

**The WHO Steering Committee is fully responsible for decisions about guidance production and convening the GDG.**

**WHO convened GDG panel members:** Wagdy Amin (Ministry of Health and Population, Egypt); Erlina Burhan (Infection Division Department of Pulmonology and Respiratory Medicine Faculty of Medicine Universitas Indonesia); Frederique Bausch (Geneva University Hospital, Switzerland); Darren Brown (Physiotherapy, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom); Maurizio Cecconi (Humanitas Research Hospital Milan, Italy); Duncan Chanda (Adult Infectious Disease Centre, University Teaching Hospital, Lusaka, Zambia); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Hanoi, Viet Nam); Bin Du (Peking Union Medical College Hospital); Heike Geduld (Emergency Medicine, Stellenbosch University, South Africa); Patrick Gee (patient panel member, United States of America); Madiha Hashimi (Ziauddin University, Karachi, Pakistan); Manai Hela (Emergency Medical Service Tunis, Tunisia); Beverly Hunt (Thrombosis and Haemostasis, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom); Sushil Kumar Kabra (All India Institute of Medical Sciences, New Delhi India); Seema Kanda (patient panel member, Ontario, Canada); Leticia Kawano-Dourado (Research Institute, Hospital do Coração, São Paulo, Brazil); Yae-Jean Kim (Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea); Niranjan Kissoon (Department of Paediatrics and Emergency Medicine, University of British Columbia, Vancouver, Canada); Arthur Kwizera (Makerere College of Health Sciences, Kampala, Uganda); Claire McLintock (Haematology, Auckland City Hospital, Auckland, New Zealand); Imelda Mahaka (patient panel member, Pangaea Harare, Zimbabwe); Greta Mino (Alcivar Hospital in Guayaquil, Ecuador); Emmanuel Nsutebu (Sheikh Shakhbout Medical City, Abu Dhabi); Natalia Pshenichnaya (Central Research Institute of Epidemiology of Rospotrebnadzor, Moscow, Russia); Nida Qadir (Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, United States of America); Saniya Sabzwari (Aga Khan University, Karachi, Pakistan); Rohit Sarin (National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India); Michael Sharland (St George's University, London); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Sally Singh (Pulmonary and Cardiac Rehabilitation, University of Leicester, United Kingdom); Joao Paulo Souza (University of São Paulo Brazil); Shalini Sri Ranganathan (University of Colombo, Sri Lanka); Miriam Stegemann (Charite, Berlin, Germany); Sebastian Ugarte (Faculty of Medicine Andres Bello University, Indisa Clinic, Santiago, Chile); Sridhar Venkatapuram (King's College, London); Dubula Vuyiseka (patient panel member, University of Stellenbosch, South Africa); Ananda Wijewickrama (Ministry of Health, Sri Lanka).

**Methodologist:** Gordon Guyatt (McMaster University, Canada).

**Clinical Chair:** Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto) and Srinivas Murthy (Associate Professor, University of British Columbia, Vancouver, Canada).

We would like to acknowledge the **Guidance Support Collaboration Committee** which provided the coordination to allow the rapid development of the WHO guidance and its dissemination: Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto); Lisa Askie (WHO); Janet V Diaz (WHO); Gordon Guyatt (McMaster University, Canada); Marta Lado (WHO); Srinivas Murthy (University of British Colombia, Canada); Kobus Preller (WHO); Archana Seahwag (WHO); Joan B Soriano (WHO); and to the MAGIC Evidence Ecosystem Foundation for their support in the publication process through MAGICapp: Per Olav Vandvik, Arnav Agarwal, Lyubov Lytvyn, Stijn Rita Patrick van de Velde, Ying Wang, Linan Zeng, Dena Zeraatkar.

**Special thanks to the following collaborators for providing systematic reviews:**

National Institute for Health and Care Excellence (NICE, United Kingdom): COVID-19 rapid evidence review: management of the long-term effects of COVID-19, facilitated by Justine Karpusheff, Sara Buckner.

American Society of Hematology guideline/McMaster University GRADE Centre systematic review (www.hematology.org/COVIDguidelines) facilitated by Holger Schünemann, Robby Nieulaat (McMaster University, Canada).

Cochrane Library: Care bundles for improving outcomes in patients with COVID-19 in intensive care – a rapid scoping review, prepared by V Smith, D Devane, A Nichol, D Roche.

Karel GM Moons (University Medical Center Utrecht, www.covprecise.org); Laure Wynants (Leuven/Maastricht); Maarten van Smeden (Utrecht): COVID-19 related prediction models for prognosis: living systematic review.

**Special thanks to experts who provided presentations to the GDG:**
Pasi Penttinen (European Centre for Disease Prevention and Control): Risk factors for severe outcomes following COVID-19 infection – results of a systematic literature review.

**Special thanks to the WHO Rapid Review team and WHO Library:**
Thomas Allen (WHO Library); Haley Holmer (WHO Quality, Norms & Standards); Ajay Rangaraj (WHO UHC, Communicable and NCDs); Vanessa Veronese (WHO Research and Training in Tropical Diseases); for conducting the evidence search.

**Special thanks to the external reviewers for their insights on the new recommendations:**
Richard Kojan (Alliance for International Medical Action); Gabriel Alcoba, Francisco Bartolome, Edward Chu, Marcio da Fonseca, Amin Lamrous, James Lee, Bhargavi Rao, Saschveen Singh, Armand Sprecher (Médecins Sans Frontières).

**Special thanks to the following reviewers of the updates on Chapter 17 (neurological and mental manifestations):**
José Luis Ayuso-Mateos (Director, Department of Psychiatry, Universidad Autónoma de Madrid, CIBERSAM and WHO Collaborating Centre for Mental Health Services Research and Training, Spain); Corrado Barbui (WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Italy); Ettore Beghi (Professor of Neurology, Department of Neuroscience, Istituto di Ricerche Farmacologiche, Milano, Italy); Sherry H-Y Chou (Associate Professor of Critical Care Medicine, Neurology, and Neurosurgery, University of Pittsburgh School of Medicine, United States of America); Mario Maj (Director, Department of Psychiatry, University of Naples, Italy); Benedict Michael (Senior Clinician Scientist Fellow, Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom); Shubham Misra (Senior Research Fellow, Department of Neurology, All India Institute of Medical Sciences, New Delhi, India); Pratima Murthy (Professor and Head, Department of Psychiatry National Institute of Mental Health and Neuro-Sciences, Bangalore, India); Alessandro Padovani (Neurologist, Director, NeuroCOVID Unit, University of Brescia, Italy); Kameshwar Prasad (Professor of Neurology, All India Institute of Medical Sciences, New Delhi, India); Shekhar Saxena (Professor, Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA, United States of America); Kiran Thakur (Neurologist, Winifred Mercer Pitkin Assistant Professor of Neurology, Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York City, United States of America).

**Special thanks to the following reviewers of the updates on Chapter 19 (rehabilitation):**
Neelum Zehra Bukhari (Head, Department Occupational Therapy, Ziauddin College of Rehabilitation Sciences, Ziauddin University, Pakistan); Professor Trish Greenhalgh (Nuffield Department of Primary Care Health Sciences, University of Oxford, United Kingdom); Peter A Lim (Rehabilitation Medicine, Singapore General Hospital, Clinical Associate Professor, Duke-NUS Medical School, Singapore, and Clinical Professor, Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX, United States of America); Professor Sally Singh (Head of Pulmonary and Cardiac Rehabilitation, University Hospitals Leicester, United Kingdom); Dr Abena Tannor (Rehabilitation Medicine, Komfo Anokye Teaching Hospital, Accra, Ghana).

**Special thanks also go to the WHO COVID-19 IPC Global Expert Panel:**
April Baller (Infection Prevention and Control, WHE); Carole Fry (Infection Prevention and Control Hub and Task Force, Integrated Health Services, WHO).

