Clinical management of COVID-19

LIVING GUIDELINE
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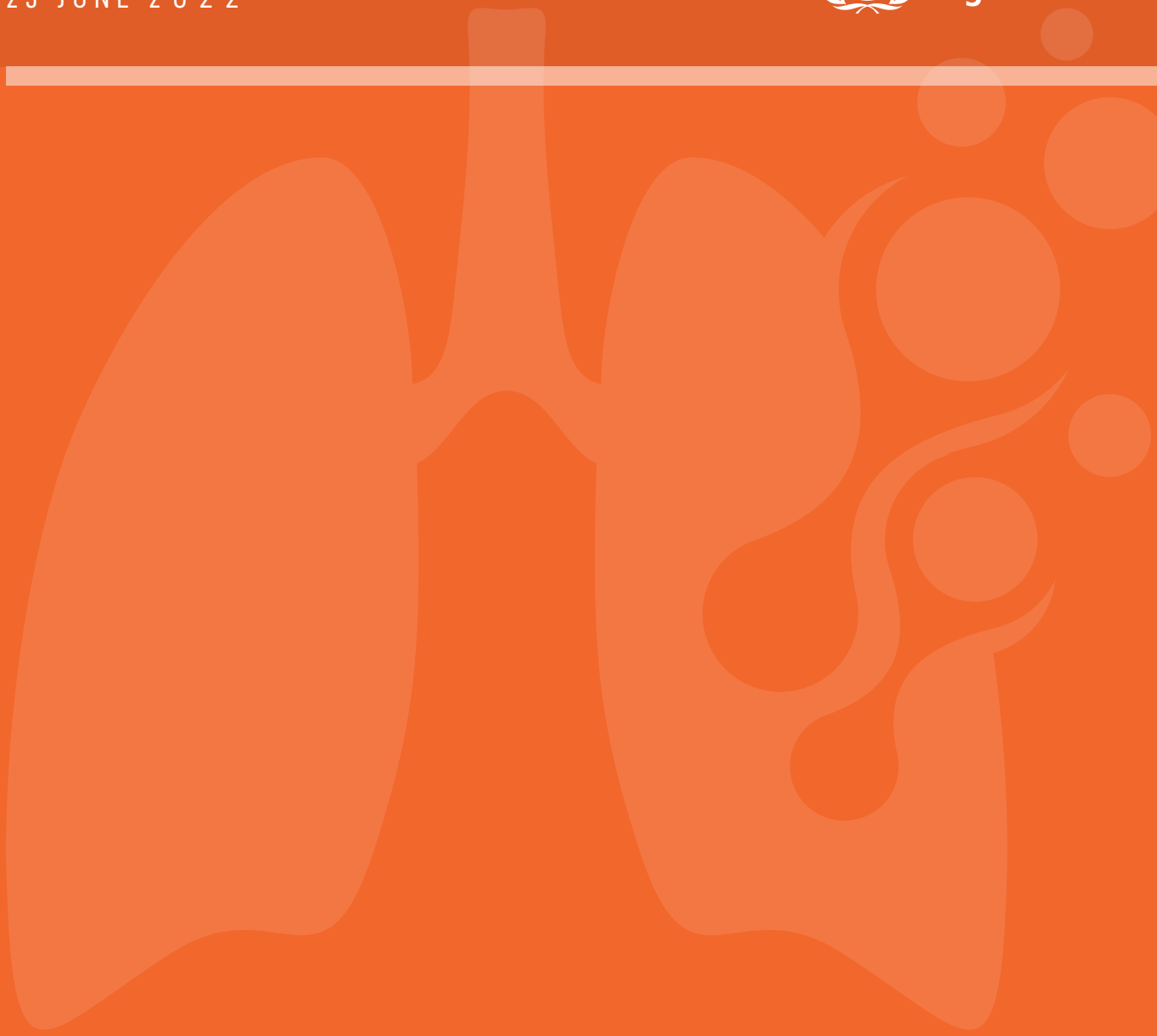
World Health Organization



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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.

Sections

Foreword

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) suppress 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 [1]* 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. This guideline 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.

This guideline is a product of the contributions of several WHO team members and independent experts from all over the world. The WHO is deeply grateful to each of the contributors for their time and expertise.

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 they are **screened for COVID-19 and becomes a suspect/confirmed 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 *[2]*.

Summary

Info Box

Clinical guideline: What are the interventions to manage patients with COVID-19?

Target audience: The target audience is anyone broadly involved directly or indirectly in the care of patients with COVID-19, i.e. clinicians, allied health care workers, and hospital administrators.

Current practice: The evidence base for clinical management of COVID-19 is increasing rapidly. Numerous randomized and observational trials are underway to inform practice. This version of *Clinical management of COVID-19: living guideline* includes three new recommendations.

New recommendations: In this update, the Guideline Development Group (GDG) makes three new recommendations:

- Conditional recommendation to use high-flow nasal oxygen (HFNO) rather than standard oxygen therapy for patients with severe and critical COVID-19 with acute hypoxaemic respiratory failure (AHRF) not requiring emergency intubation;
- Conditional recommendation to use continuous positive airway pressure (CPAP) rather than standard oxygen therapy for patients with severe and critical COVID-19 with AHRF not requiring emergent intubation;
- Conditional recommendation to use non-invasive ventilation rather than standard oxygen therapy for patients with severe and critical COVID-19 with AHRF not requiring emergent intubation.

Rationale for the new recommendations:

The recommendations were triggered by the availability of new evidence (five randomized controlled trials [RCTs] specific to COVID-19). Two systematic reviews/meta-analysis (one based on a direct PICO - COVID-19 patients and the other based on an indirect PICO of patients with acute respiratory distress syndrome (ARDS) and hypoxemic respiratory failure) provided the data for the development of these recommendations. The rationale for the broad recommendation around the use of these devices over standard oxygen therapy is explained in detail in the respective sections; key factors guiding these recommendations were the impact (benefit) of these devices on four prioritized critical outcomes: mortality, need for invasive mechanical ventilation, hospitalization, and ICU length of stay. The recommendations are conditional based on the quality and certainty of the evidence.

For sub-questions such as the choice of interface (helmet vs face mask etc.) or between-device comparisons, the GDG chose not to make a recommendation either due to the absence of direct data or the uncertainty.

How this guideline was created? A 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 or other contributors to the guideline development process. This living guideline represents an innovation from the World Health Organization (WHO), driven by the urgent need for global collaboration to provide trustworthy and evolving COVID-19 guidance informing policy and practice worldwide.

The latest evidence: The GDG's recommendations for non-invasive advanced respiratory support options for patients with severe and critical COVID-19 with AHRF not requiring emergent intubation were informed by the results of two systematic reviews, one evaluating the use of these interventions in patients with COVID-19 (direct PICO) and the other evaluating the use of these interventions in patients with non-COVID-19 ARDS (indirect PICO).

Understanding the recommendations:

When moving from evidence to recommendations, the GDG considered a combination of evidence assessing relative benefits and harms, values and preferences, equity and feasibility issues. For severe and critical COVID-19 patients with AHRF not requiring intubation, the GDG recognized that: HFNO may reduce mortality and need for invasive mechanical ventilation (IMV; direct PICO, low certainty); and probably decreases hospital length of stay (direct PICO, moderate certainty evidence) when compared with standard oxygen therapy (SOT); that CPAP may reduce mortality and length of stay (direct PICO, low certainty) and probably decreases the need for IMV (moderate certainty) when compared with SOT; and that non-invasive ventilation (NIV) probably reduces mortality and IMV (indirect PICO, moderate certainty) and may decrease hospital length of stay (indirect PICO, low certainty). The GDG emphasized that appropriate resources such as trained staff and infrastructure, as as oxygen supply, need to be in place for implementation.

Abbreviations

ADL	activities of daily living
AGP	aerosol-generating procedure
AHRF	acute hypoxaemic respiratory failure
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
EOS	end of study
FiO2	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
IMV	invasive mechanical ventilation
IPC	infection prevention and control
IQR	interquartile range
IVIG	intravenous immune globulin
LOS	length of stay
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

MIS-C	multisystem inflammatory syndrome in children
NAAT	nucleic acid amplification test
NCD	noncommunicable disease
NICU	neonatal intensive care unit
NIV	non-invasive ventilation
OI	Oxygenation Index
OSI	Oxygenation Index using SpO2
PaO2	partial pressure arterial oxygen
PBW	predicted body weight
PEEP	positive end-expiratory pressure
PICO	population, intervention, comparator, outcome
PICS	post-intensive care syndrome
PPE	personal protective equipment
PTSD	post-traumatic stress disorder
PUI	person/patient under investigation
QNS	quality assurance of norms and standards
RCT	randomized controlled trial
RDT	rapid diagnostic test
RM	recruitment manoeuvre
RT-PCR	reverse transcription polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus
SBP	systolic blood pressure
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SOT	standard oxygen therapy
SpO2	oxygen saturation
SR	systematic review
TB	tuberculosis
UNICEF	United Nations Children's Fund
URT	upper respiratory tract
VoC	variants of concern
VTE	venous thromboembolism
WHO	World Health Organization

1. Background

As of 8 June 2022, over 530 000 000 people worldwide have been diagnosed with COVID-19, with over 6.3 million deaths according to the WHO dashboard *[4]*. A new variant, Omicron, that emerged in late November 2021 is now the dominant strain across the world and has contributed to the ongoing surge in several countries *[5]*. Vaccination is having a substantial impact on case numbers and hospitalizations in a number of high-income countries, but limitations in global access to vaccines mean that many populations remain vulnerable *[6][7]*. Even in vaccinated individuals, uncertainties remain about duration of protection and efficacy of current vaccines against Omicron and other emerging SARS-CoV-2 variants. Taken together, there remains a need for more effective treatments for COVID-19. The COVID-19 pandemic – and the explosion of both research and misinformation – has highlighted the need for trustworthy, accessible and regularly updated living guidelines to place emerging findings into context and provide clear recommendations for clinical practice *[8]*.