**Acknowledgements for *Clinical management of COVID-19: interim guidance* 27 May 2020**

**WHO Steering Committee:** Janet V Diaz (Lead), Nazneen Anwar, Florence Baingana, April Baller, Anshu Banerjee, Silvia Bertagnolio, Mercedes Bonet, Andrea Bosman, Marie-Charlotte Bousseau, Andrea Bruni, Maurice Bucagu, Neerja Chowdhary, Jane Cunningham, Meg Doherty, Tarun Dua, Alexandra Fleischmann, Nathan Ford, Stéfanie Freel, Laurence Grummer-Strawn, Fahmy Hanna, Benedikt Huttner, Ernesto Jaramillo, Maria Van Kerkhove, Caron Kim, Kavitha Kolappa, Teresa Kortz, Ornella Lincetto, Aiysha Malik, Carmen Martinez, Alessandro Massazza, Jody-Ann Mills, Lorenzo Moja, Susan Norris, Olufemi Oladapo, Peter Olumese, Mark van Ommeren, Martina Penazzato, Anayda Portela, Andreas Reis, Pryanka Relan, Lisa Rogers, Nigel Rollins, Khalid Saeed, Katrin Seeher, Allison Schaefer, Nicoline Schiess, Ingrid Smith, Howard Sobel, Maria Pura Solon, Renato Souza, Yuka Sumi, Anna Thorson, Kavita Trivedi, Marco Vitoria, Prinzo Weise, Inka Weissbecker, Wilson Were, Matteo Zignol.

**United Nations Children's Fund (UNICEF):** Maya Arii.

**Guideline Development Group members:** Neill Adhikari (Sunnybrook Health Sciences Centre and University of Toronto); John Appiah (Senior Specialist, Paediatric Critical Care and Head of Paediatric Intensive Care Unit of the Komfo Anokye Teaching Hospital, Ghana); Abdullah Balkhair (Head of Infectious Diseases Unit and Infection Control Department, Sultan Qaboos University, Oman); Florence Baingana (Research Fellow, Makerere University, Kampala, Uganda); Corrado Barbui (WHO Collaborating Centre for

Research and Training in Mental Health and Service Evaluation, University of Verona, Italy); Lucille Blumberg (National Institute for Communicable Diseases, South Africa); Bin Cao (China-Japan Friendship Hospital, Capital Medical University, Beijing, China); Maurizio Cecconi (Head of Department Anesthesia and Intensive Care Units, Humanitas Research Hospital, Milan, Italy); Bronwen Connolly (Queen's University Belfast, United Kingdom of Great Britain and Northern Ireland); Vu Quoc Dat (Department of Infectious Diseases, Hanoi Medical University, Viet Nam); Jake Dunning (Head of Emerging Infections and Zoonoses, Public Health England, United Kingdom); Rob Fowler (University of Toronto, Canada); Heike Geduld (African Federation for Emergency Medicine, Cape Town, South Africa); Charles Gomersall (Chinese University of Hong Kong, Hong Kong SAR, China); Rumina Hasan (Professor, Department of Pathology and Laboratory Medicine, Aga Kahn University, Pakistan, and Honorary Professor, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom); Manai Hela (Emergency Medical Service Tunis, Tunisia); David S Hui (Chairman of the Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong SAR, China); Yae-Jean Kim (Sungkyunkwan University, Samsung Medical Center, Republic of Korea); Niranjan Kissoon (Professor in Critical Care, University of British Columbia and BC Children's Hospital, Vancouver, Canada); Arthur Kwizera (Department of Anaesthesia and Critical Care, Makerere University, Kampala, Uganda); Pisake Lumbiganon (Director WHO Collaborating Centre for Research Synthesis in Reproductive Health, Faculty of Medicine, Khon Kaen University, Thailand); Flavia Machado (Anesthesiology, Pain and Intensive Care Department, Federal University of São Paulo, Brazil); Srinivas Murthy (Associate Professor, University of British Columbia, Vancouver, Canada); Saniya Sabzwari (Aga Khan University Hospital, Karachi, Pakistan); Rohit Sarin (Director, National Center of Excellence Supranational TB Reference Laboratory, New Delhi, India); Yinzhong Shen (Shanghai Public Health Clinical Center, Fudan University, Shanghai, China); Maria Asuncion Silvestre (President, Kalusugan ng Mag-Ina (Health of Mother and Child), Quezon City, Philippines); João Paulo Souza (Professor of Public Health, Department of Social Medicine, Ribeirao Preto Medical School, University of São Paulo, Brazil).

**External reviewer panel:** Shekhar Saxena (Professor, Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA, United States of America); Francesco Castelli (Director, Department of Infectious and Tropical Diseases, University of Brescia and Brescia Civili General Hospital, Italy); Richard Kojan (President, Alliance for International Medical Action).

**External review of Chapter 15 (neurological and mental manifestations):** José Luis Ayuso-Mateos (Director, Department of Psychiatry, Universidad Autónoma de Madrid, CIBERSAM and WHO Collaborating Centre for Mental Health Services Research and Training, Spain); Corrado Barbui (WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, University of Verona, Italy); Rabih El Chammay (Director, National Mental Health Programme, Beirut, Lebanon); Oye Gureje (Director, Institute of Neurosciences, University College Hospital, Ibadan, Nigeria); Mario Maj (Director, Department of Psychiatry, University of Naples, Italy); Farrah Mateen (Associate Professor of Neurology, Harvard Medical School, Boston, MA, United States of America); Pratima Murthy (Professor and Head, Department of Psychiatry National Institute of Mental Health and Neuro-Sciences, Bangalore, India); Giovanni Ostuzzi (Psychiatrist, University of Verona, Italy); Chuan Shi (Psychiatrist, University of Peking, Beijing, China); Felicia Smith (Psychiatrist, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States of America); Graham Thornicroft (Professor of Community Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, and Health Service & Population Research Department, King's College London, United Kingdom); Peter Ventevogel (Senior Mental Health Advisor, United Nations High Commissioner for Refugees, Geneva, Switzerland).

**Special thanks also go to the WHO COVID-19 IPC Global Expert Panel:**
April Baller (Infection Prevention and Control, WHE); Fernanda Lessa (US CDC (WHO secondment)); Madison Moon (Infection Prevention and Control, WHE); Alice Simniceanu (Infection Prevention and Control, WHE); Benedetta Allegranzi (Infection Prevention and Control Hub and Task Force, Integrated Health Services, WHO).

# References


1. WHO. Country & Technical Guidance – coronavirus disease (COVID-19). Geneva: World Health Organization; 2020.
2. Somsen GA, van Rijn C, Kooij S, Bem RA, Bonn D. Small droplet aerosols in poorly ventilated spaces and SARS-CoV-2 transmission. Lancet Respir Med. 2020;8(7):658-659.
3. Burke RM, Midgley CM, Dratch A, Fenstersheib M, Haupt T, Holshue M, al. Active monitoring of persons exposed to patients with confirmed COVID-19 – United States, January–February 2020. MMWR Morb Mortal Wkly Rep. 2020.
4. Ong SWX, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA. 2020.
5. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020.
6. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020.
7. WHO. Transmission of SARS-CoV-2: implications for infection prevention precautions. Scientific brief, 9 July 2020. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/333114, accessed 21 November 2020).
8. Yu P, Zhu J, Zhang Z, Han Y, Huang L. A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period. J Infect Dis. 2020.
9. Huang R, Xia J, Chen Y, Shan C, Wu C. A family cluster of SARS-CoV-2 infection involving 11 patients in Nanjing, China. Lancet Infect Dis. 2020;20(5):534-535.
10. Pan X, Chen D, Xia Y, Wu X, Li T, Ou X, et al. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. Lancet Infect Dis. 2020;20(4):410-411.
11. Tong ZD, Tang A, Li KF, Li P, Wang HL, Yi JP, et al. Potential presymptomatic transmission of SARS-CoV-2, Zhejiang Province, China, 2020. Emerg Infect Dis. 2020;26(5):1052-1054.
12. Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al. Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility - King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020;69(13):377-381.
13. WHO. Criteria for releasing COVID-19 patients from isolation. Scientific brief. Geneva: World Health Organization; 2020.
14. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26(5):672-675.
15. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):411-415.
16. Gandhi RT, Lynch JB, del Rio C. Mild or moderate Covid-19. NEJM. 2020;383(18):1757-1766.
17. US CDC. Symptom based strategy to discontinue isolation for persons with COVID-19. Atlanta (GA): Centers for Disease Control and Prevention (https://www.cdc.gov/coronavirus/2019- ncov/community/strategy-discontinue-isolation.html, accessed 21 November 2020).
18. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-469.
19. van Kampen J, van de Vijver D, Fraaij D, Haagmans B, Lamers M, Okba N. Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID19): duration and key determinants. MedRxiv. 2020. doi:10.1101/2020.06.08.20125310.
20. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. PLoS Med. 2020;17(9):e1003346.
21. Byambasuren O, Cardona M, Bell K, Clark J, McLaws ML, Glasziou P. Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis. JAMMI. 2020;5(4):223-234.
22. Yanes-Lane M, Winters N, Fregonese F, Bastos M, Perlman-Arrow S, Campbell JR, et al. Proportion of asymptomatic infection among COVID-19 positive persons and their transmission potential: a systematic review and meta-analysis. PloS One. 2020;15(11):e0241536.
23. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill. 2020;25(10):2000180.
24. Clarke C, Prendecki M, Dhutia A, Ali MA, Sajjad H, Shivakumar O, et al. High prevalence of asymptomatic COVID-19 infection in hemodialysis patients detected using serologic screening. JASN. 2020;31(9):1969-1975.
25. The novel coronavirus pneumonia emergency response epidemiology team. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 Novel Coronavirus diseases (COVID-19) -China 2020. China CDC Weekly. 2020;2(8):113-22.
26. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, et al. Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: a rapid systematic review and meta-analysis. PLoS One. 2020;15(5):e0233147.
27. WHO. WHO statement: Tobacco use and COVID-19. 11 May 2020. Geneva: World Health Organization; 2020.

28. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
29. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062.
30. Aydillo T, Gonzalez-Reiche AS, Aslam S, van de Guchte A, Khan Z, Obla A, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. NEJM. 2020;383(26):2586-2588.
31. Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 Infection. JAMA. 2020;323(20):2089-2090.
32. Favas TT, Dev P, Chaurasia RN, Chakravarty K, Mishra R, Joshi D et al. Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. Neurol Sci. 2020;41(12):3437-3470.
33. Abdullahi A, Candan SA, Abba MA, Bello AH, Alshehri MA, Afamefuna V et al. Neurological and musculoskeletal features of COVID-19: a systematic review and meta-analysis. Front Neurol. 2020;11:687.
34. Kantonen J, Mahzabin S, Mäyränpää MI, Tynninen O, Paetau A, Andersson N et al. Neuropathologic features of four autopsies COVID-19 patients. Letter to the editor. Brain Pathol. 2020.
35. Koutroumanidis M, Gratwicke J, Sharma S, Whelan A, Tan V, Glover G et al. Alpha coma EEG pattern in patients with severe COVID-19 related encephalopathy. Clin Neurophysiol. 2020;S1388-2457(0):30480-6.
36. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020.
37. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62354 COVID-19 cases in the USA. Lancet Psychiatry. 2020;S2215-0366(20):30462-4.
38. Liotta EM, Batra A, Clark JR, Shlobin NA, Hoffman SC, Orban ZS, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol. 2020;7(11):2221-2230.
39. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. NEJM. 2020.
40. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
41. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. NEJM. 2020.
42. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020.
43. Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry. 2020;7(10):875-882.
44. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence?. Lancet Neurol. 2020;19(5):383-384.
45. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features. Radiol. 2020;201187.
46. Nanda S, Handa R, Prasad A, Anand R, Zutshi D, Dass SK, et al. COVID-19 associated Guillain-Barré syndrome: contrasting tale of four patients from a tertiary care centre in India. Am J Emerg Med. 2020;39:125-8.
47. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatrica. 2020;109(6):1088-1095.
48. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020;20(6):669-677.
49. Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr. 2020;179(7):1029-1046.
50. Salvatore CM, Han J-Y, Acker KP, Tiwari P, Jin J, Brandler M, et al. Neonatal management and outcomes during the COVID-19 pandemic: an observation cohort study. Lancet Child Adolesc Health. 2020;4(10):721-727.
51. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):P1607-1608.
52. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J. 2020;39(11):e340-e346.
53. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
54. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute-covid-19 in primary care. BMJ. 2020;370:m3026.
55. The Lancet. Facing up to long COVID. Lancet. 2020;396(10266):1861.
56. WHO. WHO Handbook for guideline development (2nd edition). Geneva: World Health Organization; 2014.
57. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.
58. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ. 2008;336(7652):1049-51.
59. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

60. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation: direction and strength. J Clin Epidemiol. 2013;66(7):726-35.
61. WHO. Operational considerations for case management of COVID-19 in health facility and community. Geneva: World Health Organization; 2020.
62. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. NEJM. 2020;382(22):2081-2090.
63. McMichael TM, Currie DW, Clark S, Pogosjans S, Kay M, Schwartz NG, et al. Epidemiology of Covid-19 in a long-term care facility in King County, Washington. NEJM. 2020;382(21):2005-2011.
64. Tay HS, Harwood R. Atypical presentation of COVID-19 in a frail older person. Age Ageing. 2020;affaa068.
65. WHO. Dengue guidelines, for diagnosis, treatment, prevention and control. Geneva: World Health Organization; 2009.
66. WHO. Guidelines for the treatment of malaria (3rd edition). Geneva: World Health Organization; 2015.
67. WHO. Guidelines on tuberculosis infection prevention and control. Geneva: World Health Organization; 2019.
68. WHO. Tuberculosis and COVID-19: information note. Geneva: World Health Organization; 2020.
69. WHO. Guidelines for treatment of drug-susceptible tuberculosis and patient care. Geneva: World Health Organization; 2017.
70. WHO. Infection prevention and control for long-term care facilities in the context of COVID-19. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/338481, accessed 21 January 2021).
71. WHO. Community based health care including outreach and campaigns in the context of the COVID-19 pandemic: interim guidance, May 2020. WHO IFRC UNICEF. Geneva: World Health Organization; 2020.
72. WHO. WHO-ICRC Basic emergency care: approach to the acutely ill and injured. Geneva: World Health Organization; 2018.
73. WHO. Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation. Geneva: World Health Organization; 2020.
74. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242.
75. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):P475-481.
76. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. Ann Intern Med. 2019;170(1):W1-W33.
77. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
78. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11)1061-1069.
79. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. NEJM. 2020;382(18):1708-1720.
80. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020;71(15):889-890.
81. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2020;163(1):3-11.
82. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynaecol Obstet. 2020.
83. CDC COVID-19 Response Team. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-426.
84. Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. World Psychiatry. 2020;10.1002/wps.20806.
85. Li L, Li F, Fortunati F, Krystal JH. Association of a prior psychiatric diagnosis with mortality among hospitalised patients with coronavirus disease 2019 (COVID-19) Infection. JAMA Netw Open. 2020;3(9):e2023282.
86. WHO. IMAI district clinician manual: hospital care for adolescents and adults. Geneva: World Health Organization; 2011.
87. WHO. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses (second edition). Geneva: World Health Organization; 2013.
88. Russell FM, Reyburn R, Chan J, Tuivaga E, Lim R, Lai J, et al. Impact of the change in WHO's severe pneumonia case definition on hospitalized pneumonia epidemiology: case studies from six countries. Bull World Health Organ. 2019;97(6):386-393.
89. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-33.
90. Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5 Suppl 1):S23-40.

91. Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-Goodspeed VM, Officer L, et al. Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali Modification of the Berlin Definition. Am J Respir Crit Care Med. 2016;193(1):52-9.
92. 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):304-377.
93. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med. 2020;46(Suppl 1):10-67.
94. Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, et al. American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. Crit Care Med. 2017;45(6):1061-1093.
95. WHO. Infection, prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed: interim guidance. Geneva: World Health Organization; 2020.
96. WHO. Mask use in the context of COVID-19: interim guidance. Geneva: World Health Organization; 2020.
97. WHO. Five moments of hand hygiene. World Health Organization; 2009.
98. WHO. How to put on and how to remove personal protective equipment (PPE): infographic. World Health Organization; 2015.
99. WHO. Diagnostic testing for SARS-CoV-2: interim guidance. World Health Organization; 2020.
100. Lee TH, Lin RJ, Lin RTP, Barkham T, Rao P, Yeo YS et al. Testing for SARS-CoV-2: Can we stop at 2? Clin Infect Dis. 2020;71(16):2246-2248.
101. WHO. Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages: interim guidance. World Health Organization; 2020.
102. WHO. Transmission of SARS-CoV-2: implications for infection prevention precautions. Scientific brief. World Health Organization; 2020.
103. WHO. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays: interim guidance. World Health Organization; 2020.
104. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020;71(9):2459-2468.
105. WHO. Compendium of WHO malaria guidance – prevention, diagnosis, treatment, surveillance and elimination. World Health Organization; 2019.
106. Yan G, Lee CK, Lam LTM, Yan B, Chua YX, Lim AYN, et al. Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis. 2020;20(5):536.
107. WHO. Readiness for influenza during the COVID-19 pandemic. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-2019-nCoV-Influenza-readiness-COVID-19-2020.1, accessed 17 January 2021).
108. WHO. Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts. Geneva: World Health Organization; 2020.
109. WHO. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19. Geneva: World Health Organization; 2020.
110. Greenhalgh T, Koh GCH, Car J. Covid-19: a remote assessment in primary care. BMJ. 2020;368:m1182.
111. Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365(9459):579-87.
112. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014;5(6):229-41.
113. WHO. AWARE classification of antibiotics. World Health Organization; 2019.
114. Duncan H, Hutchison J, Parshuram CS. The Pediatric Early Warning System score: a severity of illness score to predict urgent medical need in hospitalized children. J Crit Care. 2006;21(3):271-8.
115. WHO. Oxygen sources and distribution for COVID-19 treatment. World Health Organization; 2020.
116. WHO. Paediatric emergency triage, assessment and treatment. World Health Organization; 2016.
117. Thomas P, Baldwin C, Bissett B, Boden I, Gosselink R, Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: clinical practice recommendations. J Physiother. 2020;66(2):73-82.
118. WHO. Oxygen therapy for children: a manual for health workers. World Health Organization; 2016.
119. Schultz MJ, Dünser MW, Dondorp AM, Adhikari NK, Shivakumar I, Kwizera A et al. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. Intensive Care Med. 2017;43(5):612-624.
120. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J. 2017;50(2).
121. Lee MK, Choi J, Park B, Kim B, Lee SJ, Kim SH, et al. High flow nasal cannulae oxygen therapy in acute-moderate hypercapnic respiratory failure. Clin Respir J. 2018;12(6):2046-2056.
122. Luo Y, Ou R, Ling Y, Qin T. [The therapeutic effect of high flow nasal cannula oxygen therapy for the first imported case of Middle East respiratory syndrome to China]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2015;27(10):841-4.
123. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. Ann Intern Med. 2014;160(6):389-97.

124. Ekhaguere OA, Mairami AB, Kirpalani H. Risk and benefits of bubble continuous positive airway pressure for neonatal and childhood respiratory diseases in low- and middle-income countries. Paediatr Respir Rev. 2019;29:31-36.
125. Peng PWH, Ho PL, Hota SS. Outbreak of a new coronavirus: what anaesthetists should know. Br J Anaesth. 2020;124(5):497-501.
126. Cheung JC, Ho LT, Cheng JV, Cham EYK, Lam KN. Staff safety during emergency airway management for COVID-19 in Hong Kong. Lancet Respir Med. 2020;8(4):e19.
127. Detsky ME, Jivraj N, Adhikari NK, Friedrich JO, Pinto R, Simel DL, et al. Will this patient be difficult to intubate?: the rational clinical examination systematic review. JAMA. 2019;321(5):493-503.
128. Rimensberger PC, Cheifetz IM, Pediatric Acute Lung Injury Consensus Conference Group. Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16(5 Suppl 1):S51-60.
129. NIH NHLBI ARDS Clinical Network. Mechanical ventilation protocol summary. 2008.
130. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. NEJM. 2013;368(23):2159-68.
131. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. Am J Respir Crit Care Med. 2002;165(10):1359-63.
132. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, et al. Comparison of two fluid-management strategies in acute lung injury. NEJM. 2006;354(24):2564-75.
133. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. NEJM. 2004;351(4):327-36.
134. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. NEJM. 2015;372(8):747-55.
135. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010;303(9):865-73.
136. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial Investigators, Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA. 2017;318(14):1335-1345.
137. Goligher EC, Kavanagh BP, Rubenfeld GD, Adhikari NK, Pinto R, Fan E, et al. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome. A secondary analysis of the LOVS and ExPress trials. Am J Respir Crit Care Med. 2014;190(1):70-6.
138. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. NEJM. 2010;363(12):1107-16.
139. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N EJM. 2019;380(21):1997-2008.
140. Vitacca M, Lazzeri M, Guffanti E, Frigiero P, D'Abrosca F, Gianola S, et al. Italian suggestions for pulmonary rehabilitation in COVID-19 patients recovering from acute respiratory failure: results of a Delphi process. Monaldi Arch Chest Dis. 2020;90(2).
141. Felten-Barentsz K, van Oorsouw R, Klooster E, Koenders N, Driehuis F, Hulzebos EH, van der Schaaf M, Hoogeboom TJ, van der Wees PJ. Recommendations for hospital-based physical therapists managing patients with COVID-19. Physical Therapy 2020;100(9):1444-1457.
142. Combes A, Hajage D, Capellier G, Demoule A, Lavoue S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. NEJM. 2018;378(21):1965-1975.
143. Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Jüni P, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. JAMA. 2018;320(21):2251-2259.
144. Combes A, Brodie D, Bartlett R, Brochard L, Brower R, Conrad S, et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med. 2014;190(5):488-96.
145. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. Lancet Respir Med. 2019;7(2):163-172.
146. Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, et al. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: a randomized clinical trial. JAMA. 2017;318(13):1233-1240.
147. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. NEJM. 2011;364(26):2483-95.
148. Bridwell RE, Carius BM, Long B, Oliver JJ, Schmitz G. Sepsis in pregnancy: recognition and resuscitation. West J Emerg. 2019;20(5):822-832.
149. Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014;161(5):347-55.