Clinical characterization

Asymptomatic infection with SARS-CoV-2: The proportion of persons who become infected with SARS-CoV-2 and remain asymptomatic remains to be better understood. A meta-analysis from earlier in the pandemic reported an overall estimate of 31%, from seven studies with predefined screened populations, prediction interval ranging between 26–37% *[9]*. One systematic review of 79 studies found that 20% (17–25%) of people remained asymptomatic throughout the course of infection *[9]*. Another systematic review, which included 13 studies considered to be at low risk of bias, estimated that 17% of cases remain asymptomatic (14–20%) *[10]*. 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 *[11]*. In a recent systematic review and meta-analysis of 28 studies (n= 6071 COVID-19 cases) the proportion of asymptomatic infections ranges from 1.4% to 78.3% with a weighted pooled proportion of patients who remained asymptomatic throughout the infection episode of 25% (95% CI: 16–38%) and 28% to 31.4% using a leave-out-one result *[12]*. 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%) *[13]* 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 was done *[14]*.

Severity classification: In those patients that do become symptomatic, most people with COVID-19 develop only mild (40%) or moderate (40%) disease (see Table 6.3 for definitions), approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, ARDS, sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury *[15]*. One can expect that these proportions will be influenced by surveillance strategies, the use of therapeutics and other interventions, regional variance in demographics, vaccination, and evolving variants. See Table 6.2 for updated list of risk factors associated with severe disease or death.

Mental and neurologic manifestations: COVID-19 is associated with a spectrum of mental and neurological manifestations, including anxiety, depression, sleep problems, headache, dizziness, impaired sense of smell or taste *[16]*, myalgias, delirium/encephalopathy, agitation, stroke, hypoxic ischaemic brain injury, seizures, coma, meningo-encephalitis and Guillain-Barré syndrome *[17][18][19][20][21]*. People with pre-existing mental or neurological conditions, such as dementia, depression or psychosis have higher mortality and fare worse when acutely infected with SARS-CoV-2 *[22][23]*. Following the acute phase, people with post-COVID-19 condition also often suffer from cognitive dysfunction *[24]* and have lower general cognition compared with healthy controls up to 7 months post-infection *[25]*. 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 *[26]*. 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 *[27]*.

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 *[28]*. 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 *[29]*. Delirium, in particular, has been associated with increased mortality risk in the context of COVID-19 *[30]*. 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 of Great Britain and Northern Ireland, and the United States of America *[26][29][31][32][33]*. Case reports of Guillain-Barré syndrome and meningo-encephalitis among people with COVID-19 have also been reported *[34][35][36]*.

Clinical characterization in children: The clinical manifestations of COVID-19 are similar in children and adults, but generally milder with varying frequency of symptoms *[37]*. Although severe cases of COVID-19 in children, including fatal cases, have been reported, most children appear to have asymptomatic, mild, or moderate disease and recover within 1 to 2 weeks of disease onset *[38][39][40]*. The clinical findings overlap with those of multiple other clinical syndromes (e.g., pneumonia, bronchiolitis, gastroenteritis and common febrile illnesses with fever or chills and cough being the most common reported symptoms *[41][42]*. Relatively few cases of infants confirmed with COVID-19 have been reported; additional clinical findings include feeding difficulty and fever without an obvious source *[41][43]*.

As in adults, children with underlying medical conditions are at risk for severe disease, and chronic pulmonary disease (including asthma), obesity, neurologic and developmental conditions, cardiovascular disease and immunosuppression conditions are the most frequently reported risk factors *[44]*. Elevated inflammatory markers (e.g. CRP, procalcitonin, interleukin 6, ferritin, D-dimer) at admission or during hospitalization; dyspnoea, tachypnoea, and/or hypoxia at admission; and gastrointestinal symptoms at admission have been associated with severe disease in children *[45][46]*. In addition, a rare but serious multisystem inflammatory syndrome in children and adolescents (MIS-C). leading to multiorgan failure and shock has been reported *[47][48]*. Clinical features of MIS-C may be similar to those of Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome *[49]*. They include persistent fever, hypotension, gastrointestinal symptoms, rash, myocarditis, and laboratory findings associated with increased inflammation but respiratory symptoms may be lacking *[50][51]*.

Clinical characterization in pregnant women: The results of a living systematic review (as of 27 April 2021) show that pregnant and recently pregnant women with COVID-19 appear to be less likely to be symptomatic (0.66, 95% CI 0.52–0.86; 15 studies, 2 017 808 women), or manifest common symptoms such as fever, dyspnoea, cough and myalgia, compared with non-pregnant women of reproductive age *[52]*. 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 odds of requiring admission to an ICU (OR=2.61, 95% CI 1.84–3.71; 10 studies, 2 027 360 women), invasive ventilation (OR=2.41, 95% CI 2.13–2.71; 8 studies, 1 889 174 women). Older maternal age, high body mass index (BMI), non-white ethnicity, any pre-existing comorbidities, including chronic hypertension and diabetes, and pregnancy specific complications such as gestational diabetes and pre-eclampsia associated with serious complications (severe Covid-19, admission to intensive care unit, invasive ventilation and maternal death). 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.

Post COVID-19 condition: WHO released *A clinical case definition of post COVID-19 condition by a Delphi consensus [53]*, also known as “Long COVID-19." To harmonize coding, the Classification and Terminologies unit at the WHO created ICD-10 and ICD-11 codes for "post COVID-19 condition" *[54]*. Having a single name and definition for post COVID-19 condition is important as it allows physicians, patients, epidemiologists, ministers of health, policy-makers, and governments to be aligned in their understanding and informed to make policy decisions. It also allows researchers to aggregate data in a consistent and reliable manner and to conduct interventional studies using common enrolment criteria, case report forms, and core outcome sets.

Recognition and evidence regarding post COVID-19 condition is emerging. A recent meta-analysis of 10 cohort studies suggests the following factors may be associated with post COVID-19 condition: female gender, poor pre-pandemic mental health, poor general health, asthma, or being overweight or obese; and that non-white ethnic minority may be protective *[55]*. A cohort study found that neurological and psychological diagnosis were more common in those who had “severe” COVID-19, which was defined as being hospitalized, needing intensive care treatment, and having encephalopathy *[56]*. Three meta-analysis suggest the following symptoms to be more common: fatigue, dyspnea, cough, sleep disturbances, anxiety, depression, cognitive impairment, and difficulty concentrating *[57][58][59]*. Of these, fatigue and concentration problems were noted to last beyond 12 weeks *[60]*.

Variants of concern and severity of disease: At present, there are five variants of concern (VoC) recognized by WHO: Alpha, Beta, Gamma, Delta and Omicron (*Coronavirus disease - Answers*) *[61]*. VoCs seem to be more transmissible with Omicron currently outcompeting the other variants *[62][63][64][65][66][5][40][67]*. However, it is complex to determine whether a VoC causes more severe disease or higher mortality, as many other factors may also impact mortality. In a WHO-led analysis using data provided by country-level collaborators from South Africa *[68]*, Omicron was observed to cause less severe disease as well as have a lower risk of mortality. Similar reports of lower severity for Omicron have emerged from United States, United Kingdom, Denmark, Portugal and Canada. However, caution must be exercised in interpreting these reports due to the incomplete adjustment for the impact of confounding variables such as vaccination and prior infection. Additionally, in the WHO analysis, nearly a third of the hospitalized Omicron patients developed severe disease and 15% died, numbers which are not insignificant. Omicron with its enhanced transmissibility has and continues to overwhelm health care systems globally and international efforts to bring the pandemic to an end must continue with enhanced urgency. Among vulnerable populations, i.e. patients at the extremes of age, in populations with high comorbid burden, in frail patients and among the unvaccinated, COVID-19 (all VoCs) continues to contribute to substantial morbidity and mortality.

Guideline development and implementation

What triggered this version of the guideline?

The current version of the WHO living guideline addresses the use of advanced non-invasive respiratory support options for patients with severe and critical COVID-19 with acute hypoxaemic respiratory failure not requiring emergent intubation. It follows the availability of data from five RCTs *[69][70][71][72][73]*.

Who made this guideline?

For these new recommendations, the WHO selected additional Guideline Development Group (GDG) members with expertise on the subject matter. The GDG for this update was made up of 20 individuals, of whom 19 were content experts (clinicians, methodologists, scientists) and one was a patient partner. The methods chair (methodological expertise) and two clinical chairs (content expertise) guided the GDG discussions. See link here for short bios of GDG members.

WHO selected GDG members to ensure global geographical representation, gender balance, and appropriate technical and clinical expertise, thus not all of the standing GDG members participated in this current update. The technical unit collected and managed declarations of interests (DOIs) and found no GDG member to have a conflict of interest. In addition to distribution of a DOI form, during the meeting, the WHO Secretariat described the DOI process and an opportunity was given to GDG members to declare any interests not provided in written form. Web searches also did not identify any conflicts.

How to access and use this guideline?

This is a living guideline from WHO. The guideline is written, disseminated and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation *[74]*. It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline. Section 2 outlines key methodological aspects of the living guideline process.

The guideline is available via:

- WHO website in PDF format;
- MAGICapp in online, multilayered format.

The purpose of the online formats and additional tools, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making (clinical encounter decision aids) *[74]*.

Additional educational modules and implementation tools for health workers can be found via:

- WHO COVID-19 essential supplies forecasting tool (COVID-ESFT);
- WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation;
- WHO Openwho.org clinical management course series;
- WHO Academy;
- https://www.who.int/tools/covid-19-clinical-care-pathway.

2. Methods

Earlier versions (v1, v2) of this document were 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 2019, and were adapted from previously published *Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected: interim guidance [75]*.

For the **third version (v3)** of the COVID-19 clinical guideline the WHO Steering Committee expanded the scope from the previous versions to include recommendations on the full spectrum of disease (mild, moderate in addition to severe) and the full patient care pathway from screening to rehabilitation. A Guideline Development Group (GDG) comprising individuals with broad expertise spanning multiple specialties and all regions was convened. 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) for each recommendation. Instead, PICOs were drafted and published evidence was synthesized under the coordination of the Science Division in rapid systematic reviews. The WHO Steering Committee drafted the recommendations about interventions based on these reviews. These draft recommendations and evidence summaries were pre-circulated to the GDG. The GDG was convened over multiple meetings, and consensus was achieved for all recommendations. The direction and strength of recommendations were 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 the **fourth (v4), fifth (v5),** and **current versions (v6)** of the guideline, new recommendations were 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 [76]*.

Related guidelines
This living WHO guideline for the clinical management of COVID-19 is related to the *Living Guideline for therapeutics and COVID-19 [77]*, also published in the BMJ *[78]* and available in MAGICapp.

Timing
This guideline aims to be trustworthy and living; dynamically updated and globally disseminated once new evidence warrants a change in recommendations for COVID-19. The aim is to produce at least two updates per year, maintaining standards for trustworthy guidelines.

Stepwise approach
Here we outline the stepwise approach we take to improve efficiency and timeliness of the living, trustworthy guideline, 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 February 2021, the WHO Steering Committee triggered this guideline 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
WHO selected GDG members to ensure global geographical representation, gender balance, and appropriate technical and clinical expertise, and patient representatives. The technical unit collected and managed declarations of interests (DOIs) and found no GDG member to have a conflict of interest. In addition to the distribution of a DOI form, during the meeting, the WHO Secretariat described the DOI process and an opportunity was given to GDG members to declare any interests not provided in written form. No verbal

conflicts were declared. Web searches did not identify any additional interests that could be perceived to affect an individual's objectivity and independence during the development of the recommendations.

The pre-selected expert GDG (see Acknowledgements) convened on March 17 2022 to address advanced non-invasive respiratory support interventions i.e. HFNO, CPAP and NIV. The meeting involved a review of the basics of GRADE methodology including formulating population, intervention, comparator, outcome (PICO) questions and subgroups of interests, and prioritization of patient-important outcomes (see step 4 below). For the new GDG members, an additional preparatory session on methodological issues and orientation to the WHO guideline development process was conducted on 16 March 2022 ahead of the main GDG meeting. The GDG subsequently reviewed analyses, including pre-specified subgroup analyses presented in summary of findings tables, considered an individual patient perspective and feasibility issues specific to this intervention, and formulated recommendations.

Step 3: Evidence synthesis
The WHO Clinical Management Unit with support of the Quality Assurance of Norms and Standards (QNS) unit, commissioned an independent systematic review to examine the benefits and harms of the intervention. The systematic review team included librarian, methodologists, and clinicians and had experience in GRADE methodology and rating certainty of evidence (see Acknowledgements). The technical unit collected and managed declarations of interests (DOIs) and found no systematic review team members to have a conflict of interest.

Step 4: Development of recommendations
The GDG panel members are responsible for the following critical activities:

- To advise on the priority questions and scope of guideline;
- 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 *[79][80]*. 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 indirect 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 *[79][81]*;
- values and preferences of patients *[82]*;
- resources and other considerations (including considerations of feasibility, applicability, equity) *[82]*;
- 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 and Guideline Review Committees. The members of the External Review Group reviewed the final guideline document to identify any factual errors, and to comment on clarity of the language, contextual issues and implications for implementation. The technical unit collected and managed declarations of interests (DOIs) and found no External Review Group member to have a conflict of interest.

Benefits and harms

For these recommendations, the GDG members prioritized outcomes (rating from 9 [critical] to 1 [not important]) with severe and critical COVID-19, taking a patient perspective (Table 2.1).

Baseline risk estimates

The evidence summaries that informed the guideline recommendations report the anticipated absolute effects of non-invasive advanced respiratory support options compared with standard oxygen therapy across all patient-important outcomes. The absolute effects of treatment are informed by the prognosis (i.e., baseline risk estimates) combined with the relative estimates of effects (e.g., RR, OR) obtained from the meta-analysis.

Values and preferences

We had insufficient information to provide the GDG with an evidence-based description of patient experiences or values and preferences regarding treatment decisions. 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. Judgments on values and preferences were crucially informed through the experiences of former COVID-19 patients, represented in the GDG.

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

- Most patients would be reluctant to use a medication/intervention for which the evidence left high uncertainty regarding effects on outcomes they consider important. 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.

In addition to taking an individual patient perspective, the GDG also considered a population perspective in which feasibility, acceptability, equity and cost were important considerations.

Specific deliberations on values and preferences and associated feasibility and resource related considerations are presented for each recommendation.

For these new recommendations (see Section 11) , the majority of GDG members inferred that most well-informed patients, and their families, would, despite the low certainty of evidence, want to receive non-invasive advanced respiratory support options, as compared with standard oxygen therapy. In doing so, patients would be placing a high value on uncertain benefit and a low value on avoiding any mild adverse effects associated with treatment.

Selecting and rating the importance of outcomes

GDG members prioritized outcomes from the perspective of patients with severe/critical COVID-19.

Table 2.1 Panel outcome rating from a patient perspective for severe/critical COVID-19

Outcome	Mean	SD	Range
Death at 28 days	9	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
Serious adverse effects (e.g. adverse events 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	2-8
Diarrhea	4.3	1.5	2-8

SD: standard deviation.
Note: 7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance.

3. Who the recommendations apply to

The recommendations in the Clinical Management living guidelines are broadly applicable to anyone involved directly or indirectly in the care of patients with COVID-19 i.e. clinicians, allied health care workers, and hospital administrators.

Info Box

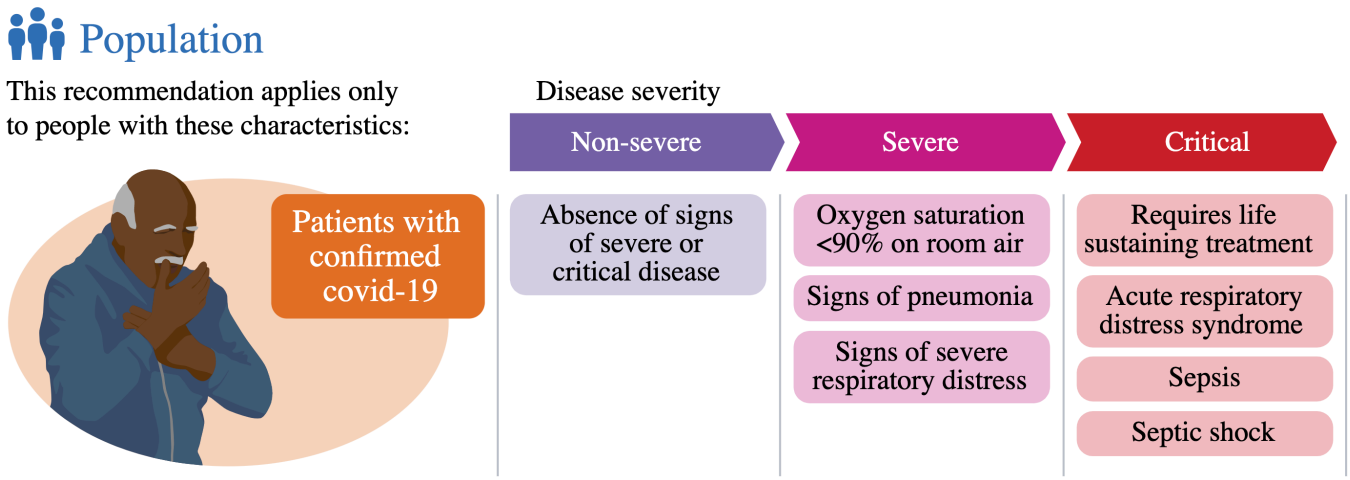
This guideline applies to all patients with COVID-19. Recommendations may differ based on the severity of COVID-19, according to WHO severity definitions (see below) *[6]*. These definitions avoid reliance on access to health care to define patient subgroups.