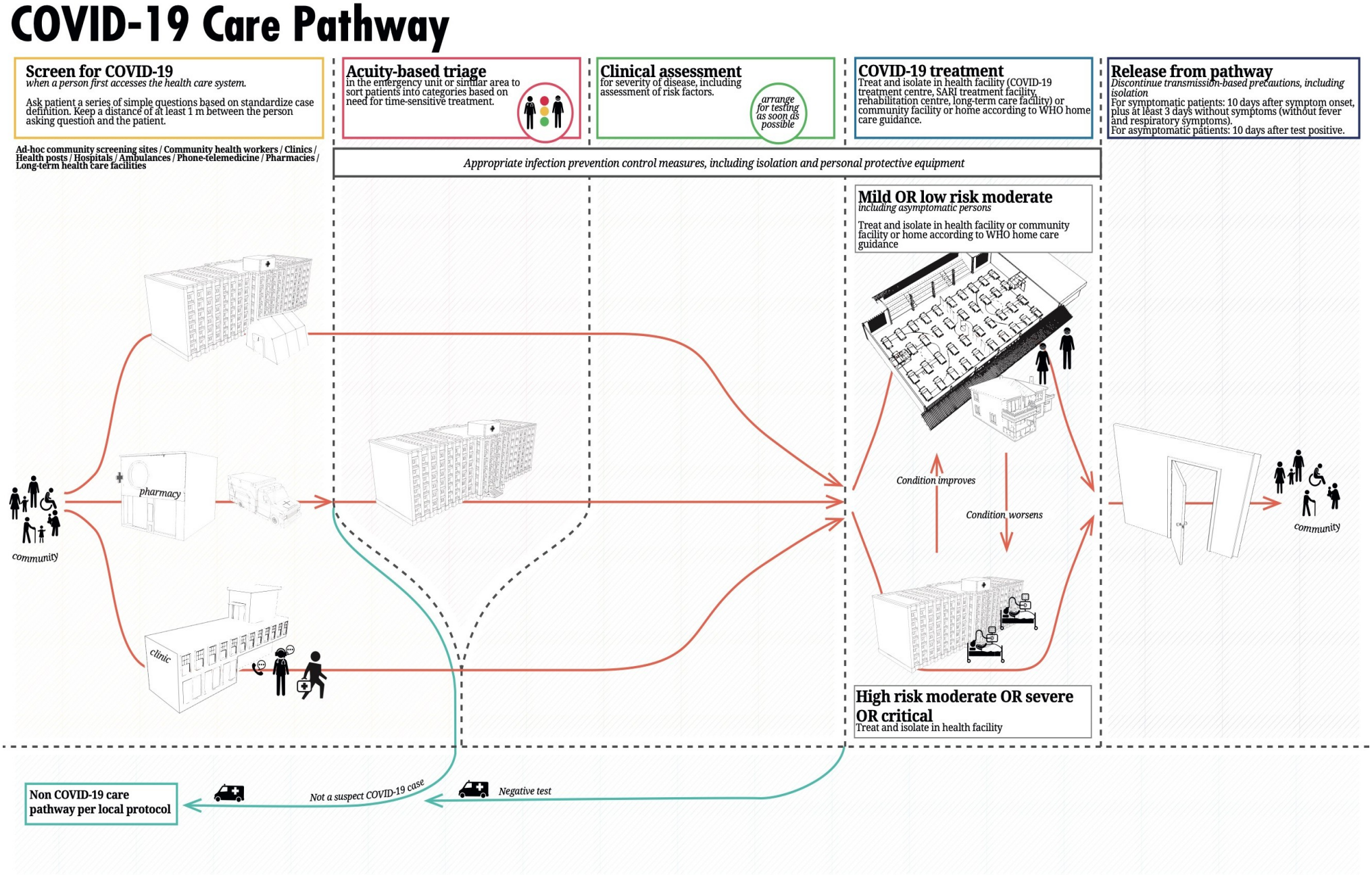
150. Loubani OM, Green RS. A systematic review of extravasation and local tissue injury from administration of vasopressors through peripheral intravenous catheters and central venous catheters. J Crit Care. 2015;30(3):653.e9-17.
151. Lamontagne F, Richards-Belle A, Thomas K, Harrison DA, Sadique MZ, Grieve RD, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. JAMA. 2020;323(10):938-949.
152. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of Pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825-e873.
153. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, Lee G, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(Suppl 2):S133-54.
154. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9):e162-93.
155. Klompas M, Li L, Kleinman K, Szumita PM, Massaro AF. Associations between ventilator bundle components and outcomes. JAMA Intern Med. 2016;176(9):1277-83.
156. Violi F, Pastori D, Cangemi R, Pignatelli P, Loffredo L. Hypercoagulation and antithrombotic treatment in coronavirus 2019: a new challenge. Thromb Haemost. 2020;120(6):949-956.
157. Siddamreddy S, Thotakura R, Dandu V, Kanuru S, Meegada S. Corona virus disease 2019 (COVID-19) presenting as acute ST elevation myocardial infarction. Cureus. 2020;12(4):e7782.
158. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med. 2020;M20-2003.
159. Marschall J, Mermel LA, Fakih M, Hadaway L, Kallen A, O'Grady NP, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35(7):753-71.
160. Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. J Crit Care. 2008;23(1):126-37.
161. Schmidt GA, Girard TD, Kress JP, Morris PE, Ouellette DR, Alhazzani W, et al. Official executive summary of an American Thoracic Society/American College of Chest Physicians clinical practice guideline: liberation from mechanical ventilation in critically ill adults. Am J Respir Crit Care Med. 2017;195(1):115-119.
162. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Crit Care. 2020;24(1):176.
163. Struelens MJ. The epidemiology of antimicrobial resistance in hospital acquired infections: problems and possible solutions. BMJ. 1998;317(7159):652-4.
164. WHO. Off-label use of medicines for COVID-19. Scientific brief. Geneva: World Health Organization; 2020.
165. Aldeyab MA, Kearney MP, McElnay JC, Magee FA, Conlon G, MacIntyre J, et al. A point prevalence survey of antibiotic use in four acute-care teaching hospitals utilizing the European Surveillance of Antimicrobial Consumption (ESAC) audit tool. Epidemiol Infect. 2012;140(9):1714-20.
166. Davies MA. HIV and risk of COVID-19 death: a population cohort study from the Western Cape Province, South Africa. MedRxiv. 2020.
167. Beaud V, Crottaz-Herbette S, Dunet V, Vaucher J, Bernard-Valnet R, Du Pasquier R, et al. Pattern of cognitive deficits in severe COVID-19. J Neurol, Neurosurg Psychiatry. 2020;jnnp-2020-325173.
168. Volkow ND. Collision of the COVID-19 and addiction epidemics. Ann Intern Med. 2020;173(1):61-62.
169. Bianchetti A, Rozzini R, Guerini F, Boffelli S, Ranieri P, Minelli G, et al. Clinical presentation of COVID-19 in dementia patients. J Nutr Health Aging. 2020;24(6):560-562.
170. Hwang JM, Kim JH, Park JS, Chang MC, Park D. Neurological diseases as mortality predictive factors for patients with COVID-19: a retrospective cohort study. Neurol Sci. 2020;41(9):2317-2324.
171. Woolf S, Chapman DA, Sabo RT, Weinberger DM, Hill L. Excess deaths from COVID-19 and other causes March-April 2020. JAMA. 2020;324(5):510-513.
172. Bourne RS, Mills GH. Sleep disruption in critically ill patients – pharmacological considerations. Anaesthesia. 2004;59(4):374-84.
173. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263-306.
174. Ostuzzi G, Papola D, Gastaldon C, Schoretsanitis G, Bertolini F, Amaddeo F, et al. Safety of psychotropic medications in people with COVID-19: evidence review and practical recommendations. BMC Med. 2020;18(1):215.
175. Ostuzzi G, Gastaldon C, Papola D, Fagiolini A, Dursun S, Taylor D, et al. Pharmacological treatment of hyperactive delirium in people with COVID-19: rethinking conventional approaches. Ther Adv Psychopharmacol. 2020;10:1-9.
176. WHO. Interim briefing note addressing mental health and psychosocial aspects of COVID-19 outbreak (developed by the IASC's Reference Group on Mental Health and Psychosocial Support). Geneva: World Health Organization; 2020.
177. WHO. Basic psychosocial skills: a guide for COVID-19 responders. Geneva: World Health Organization; 2020.
178. WHO. mhGAP Evidence Resource Centre. Support based on psychological first aid principles in people recently exposed to a traumatic event. Geneva: World Health Organization; 2012.
179. WHO. Psychological first aid: guide for field workers. Geneva: World Health Organization; 2012.