WHO definitions of disease severity for COVID-19

- **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;
  - severe pneumonia;
  - signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness).
- **Non-severe COVID-19** – Defined as the absence of any criteria for severe or critical COVID-19.

Caution: The GDG noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary, and should be interpreted cautiously when defining disease severity. 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, clinicians may interpret a saturation of 90–94% on room air as abnormal in the patient with normal lungs, and as an early sign of severe disease in patients with a downward clinical trajectory. Generally, in cases where there is doubt, the GDG suggested erring on the side of considering disease as severe.

The infographic illustrates these three disease severity groups and key characteristics to apply in practice.



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

4. 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 (molecular (NAAT/PCR) or antigen-detection test (i.e.Ag-RDT).*

See Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities, Interim guidance June 2021 [83].

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.

See Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed, Interim guidance July 2021 and Annex Oct 2021 [84].

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.*

***The COVID-19 Clinical Care pathway should include the CARE principles: Confirm, Assess, Respond and Evaluate** [85].*

- *Confirm SARS-CoV-2 infection: ensure prompt diagnosis using molecular (NAAT(PCR) or antigen-detection test (i.e.Ag-RDT).*
- *Assess: symptoms, risk factors and severity: provide early clinical assessment and evaluation to determine if the patient has symptoms, emergency signs or risk factors that may warrant treatment, clinical referral or admission to hospital care.*
- *Respond with appropriate care and treatment: treatment selection is determined by severity of disease and risk factors.*
- *Evaluate clinical response and recovery: all patients receiving COVID-19 treatment require clinical monitoring and follow up by a health care professional throughout their illness and recovery, including those who develop post COVID-19 condition.*

UNDER REVEW

This section is under review and will be updated in the next iteration of the guidelines.

In review

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 [86].*

5. Immediate implementation of appropriate infection prevention and control measures

This guidance brings together infection prevention and control (IPC) technical guidance developed and published since the beginning of the COVID-19 pandemic. **IPC guidelines are currently under review and an updated version will be released soon.**

For additional information please see the following links:

1. *Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed [87].*
2. *Infection prevention and control in the context of coronavirus disease (COVID-19): A living guideline* (in MAGICapp).

IPC measures for patients with suspected or confirmed COVID-19:
Health facilities should adhere to key WHO recommended IPC measures, in particular, adhering to respiratory etiquette and hand hygiene best practices, contact, droplet and airborne precautions, adequate environmental cleaning and disinfection; ensuring adequate ventilation; isolation facilities of COVID-19 patients; in addition, where possible, maintaining a physical distance among all individuals in health facilities of at least 1 metre (increasing it whenever feasible), especially in indoor settings.

Apply standard precautions for all patients

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 [70]. Standard precautions also include appropriate patient placement; environmental cleaning; prevention of needle-stick or sharps injury and safe waste management.

Carefully practice hand hygiene frequently using an alcohol-based hand rub (ABHR). Wash hands if visibly dirty with soap and water and disposable towels. Perform hand hygiene, before PPE use and after PPE removal, and when indicated while providing care, according to the WHO Five Moments for hand hygiene [73].

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.

Screen 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 immediate isolation/separation.

Suspected or confirmed COVID-19 patient to wear a medical mask and placement in 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 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 pediatric patients and caregivers and ask them to wear a mask.

Adequate ventilation rates within defined spaces in health facilities are generally addressed by national regulations. Environmental and engineering controls play a key role in reducing the concentration of infectious respiratory aerosols in the air and the contamination of surfaces and inanimate objects.

Isolate and cohort patients with suspected or confirmed COVID-19

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).

Apply transmission-based precautions

In addition to standard precautions, apply transmission-based precautions (contact, droplet and/or airborne precautions) where indicated. Use contact and droplet precautions before entering a room where there is a patient with suspected or confirmed COVID-19. In settings where aerosol-generating procedures (AGP) are performed among patients with suspected or confirmed COVID-19, perform procedures in an adequately ventilated room and use appropriate PPE (N95 respirator, FFP2 or equivalent).

Mask use in health care facilities

WHO recommends using face protection as part of a comprehensive package of IPC measures to limit the spread of SARS-CoV-2. National policies and health facilities must continue to achieve and maintain IPC measures, including having an IPC programme or, at minimum, a dedicated and trained IPC focal point in place. Other necessary measures include engineering, environmental and administrative controls, standard and transmission-based precautions, screening and triage for early identification of cases and COVID-19 surveillance and vaccination of health workers. For full recommendation on mask use in health care facilities, see *Infection prevention and control in the context of coronavirus disease (COVID-19): A living guideline* (in MAGICapp).

Strong recommendation for

Universal and targeted continuous masking

In areas of known or suspected community or cluster SARS-CoV-2 transmission, universal masking is recommended (very low certainty evidence) in health care facilities:

In settings where caring for non-COVID-19 patients, unless differently specified (e.g. AGP), all health workers, including community health workers and caregivers, other staff, visitors, outpatients and service providers, should wear a well-fitting medical mask at all times within the health facility and in any common area (e.g. cafeteria, staff rooms).

Inpatients are not required to wear a medical mask unless physical distancing of at least 1 metre cannot be maintained (e.g. during examinations or bedside visits) or when outside of their care area (e.g. when being transported), provided the patient is able to tolerate the mask and there are no contraindications.

For full recommendations and additional details, see: *Infection prevention and control in the context of coronavirus disease (COVID-19): A living guideline* (in MAGICapp).

Conditional recommendation for

In areas of known or suspected sporadic SARS-CoV-2 transmission, targeted continuous medical mask use is recommended (very low certainty evidence) in health care facilities:

In settings when caring for non-COVID-19 patients, health workers, including community health workers and caregivers who work in clinical areas, should continuously wear a well-fitting medical mask during routine activities throughout the entire shift, unless differently specified (e.g. when performing AGP) and apart from when eating and drinking.

In non-patient areas, staff are not required to wear a medical mask during routine activities if they have no patient contact.

For full recommendations and additional details, see: *Infection prevention and control in the context of coronavirus disease (COVID-19): A living guideline* (in MAGICapp).

Conditional recommendation for

A respirator or a medical mask should be worn (very low certainty evidence) by health workers along with other PPE (gown, gloves and eye protection) before entering a room where there is a patient with suspected or confirmed COVID-19.

For full recommendations and additional details, see: *Infection prevention and control in the context of coronavirus disease (COVID-19): A living guideline* (in MAGICapp).

Remarks:

Respirators should be worn in the following situations:

- *In care settings where ventilation is known to be poor* or cannot be assessed, or the ventilation system is not properly maintained*
- *Based on health workers' values and preferences and on their perception of what offers the highest protection possible to prevent SARS-CoV-2 infection.*

Strong recommendation for

A respirator should always be worn (very low certainty evidence) along with other PPE* by health workers performing AGP and by health workers on duty in settings where AGP are regularly performed on patients with suspected or confirmed COVID-19, such as intensive care units, semi-intensive care units or emergency departments.

*PPE includes gown, gloves, eye protection.

For full recommendations and additional details, see: *Infection prevention and control in the context of coronavirus disease (COVID-19): A living guideline* (in MAGICapp).

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 [1].*

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 [90][91][92]. 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 [93][94][95][96][97], 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) [91]. 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) [98].

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 *[99]*.

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** *[100][101]*.
- **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 [93].
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 [102] (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 [103].
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) [104][105].
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.

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).

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.

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 *[106]*, 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 judgement, 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 popula ions

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.

Info Box

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 *[102][107][108][109]*. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported *[16][110][111]*.

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 *[17][18]*.

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 *[90][91][92]*.

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 *[112]*.

Children might not have reported fever or cough as frequently as adults *[113]*.

Info Box

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.
- In pregnant or recently pregnant: women > 35 years old, obesity, with chronic medical conditions or pregnancy specific disorders (e.g. gestational diabetes and pre-eclampsia/eclampsia).
- Smoking.
- Unvaccinated against COVID-19.
- HIV.

Info Box

Table 6.3 COVID-19 disease severity classification

Mild disease		Symptomatic patients (Table 6.1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. See the WHO website for most up-to-date case definitions [2].
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. **Child** with cough or difficulty breathing + fast breathing and/or chest indrawing and no signs of severe pneumonia. Fast breathing: < 2 months: ≥ 60 breaths/min; 2–11 months: ≥ 50; 1–5 years: ≥ 40. The diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications. **Caution:** The oxygen saturation threshold of 90% to define severe COVID-19 is 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 between 90–94% on room air may be abnormal (in patient with normal lungs) and can be an early sign of severe disease, mainly 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) plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or SpO_2 < 90% on room air. **Child:** with clinical signs of pneumonia (cough or difficulty breathing + fast breathing or chest wall indrawing) + at least one of the following: • SpO_2 < 90% • Very severe chest indrawing, grunting, central cyanosis, or presence of any other general danger sign (inability to breastfeed or drink, lethargy or unconsciousness or convulsions). 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)** [107][108][109]	**Onset:** within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. **Chest imaging:** radiograph,CT scan or lung ultrasound: bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factors present. Oxygenation impairment in adults: **Air blood gases (ABG) available** • Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH_2O)

		• Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH_2O) • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH_2O). **ABG not available (Kigali modification)** • SpO2/FiO2 < 315 suggests ARDS (including non-ventilated patients) Oxygen impairment in children: note OI and OSI.[a] Use OI when available. If PaO_2 not available, wean FiO_2 to maintain SpO2 ≤ 97% to calculate OSI or SpO2/FiO2 ratio: • Bilevel (NIV or CPAP) ≥ 5 cmH2O via full face mask: PaO2/FiO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥12.3. a 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), 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.
	Sepsis [110][111]	**Adults:** acute life-threatening organ dysfunction caused by a dysregulated host response to suspect or proven infection. Signs of organ dysfunction include: altered mental status (delirium), difficult or fast breathing, low oxygen saturation, reduced urinary output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinaemia. **Children:** suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria,[b] of which one must be abnormal temperature or white blood cell count. b 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.
	Septic shock [110][111]	**Adults:** persistent hypotension despite volume resuscitation, requiring vasopressor to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. **Children:** any hypotension (SBP < 5th centile or 2SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 beats/min [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.
	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 (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 shock syndrome AND evidence 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*.)

Note: If altitude is higher than 1000 m, then the correction factor should be calculated as follows: PaO_2/FiO_2 x barometric pressure/760.

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. Laboratory diagnosis

This guidance brings together diagnostic technical guidance developed and published since the beginning of the COVID-19 pandemic.

1. *Antigen-detection in the diagnosis of SARS-CoV-2 infection [119].*
2. *Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing [120]*; and
3. *Diagnostic testing for SARS-CoV-2 interim guidance* regarding specimen collection, processing and laboratory testing and the diagnostic algorithm *[121].*

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 *[122]*. 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 *[121]*. 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 (also refer to Section 5 on IPC) for the most up-to-date guidance [123][124].
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 [101]. 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 [121]. 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 [86].
4. NAAT testing is the reference method for the diagnosis of COVID-19. However, antigen testing can be used to diagnose current COVID-19 infection, especially in situations, where NAAT is unavailable or where prolonged turnaround times preclude clinical utility. . For details on appropriate utilization of antigen testing see interim guidance Antigen-detection in the diagnosis of SARS-CoV-2 infection [125]. 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 within an overall national testing programme. Ag-RDTs can also be used by individuals to test themselves, termed COVID-19 self testing. When used by someone who is a suspected case of COVID-19, a positive self-test result is consistent with current COVID-19 but a negative self-test result does not rule out infection. For more details. see interim guidance Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing [120].
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 NAAT results.

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 [126]. 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 [127]. In endemic settings, arbovirus infection (dengue/ chikungunya) should also be considered in the differential diagnosis of undifferentiated febrile illness, particularly when thrombocytopenia is present [95]. 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 [128]. 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 [93]. 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) [129]. 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 *[117].*

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

COVID-19 Self-testing

Strong recommendation for

COVID-19 self-testing, using SARS-CoV-2 Ag-RDTs, should be offered in addition to professionally administered testing services (low to moderate certainty evidence)

For full recommendations and additional details, see: *Use of SARS-CoV-2 antigen-detection rapid diagnostic tests for COVID-19 self-testing [120].*

Remarks:

Human rights: COVID-19 self-testing is a personal choice. It can expand access to testing by providing an additional way for people to test and make personal risk-based decisions that may affect their health and the health of their families and communities (e.g. to protect those most affected by or who may be at increased risk of severe COVID-19, or to enable individual participation in activities). COVID-19 self-testing, as with any testing, should always be voluntary and never mandatory or coercive. The practice of self-testing, regardless of test results, must always be free from stigma and discrimination. Self-testers will need to be provided with adequate information on when to test and nationally relevant post-test responsibilities and actions. Anyone uncertain of their COVID-19 self-testing result, or desiring alternative professional testing services, should be encouraged to access other testing options where available and in line with the latest national guidance. Countries should consider reviewing and contextualizing their existing policies on the age of consent to include COVID-19 self-testing and the role of assisted and caregiver-led self-testing by a parent or guardian. For adolescents and mature minors, age-of-consent policies that enable access without parental consent are important to enable COVID-19 self-testing when needed.

Epidemiology: The implications of a test result are not only a function of its inherent sensitivity and specificity. The result is also dependent on the prevalence of SARS-CoV-2 infection in the population prioritized for testing. When using COVID-19 self-testing in settings with higher pre-test probability, i.e. higher likelihood of an individual having SARS-CoV-2 infection, such as in places where there is ongoing community transmission or when an individual is at high likelihood of exposure (e.g. contacts, health and care workers), the positive predictive value of the test is high. This means a positive self-testing result is likely to be a true positive. When COVID-19 self-testing is used in a low pre-test probability setting (e.g. when testing someone without symptoms and no known exposure to the virus or when there is no or low community transmission), the positive predictive value of self-testing is lower, which will lead to increased false-positive results. In these situations, the negative predictive value of COVID-19 self-testing is high, meaning the risk of a false negative is lower.

Evolving context, priorities and messaging: Health worker and community awareness of and engagement in adapting COVID-19 self-testing is important for successful implementation. As local epidemiology changes, information on self-testing that is context-specific, correct, clear, concise and age-appropriate should be made available. Messaging should include when self-testing should be prioritized or deprioritized for specific populations or settings, the meaning of a positive or negative self-test result and any recommended follow-up actions after self testing. Messages will vary based on current local situations but should be consistent with national policies.

Emerging SARS-CoV-2 variants: This recommendation is valid for detection of all reported SARS-CoV-2 variants of concern. As SARS-CoV-2 continues to evolve, policies will need to take into consideration circulating variants and test performance. The accuracy of COVID-19 self-testing needs to be continually assessed and reviewed with the emergence and spread of new variants, just as it is for professional-use NAAT and Ag-RDT.

8. 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.

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 [94][95][97] 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 [130].

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 [131].

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 [132].

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 [133][134][135][136].

9. 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.

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 [95][94][127], 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).

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.

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 7.2 for information on definitions of who would be considered high-risk for this implementation.

Clinical Question/ PICO

Population: Patients treated at home with confirmed or suspected COVID-19 disease
Intervention: SpO2 < 92% (Pulse oximetry use at home)
Comparator: SpO2 ≥ 92% (Pulse oximetry use at home)

Outcome Timeframe	**Study results and measurements**	**Comparator** SpO2 ≥ 92% (Pulse oximetry use at home)	**Intervention** SpO2 < 92% (Pulse oximetry use at home)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospitalization	Relative risk 7 (CI 95% 3.4 — 14.5) Based on data from 77 participants in 1 studies. (Observational (non-randomized))	103 per 1000 Difference:	840 per 1000 **737 more per 1000** (CI 95% 453 more — 1,597 more)	**Very low** Due to serious risk of bias, Due to serious imprecision [1]	SpO2 <92% possibly increases need for hospitalization
ICU admission	Relative risk 9.8 (CI 95% 2.2 — 44.6) Based on data from 77 participants in 1 studies. (Observational (non-randomized))			**Very low** Due to serious risk of bias, Due to serious imprecision [2]	SpO2 <92% possibly increases need for ICU admission
ARDS	Relative risk 8.2 (CI 95% 1.7 — 38.7) Based on data from 77 participants in 1 studies. (Observational (non-randomized))			**Very low** Due to serious risk of bias, Due to serious imprecision [3]	SpO2 <92% possibly increases the risk of ARDS
Septic shock	Relative risk 6.6 (CI 95% 1.3 — 32.9) Based on data from 77 participants in 1 studies. (Observational (non-randomized))			**Very low** Due to serious risk of bias, Due to serious imprecision [4]	SpO2 <92% possibly increases the risk of septic shock
Hospitalization	Based on data from participants in 2 studies. (Observational (non-randomized))	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 SpO2 monitors required hospitalization.		**Very low** Due to serious risk of bias, Due to serious imprecision [5]	No data re whether home SpO2 monitoring vs no monitoring affects hospitalization rates

1. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
2. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
3. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
4. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**
5. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no 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. Evidence from a living rapid review and meta-analysis of bacterial co-infection in patients who were assessed for bacterial infection presenting with COVID-19 to hospital indicates that 4.4% of patients (95%CI 3.0-6.4%; n=125 212) had coinfection identified at hospital admission [136].
2. The same review showed that 8.2% of the patients (95%CI 6.3-10.7%; n=30805) developed secondary bacterial infections while in the hospital while 41.9% (95%CI 29.5-55.4; n=8377) of the patients admitted to ICU developed secondary infections. Hence, estimates suggest that the likelihood of bacterial coinfection in patients with COVID-19 on presentation to hospital is low and empiric antibiotic therapy should not be given as standard of care at hospital admission, unless bacterial infections is strongly suspected, and COVID-19 diagnosis is not confirmed.