180. WHO. mhGAP Evidence Resource Centre. Evidence-based recommendations for management of depression in non-specialized health settings. Geneva: World Health Organization; 2012.
181. WHO. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings, version 2.0. Geneva: World Health Organization; 2016.
182. WHO. Doing what matters in times of stress: an illustrated guide. Geneva: World Health Organization; 2020.
183. WHO. COVID-19 and the use of angiotensin-converting enzyme inhibitors and receptor blockers. Scientific brief. Geneva: World Health Organization; 2020.
184. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. NEJM. 2020;382(25):e102.
185. Brodsky MB, Huang M, Shanholtz C, Mendez-Tellez PA, Palmer JB, et al. Recovery from dysphagia symptoms after oral endotracheal intubation in acute respiratory distress syndrome survivors. A 5-year longitudinal study. Ann Am Thorac Soc. 2017;14(3):376-383.
186. Mikkelsen ME, Shull WH, Biester RC, Taichman DB, Lynch S, Demissie E, et al. Cognitive, mood and quality of life impairments in a select population of ARDS survivors. Respirology. 2009;14(1):76-82.
187. Dijkstra-Kersten SMA, Kok L, Kerckhoffs MC, Cremer OL, de Lange DW, van Dijk D, et al. Neuropsychiatric outcome in subgroups of intensive care unit survivors: implications for after-care. J Crit Care. 2020;55:171-176.
188. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. 2010;38(12):2386-400.
189. Needham DM, Feldman DR, Kho ME. The functional costs of ICU survivorship. Collaborating to improve post-ICU disability. Am J Respir Crit Care Med. 2011;183(8):962-4.
190. Cuthbertson BH, Roughton S, Jenkinson D, Maclennan G, Vale L. Quality of life in the five years after intensive care: a cohort study. Crit Care. 2010;14(1):R6.
191. Pfoh ER, Wozniak AW, Colantuoni E, Dinglas VD, Mendez-Tellez PA, Shanholtz C, et al. Physical declines occurring after hospital discharge in ARDS survivors: a 5-year longitudinal study. Intensive Care Med. 2016;42(10):1557-1566.
192. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, et al. Long-term cognitive impairment after critical illness. NEJM. 2013;369(14):1306-16.
193. Huang M, Parker AM, Bienvenu OJ, Dinglas VD, Colantuoni E, Hopkins RO, et al. Psychiatric symptoms in acute respiratory distress syndrome survivors: A 1-year national multicenter study. Crit Care Med. 2016;44(5):954-65.
194. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JFJ. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005;171(4):340-7.
195. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. NEJM. 2011;364(14):1293-304.
196. Dinglas VD, Aronson Friedman L, Colantuoni E, Mendez-Tellez PA, Shanholtz CB, et al. Muscle weakness and 5-year survival in acute respiratory distress syndrome survivors. Crit Care Med. 2017;45(3):446-453.
197. Jaffri A, Jaffri UA. Post-intensive care syndrome and COVID-19: crisis after crisis? Heart Lung. 2020;49(6):883-884.
198. Van Aerde N, Van den Berghe G, Wilmer A, Gosselink R, Hermans G, COVID-19 Consortium. Intensive care unit acquired muscle weakness in COVID-19 patients. Intensive Care Med. 2020;46(11):2083-2085.
199. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med. 2016;42(5):725-738.
200. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. NEJM. 2003;348(8):683-93.
201. Ong KC, Ng AWK, Lee LSU, Kaw G, Kwek SK, Leow MKS, et al. 1-year pulmonary function and health status in survivors of severe acute respiratory syndrome. Chest. 2005;128(3):1393-400.
202. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. J Med Virol. 2021;93(2):1013-1022.
203. Carfi A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324(6):603-605.
204. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome: a case-controlled study. BMC Neurol. 2011;11:37.
205. Dennis A, Wamil M, Kapur S, Alberts J, Badley AD, Decker GA, et al. Multi-organ impairment in low-risk individuals with long COVID. MedRxiv. 2020.
206. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Clark Files D et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistage health care systems network-United States, March-June 2020. MMWR Morb Mortal Wkly Rep. 2020;69(30):993-998.
207. Vaes AW, Machado FVC, Meys R, Delbressine JM, Goertz YMJ, Van Herck M, et al. Care dependency in non-hospitalized patients with COVID-19. J Clin Med. 2020;9(9):2946.
208. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall consensus statement for post COVID-19 rehabilitation. Br J Sports Med. 2020;54(16) 949-959.
209. Chartered Society of Physiotherapy. Rehabilitation of adults who are hospitalised due to COVID-19: physiotherapy service delivery. London: Chartered Society of Physiotherapy 2020.
210. Leochico CFD. Adoption of telerehabilitation in a developing country before and during the COVID-19 pandemic. Ann Phys Rehab Med. 2020;63(6) 563-564.