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 [137].

10. Management of severe COVID-19: severe pneumonia treatment

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% [100][138].*
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 [101].*
4. *In adults, techniques such as positioning, e.g. high supported sitting, may help to optimize oxygenation, ease breathlessness and reduce energy expenditure [139].*
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 [139].*

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 ≥ 94% [100][138][140].*
2. *Once patient is stable, the target is > 90% SpO_2 [140].*
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 [137].*
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.*

UNDER REVIEW

This recommendation is currently under review and will be updated in the next iteration of the guidelines.

Conditional recommendation for

In review

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).

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.

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.

Clinical Question/ PICO

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Usual care	**Intervention** Awake prone positioning + usual care	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality	Based on data from 334 participants in 17 studies. (Observational (non-randomized))	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 [1]	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 participants in 25 studies. (Observational (non-randomized))	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 [2]	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 participants in 6 studies. (Observational (non-randomized))	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 [3]	There are no comparative data assessing the effect of awake proning in COVID-19 patients with regards to adverse events.

1. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
2. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
3. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no 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 [141]. This applies to both children and adults.*

11. 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 *[117]*.

Assessment and recognition

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 [117].

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 [142].

Advanced non-invasive respiratory support

Info Box

What are advanced non-invasive respiratory support devices?

Broadly, these are devices that can provide respiratory support through their ability to provide higher oxygen flows or positive pressure or a combination of both. They are referred to as non-invasive as they do not involve the placement of a tube (e.g, endotracheal tube or tracheostomy tube) in the patient's airway (referred to as invasive approach).

There are three broad categories of devices that are referred to in our guidelines: high-flow nasal oxygen (HFNO); continuous positive airway pressure (CPAP); and non-invasive ventilation (NIV), also referred to as bilevel positive airway pressure (BiPAP). HFNO provides respiratory support predominantly through higher flows whereas CPAP and NIV provide support through a combination of higher flows and higher pressure.

Summary of recommendations (see sections below for additional details and in-depth explanation)

- In hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure (AHRF) not needing emergent intubation, we suggest high-flow nasal oxygen (HFNO) rather than standard oxygen therapy (SOT) (conditional recommendation).
- In hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure (AHRF) not needing emergent intubation, we suggest continuous positive airway pressure (CPAP) rather than standard oxygen therapy (SOT) (conditional recommendation).
- In hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure (AHRF) not needing emergent intubation, we suggest non-invasive ventilation (NIV) rather than standard oxygen therapy (SOT) (conditional recommendation).

The GDG chose not to make a recommendation regarding HFNO versus CPAP vs NIV due to the uncertainty of the data. Clinicians should therefore choose between the these devices on the basis of considerations such as availability of devices and the supply of oxygen, their personal comfort and experience, and patient-specific considerations (such as claustrophobia that some patients experience with CPAP masks, and nasal discomfort that some patients experience with HFNO).

Conditional recommendation for

New

In hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure (AHRF) not needing emergent intubation, we suggest high-flow nasal oxygen (HFNO) rather than standard oxygen therapy (SOT) (conditional recommendation).

The GDG chose not to make a recommendation regarding high-flow nasal oxygen (HFNO) versus continuous positive airway pressure (CPAP) due to uncertainty of the data. Clinicians should therefore choose between the two on the basis of considerations such as availability of devices and the supply of oxygen, their personal comfort and experience, and patient-specific considerations (such as claustrophobia that some patients experience with CPAP masks, and nasal discomfort that some patients experience with HFNO).

The GDG elected to extend this recommendation to the paediatric age range (despite the absence of data), given the likely similar direction of benefit, but emphasized the need for more research in this population.

Practical Info

There is no specific recommendation for the initial flow rate, FiO_2, or titration scheme. Based on clinical experience of the panel, initial flow rates of between 50 and 60 L/min and initial FiO_2 of 100% are suggested, titrated to patient SpO_2 and work of breathing. In children, a fixed rate of 2 L/min/kg of body weight is suggested.

For infection prevention precautions related to the use of these respiratory support devices, please refer to Section 5 on IPC. See also research needs.

Resources:

1. https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit
2. https://openwho.org/courses/clinical-management-COVID-19-general-considerations
3. https://www.who.int/health-topics/oxygen#tab=tab_1

Evidence To Decision

Benefits and harms

High-flow nasal oxygen, in comparison to standard oxygen therapy, may reduce mortality and need for invasive ventilation (direct PICO, low certainty evidence), probably reduces hospital length-of-stay and ICU length of stay (direct PICO, moderate certainty evidence) in patients with severe or critical COVID-19 experiencing AHRF but not requiring emergent intubation. Based on overall clinical experience with the device and its use among critically ill patients, the GDG was of the opinion that benefits are likely to supersede any potential harms.

Certainty of the Evidence

Comparisons with SOT:

Among trials in patients with AHRF and COVID-19, for the outcomes of mortality and need for invasive mechanical ventilation there is low certainty in the evidence, due to very serious imprecision. For the outcome of hospital length of stay and ICU length-of-stay, there is moderate certainty in the evidence, due to serious imprecision.

Trials in non-COVID-19 ARDS provided low certainty evidence that high-flow nasal oxygen had little or no difference on mortality, compared with standard oxygen therapy, due to very serious imprecision. These trials also, however, also provided moderate certainty evidence of a decrease in the need for invasive mechanical ventilation and hospital length of stay. Effect on ICU length of stay was uncertain.

Comparisons between devices or interfaces:

Trials in patients with COVID-19 and AHRF provided very low certainty evidence for the comparison between HFNO and helmet NIV for outcomes of mortality, hospital length of stay, ICU length of stay due to extremely serious imprecision; whereas there is low certainty evidence for outcome of need for invasive ventilation due to very serious imprecision, and low certainty evidence for the outcome of device-related comfort due to serious risk of bias and serious imprecision.

One trial in patients with COVID-19 and AHRF for the comparison of HFNO and CPAP provided very low certainty evidence for the outcome of mortality due to extremely serious imprecision. For the outcomes of need for invasive mechanical ventilation, hospital and ICU length of stay, the certainty of the evidence is low due to very serious imprecision.

Trials in non-COVID-19 ARDS provided very low certainty evidence for the comparison of HFNO and face mask NIV on the outcomes of mortality and need for invasive mechanical ventilation due to a combination of serious indirectness, serious risk of bias and very serious or serious imprecision. For the outcome of ICU length of stay, the certainty of evidence is low due to very serious imprecision.

Values and preferences

Applying the agreed upon values and preferences, the GDG inferred that most well-informed patients with AHRF not requiring emergent intubation would choose to receive HFNO rather than standardoxygen therapy.

Resources and other considerations

Studies of HFNO, CPAP, and NIV were conducted in high-resource settings with ICUs, health care workers experienced in these interventions, and resources for patient monitoring and rescue in case of clinical deterioration. The GDG emphasized that implementation of any non-invasive respiratory support intervention requires consideration of the local context of oxygen supply, training of health care providers, additional equipment for patient monitoring, considerations around maintenance of equipment, cost, and organization of service delivery. Availability of these additional resources has traditionally been restricted to areas within hospitals that provide intensive care. The GDG believed that the availability of these additional resources should be expanded to facilitate safe delivery of non-invasive respiratory support interventions globally.

A specific consideration for HFNO is that these devices may require a higher oxygen flow compared with other non-invasive respiratory support devices. Appropriate calculations of oxygen needs should be made at the facility level when expanding clinical use of HFNO and other non-invasive respiratory devices.

Justification

When moving from evidence to the conditional recommendation for patients hospitalized for COVID-19 with AHRF and not requiring emergent intubation, the panel emphasized the low certainty of evidence from direct comparisons in patients with COVID-19 for the important outcomes of mortality and need for invasive mechanical ventilation. The GDG incorporated the indirect evidence from patients without COVID-19 and AHRF, which had moderate certainty evidence for reducing invasive mechanical ventilation and hospital length-of-stay.

The GDG integrated the available evidence on the risk to health care workers due to infection transmission with the use of high-flow nasal oxygen. There is currently insufficient evidence to inform recommendations for the outcome of health care worker transmission.

Choosing between devices:

The GDG chose not to make recommendations among non-invasive respiratory support devices because of the very low or low certainty of evidence and variable contextual factors of oxygen supply, staff training, and patient monitoring that would weigh more heavily in utilization decisions, compared with evidence of clinical effectiveness.

Research Needs

Further research is needed about:

- Between-device comparisons such as between HFNO and CPAP;
- The impact of varying levels of positive pressure provided by these devices on evolving lung injury in patients with ARDS;
- The risks of aerosol generation and risk of transmission to HCWs based on choice of respiratory support device;
- Staffing requirements and skills in deploying these devices in resource-limited settings as well as on cost and oxygen requirements from the use of these devices;
- Specific populations such as children and pregnant women.

Clinical Question/ PICO

Population:	Hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation
Intervention:	HFNO
Comparator:	SOT

Summary

Evidence Summary

The meta-analysis for the comparison of HFNO vs SOT was informed by 4 RCTs *[69][71][72][73]* which enrolled a total of 1053 participants* (direct PICO, i.e. COVID-19 patients with AHRF), and by 5 RCTs which enrolled a total of 1425 participants* (indirect PICO, i.e. non-COVID-19 ARDS patients) *[3]*. All the RCTs for the direct PICO were published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or results sections of the trial *[3]*.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of HFNO compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** SOT	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 9 Critical	Relative risk 0.87 (CI 95% 0.66 — 1.13) Based on data from 1,006 participants in 3 studies. (Randomized controlled)	188 per 1000 Difference:	164 per 1000 **24 fewer per 1000** (CI 95% 64 fewer — 24 more)	**Low** Due to very serious imprecision [1]	HFNO may decrease mortality
IMV 9 Critical	Relative risk 0.89 (CI 95% 0.77 — 1.03) Based on data from 1,053 participants in 3 studies. (Randomized controlled)	417 per 1000 Difference:	371 per 1000 **46 fewer per 1000** (CI 95% 96 fewer — 13 more)	**Low** Due to very serious imprecision [2]	HFNO may decrease IMV
Hospital LOS 9 Critical	Lower better Based on data from 1,003 participants in 3 studies. (Randomized controlled)	16.28 days (Mean) Difference:	14.92 days (Mean) **MD 1.08 fewer** (CI 95% 2.48 fewer — 0.35 more)	**Moderate** Due to serious imprecision [3]	HFNO probably decreases hospital LOS
ICU LOS 6 Important	Lower better Based on data from 1,003 participants in 3 studies. (Randomized controlled)	5.83 days (Mean) Difference:	4.65 days (Mean) **MD 0.77 fewer** (CI 95% 1.45 fewer — 0.08 fewer)	**Moderate** Due to serious imprecision [4]	HFNO probably has little or no difference on ICU LOS

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence interval that includes important benefit and harm. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence interval that includes important benefit and harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval that includes benefit and harm. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious. Publication bias: no serious.**

Clinical Question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: HFNO
Comparator: SOT

Summary

The meta-analysis for the comparison of HFNO vs SOT was informed by 4 RCTs *[69][71][72][73]*, which enrolled a total

of 1053 participants* (direct PICO, i.e. COVID-19 patients with AHRF) and by 5 RCTs which enrolled a total of 1425 participants* (indirect PICO, i.e. non-COVID ARDS patients) *[3]*. All the RCTs for the direct PICO were published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or in the results sections *[3]*.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of HFNO compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** SOT	**Intervention** HFNO	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality [1] 9 Critical	Relative risk 0.98 (CI 95% 0.83 — 1.15) Based on data from 1,344 participants in 4 studies. (Randomized controlled)	**291** per 1000 Difference:	**285** per 1000 **6 fewer per 1000** (CI 95% 49 fewer — 44 more)	**Low** Due to very serious imprecision [2]	HFNO may have little or no difference on mortality
IMV 9 Critical	Relative risk 0.74 (CI 95% 0.56 — 0.99) Based on data from 668 participants in 4 studies. (Randomized controlled)	**207** per 1000 Difference:	**153** per 1000 **54 fewer per 1000** (CI 95% 91 fewer — 2 fewer)	**Moderate** Due to serious imprecision [3]	HFNO probably decreases IMV
Hospital LOS 9 Critical	Lower better Based on data from 998 participants in 2 studies. (Randomized controlled)	**16.26** days (Median) Difference:	**14.46** days (Median) **MD 1.17 fewer** (CI 95% 3.16 fewer — 0.83 more)	**Moderate** Due to serious imprecision [4]	HFNO probably decreases hospital LOS
ICU LOS 6 Important	Based on data from 996 participants in 2 studies. (Randomized controlled)			**Very low** Due to extremely serious inconsistency [5]	We are very uncertain of the impact of HFNO on ICU LOS

1. Longest duration mortality data available, includes mix of hospital and end of study (EOS) outcomes
2. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was moderate, with I^2: 44%. **Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals that include important benefit and harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Number of patients does not meet the optimal information size. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval. **Publication bias: no serious.**
5. **Inconsistency: extremely serious.** The magnitude of statistical heterogeneity was high, with I^2: 85%, the direction of the

(effect is not consistent between the included studies. One RCT suggested large benefit while one RCT suggested large harm rated down by three). **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

Conditional recommendation for

New

In hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation, we suggest CPAP, rather than standard oxygen therapy (conditional recommendation).

The GDG chose not to make a recommendation regarding optimal interface for CPAP, whether helmet or face mask, given the lack of direct data available for the comparison. The choice between interface should be guided by clinician experience, availability, and patient comfort.

The GDG chose not to make a recommendation regarding HFNO versus CPAP due to the uncertainty of the data. Clinicians should choose between the three on the basis of considerations such as availability of devices and the local supply of oxygen, their personal comfort and experience with the relevant devices, and patient-specific considerations (such as claustrophobia that some patients experience with CPAP/NIV masks, and nasal discomfort that some patients experience with HFNO).

Given the likely similar direction of benefit, the GDG chose to extend this recommendation to the paediatric age range (despite the absence of data), while emphasizing the need for more research in this population.

Practical Info

There is no specific recommendation as to the initial pressure to be used for CPAP, leaving to local clinical decision-making and patient-specific factors. Based on clinical experience of the GDG, there is a suggestion to start with a pressure of 5–10 cm H_2O, titrated to patient comfort and work of breathing, with FiO_2 titrated to achieve the target oxygen saturation when using facemask or oral-nasal mask. For use of helmet interfaces, additional information can be found in recent publications *[296]*.

For infection prevention precautions related to the use of these respiratory support devices, please refer to Section 5 on IPC. See also Research needs.

Resources:

1. https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit
2. https://openwho.org/courses/clinical-management-COVID-19-general-considerations
3. https://www.who.int/health-topics/oxygen#tab=tab_1

Evidence To Decision

Benefits and harms

In patients with severe or critical COVID-19 and AHRF not requiring emergent intubation, CPAP, in comparison with standard oxygen therapy, may decrease mortality (direct PICO, low certainty evidence), probably decreases the need for invasive mechanical ventilation (direct PICO, moderate certainty evidence), may decrease hospital length-of-stay (direct PICO, low certainty evidence), and may have little or no impact on ICU length-of-stay (direct PICO, low certainty evidence). Based on overall clinical experience with the device and its use among critically ill patients, the GDG was of the opinion that benefits are likely to supersede any potential harms.

Certainty of the Evidence

Comparisons with SOT:

In the direct population of patients with severe or critical COVID-19 experiencing acute hypoxaemic respiratory failure but not requiring emergent intubation, for the outcome of mortality, there is low-certainty evidence due to very serious imprecision. For the outcome of need for invasive mechanical ventilation, there is moderate certainty evidence due to serious imprecision. For the outcomes of ICU and hospital length-of-stay, there is low certainty evidence, due to very serious imprecision.

In the indirect population of patients with non-COVID-19 ARDS, there were studies evaluating both helmet CPAP and face mask CPAP, compared with standard oxygen therapy, largely with very low certainty evidence due to extremely serious imprecision.

Comparison between devices or interfaces:

One trial in patients with COVID-19 and AHRF for the comparison of CPAP and HFNO provided very low certainty evidence for the outcome of mortality due to extremely serious imprecision. For the outcomes of need for invasive mechanical ventilation, hospital and ICU length of stay, the certainty of the evidence is low due to very serious imprecision.