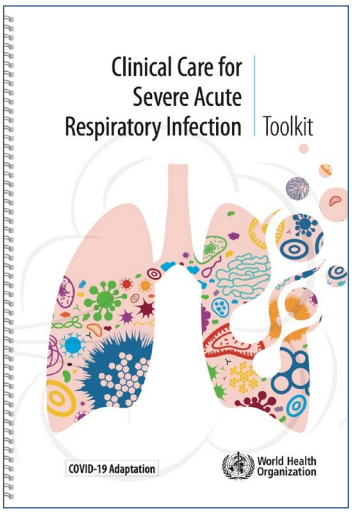
211. Hart JL, Turnbull AE, Oppenheim IM, Courtright KR. Family-centered care during the COVID-19 era. J Pain Symptom Manage. 2020;60(2):e93-e97.
212. Brodsky MB, Nollet JL, Spronk PE, Gonzalez-Fernandez M. Prevalence, pathophysiology, diagnostic modalities and treatment options for dysphagia in critically ill patients. Am J Phys Med Rehab. 2020;99(12):1164-1170.
213. Johnson JK, Lapin B, Free K, Stilphen M. Frequency of physical therapist intervention is associated with mobility status and disposition at hospital discharge for patients with COVID-19. Phys Ther. 2020; pzaa181.
214. Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society and American Thoracic Society-coordinated international task force. Eur Respir J. 2020;56(6):2002197.
215. Greenhalgh T, Javid B, Knight M, Inada-Kim M. What is the efficacy and safety of rapid exercise tests for exertion desaturation in covid-19. Oxford: Centre for Evidence-Based Medicine; 2020.
216. Metzl JD, McElheny K, Robinson JN, Scott DA, Sutton KM, Toresdahl BG. Considerations for return to exercise following mild-to-moderate COVID-19 in the recreational athlete. HSS J. 2020;16(Suppl 1):1-6.
217. Phelan D, Kim JH, Chung EH. A game plan for the resumption of sport and exercise after coronavirus disease 2019 (COVID-19) infection. JAMA Cardiology. 2020;5(10):1085-1086.
218. Hanquet G, Benahmed N, Castaneres-Zapatero D, Dauvrin M, Desomer A, Rondia K. COVID-19 KCE contributions. Post intensive care syndrome in the aftermath of COVID-19: appendices. KCE Belgian Health Care Knowledge Centre; 2020.
219. British Thoracic Society. Quality standards for pulmonary rehabilitation in adults. London: British Thoracic Society; 2014.
220. Royal Dutch Society for Physical Therapy (KNGF). KNGF position statement: recommendations for physiotherapy in patients with COVID-19, July 2020.
221. Lewis C, Roberts NP, Bethell A, Robertson L, Bisson JI. Internet-based cognitive and behavioural therapies for post-traumatic stress disorder (PTSD) in adults. Cochrane Database Systems Rev. 2018;12(12):CD11710.
222. Belsher BE, Beech E, Evatt D, Smolenski DJ, Shea MT, Otto JL, et al. Present-centered therapy (PCT) for post-traumatic stress disorder (PTSD) in adults. Cochrane Database Systems Rev. 2019;(11):CD012898.
223. WHO. Q&A on COVID-19 and pregnancy and childbirth. Geneva: World Health Organization; 2020.
224. WHO. WHO releases first guideline on digital health interventions. World Health Organization; 2020.
225. WHO. Safe abortion: technical and policy guidance for health systems (second edition). World Health Organization; 2012.
226. WHO. WHO Consolidated guideline on self-care interventions for health: sexual and reproductive health and rights. Geneva: World Health Organization; 2019.
227. WHO. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016.
228. WHO. WHO recommendations for induction of labour. Geneva: World Health Organization; 2011.
229. WHO. WHO recommendations: intrapartum care for a positive childbirth experience. Geneva: World Health Organization; 2018.
230. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809-815.
231. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020;9(1):51-60.
232. Buonsenso D, Costa S, Sanguinetti M, Cattani P, Posteraro B, Marchetti S, et al. Neonatal late onset infection with severe acute respiratory syndrome coronavirus 2. Am J Perinatol. 2020;37(8):869-872.
233. Cui Y, Tian M, Huang D, Wang X, Huang Y, Fan LI, et al. A 55-day-old female infant infected with 2019 novel coronavirus disease: presenting with pneumonia, liver injury, and heart damage. J Infect Dis. 2020;221(11):1775-1781.
234. Dong L, Tian J, He S, Zhu C, Wang J, Liu C, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020;323(18):1846-1848.
235. Fan C, Lei DI, Fang C, Li C, Wang M, Liu Y, et al. Perinatal transmission of COVID-19 associated SARS-CoV-2: should we worry? Clin Infect Dis. 2020;ciaa226.
236. Ferrazzi E, Frigerio L, Savasi V, Vergani P, Prefumo F, Barresi S, et al. Vaginal delivery in SARS-CoV-2-infected pregnant women in Northern Italy: a retrospective analysis. BJOG. 2020;127(9):1116-1121.
237. Seo G, Lee G, Kim MJ, Baek S-H, Choi M, Ku KB, et al. Rapid detection of COVID-19 causative virus (SARS-CoV-2) in human nasopharyngeal swab specimens using field-effect transistor-based biosensor. ACS nano. 2020;14(4):5135-5142.
238. Kam K-Q, Yung CF, Cui L, RTP Lin, Mak TM, Maiwald M, et al. A well infant with coronavirus disease 2019 with high viral load. Clin Infect Dis. 2020;71(15):847-849.
239. Li Y, Zhao R, Zheng S, Chen XU, Wang J, Sheng X, et al. Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China. Emerg Infect Dis. 2020;26(6):1335-1336.
240. Wang S, Guo L, Chen L, Liu W, Cao Y, Zhang J, et al. A case report of neonatal 2019 coronavirus disease in China. Clin Infect Dis. 2020;71(15):853-857.
241. WHO. WHO Essential newborn care and breastfeeding. Geneva: World Health Organization; 2002.

242. Laosa O, Pedraza L, Alvarez-Bustos A, Carnicero JA, Rodriguez-Artalejo F, Rodriguez-Mañas L. Rapid assessment at hospital admission of mortality risk from COVID-19: the role of functional status. J Am Med Dir Assoc. 2020;21(12):1798-1802.
243. Petermann-Rocha F, Hanlon P, Gray SR, Welsh P, Gill JMR, Foster H. Comparison of two different frailty measurements and risk of hospitalisation or death from COVID-19: findings from UK Biobank. BMC Med. 2020;18(1):355.
244. Chinnadurai R, Ogedengbe O, Agarwal P, Money-Coomes S, Abdurrahman AZ, Mohammed S, et al. Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting – a cohort study. BMC Geriatrics. 2020;20(1):409.
245. WHO. Preventing and managing COVID-19 across long-term care services: policy brief, 24 July 2020. Geneva: World Health Organization; 2020.
246. WHO. Integrated care for older people (ICOPE): guidance for person-centred assessment and pathways in primary care. Geneva: World Health Organization; 2019.
247. Wang H, Li T, Barbarino P, Gauthier S, Broadly H, Molinuevo JL, Xie H, et al. Dementia care during COVID-19. Lancet. 2020;395(10231):1190-1191.
248. Wang H. Delirium: a suggestive sign of COVID-19 in dementia. EClinicalMedicine. 2020;100524.
249. WHO. Mental health of older adults: key facts. Geneva: World Health Organization; 2017 (https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults, accessed 21 January 2021).
250. Albutt K, Luckhurst CM, Alba GA, Hechi ME, Mokhati A, Breen K, et al. Design and Impact of a COVID-19 multidisciplinary bundled procedure team. Ann Surg. 2020;272(2):e72-e73.
251. Galluccio F, Ergonenc T, Martos AG, El-Sayed Allam A, Pérez-Herrero M, Aguilar R, Emmi G et al. Treatment algorithm for COVID-19: a multidisciplinary point of view. Clin Rheumatol. 2020;39(7):2077-2084.
252. Meisner BA, Boscart V, Gaudrenau P, Stolee P, Ebert P, Heyer M. Interdisciplinary and collaborative approaches needed to determine Impact of COVID-19 on older adults and aging: CAG/ACG and CJA/RCV joint statement. Can J Age. 2020;39(3):333-343.
253. Wang H, Li T, Gauthier S, Yu E, Tang Y, Barbarino P, et al. Coronavirus epidemic and geriatric mental healthcare in China: how a coordinated response by professional organisations helped older adults during an unprecedented crisis. Int Psychogeriatr. 2020;32(10):1117-1120.
254. WHO. Disability considerations during the COVID-19 outbreak. Geneva: World Health Organization; 2020.
255. WHO. WHO Guide integrating palliative care and symptom relief into responses to humanitarian emergencies and crises. Geneva: World Health Organization; 2018.
256. Krakauer EL, Daubman BR, Aloudat T, Bhadelia N, Black L, Janjanin S, et al. Palliative care needs of people affected by natural hazards, political or ethnic conflict, epidemics of life-threatening infections, and other humanitarian crises. In: L Waldman E, Glass M, (eds). A field manual for palliative care in humanitarian crises. New York: Oxford University Press; 2019;4-13.
257. Mahler DA, Selecky PA, Harrod CG, Benditt JO, Carrieri-Kohlman V, Curtis JR, et al. American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. Chest. 2010;137(3):674-91.
258. Andrenelli E, Negrini F, De Sire A, Patrini M, Lazzarini SG, Ceravolo MG. Rehabilitation and COVID-19: a rapid living systematic review 2020 by Cochrane Rehabilitation Field. Update as of September 30th, 2020. Eur J Phys Rehab Med. 2020.
259. WHO. Ethics and COVID-19: resource allocation and priority setting. Geneva: World Health Organization; 2020.
260. WHO. Managing ethical issues in infectious disease outbreaks. Geneva: World Health Organization; 2016.
261. WHO. COVID-19: operational guidance for maintaining essential health services during an outbreak March 2020. Geneva: World Health Organization; 2020.
262. Pfefferbaum B, North CS. Mental health and the Covid-19 Pandemic. NEJM. 2020;383(6):510-512.
263. WHO. International guidelines for certification and classification (coding) of COVID-19 as cause of death. Based on ICD. International Statistical Classification of Diseases. Geneva: World Health Organization; 2020;
264. The COVID-NMA Initiative: a living mapping and living systematic review of Covid-19 trials. COVID-NMA Initiative (https://covid-nma.com, accessed 15 January 2021).
265. WHO. Global COVID-19: clinical platform. Geneva: World Health Organization; 2020.
266. ISARIC. Clinical characterisation protocol. International Severe Acute Respiratory and Emerging Infection Consortium; 2020.
267. WHO. “Solidarity” clinical trial for COVID-19 treatments. Geneva: World Health Organization; 2020.

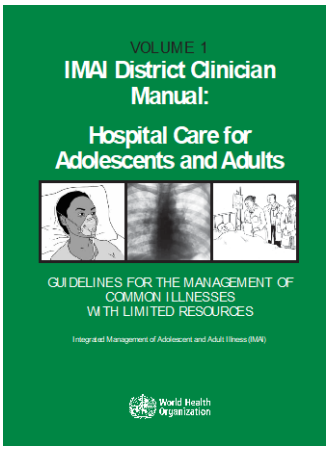
# Annex 1: COVID-19 care pathway



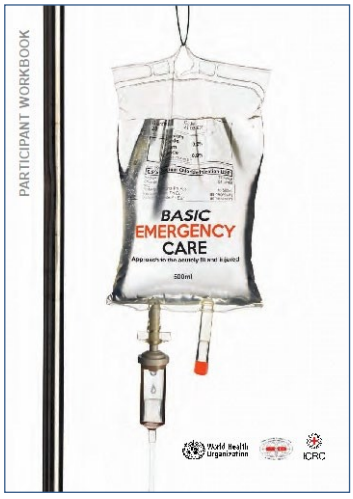
# Annex 2: Resources for supporting clinical management of COVID-19



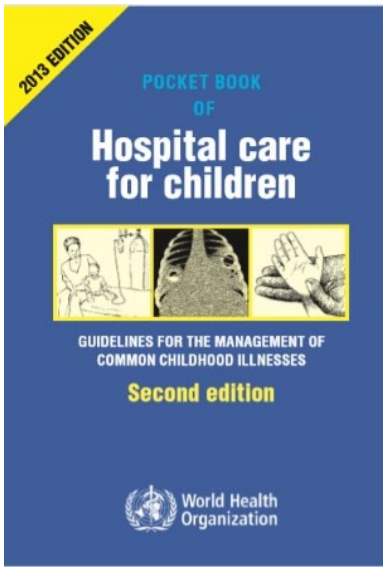

**Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (2020)**
This toolkit is intended for clinicians working in acute care hospitals in low- and middle-income countries, managing adult and paediatric patients with acute respiratory infection, including severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock. The main objective is to provide some of the necessary tools that can be used to care for the critically ill patient from hospital entry to hospital discharge.
https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit



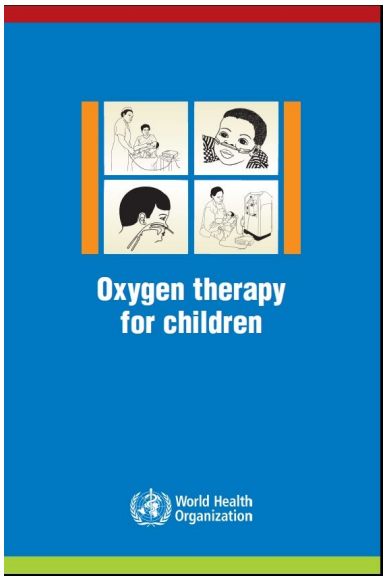

**IMAI District clinician manual: hospital care for adolescents and adults. Guidelines for the management of common illnesses with limited resources (2011)**
The manual is written for clinicians working at the district hospital (first-level referral care) who diagnose and manage sick adolescents and adults in resource-constrained settings. It aims to support clinical reasoning, and to provide an effective clinical approach and protocols for the management of common and serious or potentially life-threatening conditions at district hospitals. The target audience includes doctors, clinical officers, health officers and senior nurse practitioners. It has been designed to be applicable in both high and low HIV prevalence settings.
https://www.who.int/hiv/pub/imai/imai2011/en/



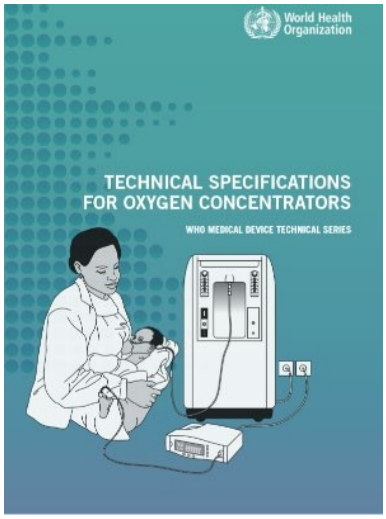

**WHO-ICRC Basic emergency care: approach to the acutely ill and injured (2018)**
Developed by WHO and ICRC, in collaboration with the International Federation for Emergency Medicine, *Basic emergency care (BEC): approach to the acutely ill and injured* is an open-access training course for frontline health care providers who manage acute illness and injury with limited resources. The BEC package includes a Participant Workbook and electronic slide decks for each module. Integrating the guidance from WHO Emergency Triage, Assessment and Treatment (ETAT) for children and the Integrated Management of Adult/Adolescent Illness (IMAI), BEC teaches a systematic approach to the initial assessment and management of time-sensitive conditions where early intervention saves lives.
https://www.who.int/publications/i/item/basic-emergency-care-approach-to-the-acutely-ill-and-injured



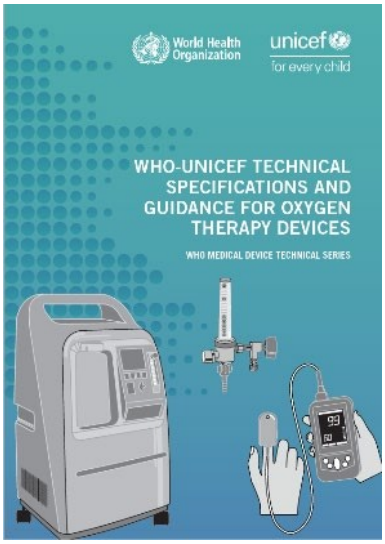

**Pocket book of hospital care for children: guidelines for the management of common childhood illnesses (second edition) (2013)**
For use by doctors, nurses, and other health workers caring for children at first-level referral hospitals with basic laboratory facilities and essential medicines. These guidelines focus on the management of the major causes of childhood mortality in most developing countries, including pneumonia, and also cover common procedures, patient monitoring, and supportive care on the wards.
https://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/




**Oxygen therapy for children (2016)**
A bedside manual for health workers to guide the provision of oxygen therapy for children. The manual focuses on the availability and clinical use of oxygen therapy in children in health facilities to guide health workers, biomedical engineers and administrators. It addresses detection of hypoxaemia, use of pulse oximetry, clinical use of oxygen, delivery systems, and monitoring of patients on oxygen therapy. The manual also addresses the practical use of pulse oximetry, and oxygen concentrators and cylinders.
http://www.who.int/maternal_child_adolescent/documents/child-oxygen-therapy/en/




**Technical specifications for oxygen concentrators (2015)** Provides an overview of oxygen concentrators and technical specifications to aid in selection, procurement, and quality assurance. It highlights the minimum performance requirements and technical characteristics for oxygen concentrators and related equipment that are suitable for the use in health facilities.
https://www.who.int/medical_devices/publications/tech_specs_oxygen-concentrators/en/




**WHO-UNICEF technical specifications and guidance for oxygen therapy devices (2019)**
The purpose of this document is to increase access to quality products to ensure the supply of oxygen, especially in low- and middle-income countries and low-resource settings within countries from all income groups. It aims to support ministries of health to ensure that oxygen supply is available, as well as to raise awareness of the importance of appropriate selection, procurement, maintenance, and use of medical devices, both capital equipment and single-use devices.
https://www.who.int/medical_devices/publications/tech_specs_oxygen_therapy_devices/en/