Values and preferences

Applying the agreed upon values and preferences, the GDG inferred that most well-informed patients with AHRF not requiring emergent intubation would choose to receive CPAP rather than standard oxygen therapy.

Resources and other considerations

Studies of HFNO, CPAP, and NIV were conducted in high-resource settings with ICUs, health care workers experienced in these interventions, and resources for patient monitoring and rescue in case of clinical deterioration. The GDG emphasized that implementation of any non-invasive respiratory support intervention requires consideration of the local context of oxygen supply, training of health care providers, additional equipment for patient monitoring, considerations around maintenance of equipment, cost, and organization of service delivery. Availability of these additional resources has traditionally been restricted to areas within hospitals that provide intensive care. The GDG believed that the availability of these additional resources should be expanded to facilitate safe delivery of non-invasive respiratory support interventions globally.

Justification

When moving from evidence to the conditional recommendation for patients hospitalized for COVID-19 with acute hypoxaemic respiratory failure not requiring emergent intubation, the panel noted the low certainty of evidence for the important outcomes of mortality, but the moderate certainty for reduction in the need for invasive mechanical ventilation. The panel incorporated indirect evidence from patients without COVID-19, but acknowledged the largely very low certainty in that evidence.

Choosing between devices:

For the direct comparison of CPAP with high-flow nasal oxygen, the GDG noted the very low certainty evidence for the important outcome of mortality. The low certainty in the available evidence that CPAP, when compared with high-flow nasal oxygen, decreases the requirement for invasive mechanical ventilation also influenced the decision-making, and the panel felt that more evidence was required to make a recommendation for this comparison.

The panel integrated the available evidence on the risk to health care workers due to infection transmission with the use of CPAP. There is currently insufficient evidence to inform recommendations for the outcome of health care worker transmission.

Research Needs

Further research is needed about:

- The optimal choice of interface while delivering CPAP (helmet vs face mask, etc);
- Between-device comparisons such as between HFNO and CPAP;
- The impact of varying levels of positive pressure provided by these devices on evolving lung injury in patients with ARDS;
- The risks of aerosol generation and risk of transmission to health care workers based on choice of respiratory support device;
- Staffing requirements and skills in deploying these devices in resource-limited settings as well as on cost and oxygen requirements from the use of these devices;
- Specific populations such as children and pregnant women.

Clinical Question/ PICO

Population: Hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation
Intervention: CPAP
Comparator: SOT

Summary

The meta-analysis for the comparison of CPAP vs SOT was informed by the results of one trial which enrolled 742 participants* (direct PICO, i.e. COVID-19 patients with AHRF) *[73]*, by 3 RCTs which enrolled a total of 168 patients* (Helmet CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *[3]* and by one additional trial that enrolled 123 patients* (face mask CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *[3]*. The trial that informed the direct PICO was published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or results sections of the trial *[3]*.

For patien with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of CPAP compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Note: for RECOVERY-RS (direct PICO- COVID-19 patients with AHRF), the denominator number of patients varied by outcome.

Outcome Timeframe	**Study results and measurements**	**Comparator** SOT	**Intervention** CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 9 Critical	Relative risk 0.87 (CI 95% 0.64 — 1.18) Based on data from 737 participants in 1 studies. (Randomized controlled)	**192** per 1000 Difference:	**167** per 1000 **25 fewer per 1000** (CI 95% 69 fewer — 35 more)	**Low** Due to very serious imprecision [1]	CPAP may decrease mortality
IMV 9 Critical	Relative risk 0.81 (CI 95% 0.67 — 0.98) Based on data from 733 participants in 1 studies. (Randomized controlled)	**413** per 1000 Difference:	**335** per 1000 **78 fewer per 1000** (CI 95% 136 fewer — 8 fewer)	**Moderate** Due to serious imprecision [2]	CPAP probably decreases IMV
Hospital LOS 9 Critical	Lower better Based on data from 737 participants in 1 studies. (Randomized controlled)	**17.3** days (Mean) Difference:	**16.4** days (Mean) **MD 0.96 fewer** (CI 95% 3.59 fewer — 1.67 more)	**Low** Due to very serious imprecision [3]	CPAP may decrease hospital LOS
ICU LOS 6 Important	Lower better Based on data from 737 participants in 1 studies. (Randomized controlled)	**9.6** days (Mean)	**9.5** days (Mean)	**Low** Due to very serious imprecision [4]	CPAP may have little or no difference on ICU LOS

Outcome Timeframe	**Study results and measurements**	**Comparator** SOT	**Intervention** CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Difference:	**MD 0.08 fewer** (CI 95% 2.23 fewer — 2.07 more)		

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes important benefit and harm. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Data from one study, number of patients does not meet the optimal information size. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes important benefit and harm. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes benefit and harm. **Publication bias: no serious.**

Clinical Question/ PICO

Population: Hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation
Intervention: CPAP
Comparator: HFNO

Summary

One RCT enrolled a total of 1273 participants into SOT, HFNO and CPAP arms *[73]*, but did not directly compare CPAP with HFNO and so the meta-analysis for the comparison of CPAP vs HFNO was informed by an indirect comparison of 793 participants (direct PICO, i.e. COVID-19 patients with AHRF). The RCT for the direct PICO is published and did not include children or pregnant women.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of CPAP vs HFNO for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality [1] 9 Critical	Relative risk 0.95 (CI 95% 0.52 — 1.71) Based on data from 793 participants in 1 studies. (Randomized controlled)	188 per 1000 Difference:	179 per 1000 **9 fewer per 1000** (CI 95% 90 fewer — 133 more)	**Very low** Due to extremely serious imprecision [2]	We are very uncertain of the impact of CPAP on mortality
IMV 9 Critical	Relative risk 0.69 (CI 95% 0.43 — 1.09) Based on data from 791 participants in 1 studies. (Randomized controlled)	411 per 1000 Difference:	284 per 1000 **127 fewer per 1000** (CI 95% 234 fewer — 37 more)	**Low** Due to very serious imprecision [3]	CPAP may decrease IMV

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Hospital LOS	Lower better Based on data from 791 participants in 1 studies. (Randomized controlled)	18.3 days (Mean) Difference:	16.4 days (Mean) **MD 1.67 fewer** (CI 95% 5.43 fewer — 2.09 more)	**Low** Due to very serious imprecision [4]	CPAP may decrease hospital LOS
ICU LOS 6 Important	Lower better Based on data from 791 participants in 1 studies. (Randomized controlled)	10.5 days (Mean) Difference:	9.5 days (Mean) **MD 1.02 fewer** (CI 95% 3.97 fewer — 1.93 more)	**Low** Due to very serious imprecision [5]	CPAP may decrease ICU LOS

1. For this outcome, mortality is at 30d
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, Wide confidence interval that includes important large benefit and harm (rated down by three). **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes moderate benefit and harm. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence intervals that include important benefit and harm.
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, Wide confidence interval that includes important benefit and harm, . **Publication bias: no serious.**

Clinical Question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Helmet CPAP
Comparator: SOT

Summary

The meta-analysis for the comparison of CPAP vs SOT was informed by the results of one trial which enrolled 742 participants* (direct PICO, i.e. COVID-19 patients with AHRF) *[73]*, by 3 RCTs which enrolled a total of 168 patients* (helmet CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *[3]* and by one additional trial that enrolled 123 patients* (face mask CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *[3]*. The trial that informed the direct PICO was published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or results sections of the trial *[3]*.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of CPAP compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Note: for RECOVERY-RS (direct PICO- COVID-19 patients with AHRF), the denominator number of patients varied by outcome.

Outcome Timeframe	Study results and measurements	Comparator SOT	Intervention Helmet CPAP	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 9 Critical	Relative risk 0.23 (CI 95% 0.1 — 0.55) Based on data from 168 participants in 3 studies. (Randomized controlled)	250 per 1000 Difference:	58 per 1000 **192 fewer per 1000** (CI 95% 225 fewer — 112 fewer)	Very low Due to serious indirectness and very serious imprecision [1]	We are very uncertain of the impact of helmet CPAP on mortality
IMV 9 Critical	Relative risk 0.45 (CI 95% 0.15 — 1.34) Based on data from 168 participants in 3 studies. (Randomized controlled)	102 per 1000 Difference:	46 per 1000 **56 fewer per 1000** (CI 95% 87 fewer — 35 more)	Very low Due to serious indirectness and very serious imprecision [2]	We are very uncertain of the impact of helmet CPAP on IMV
Hospital LOS 9 Critical	Lower better Based on data from 81 participants in 1 studies. (Randomized controlled)	14 days (Median) Difference:	14.5 days (Median) **MD 0.5 more** (CI 95% 3.75 fewer — 4.75 more)	Low Due to very serious imprecision [3]	Helmet CPAP may have little or no difference on hospital LOS
ICU LOS 6 Important					No studies were found that looked at ICU LOS

1. **Risk of Bias: no serious.** One trial stopped earlier than scheduled, potential for overestimating benefits. **Inconsistency: no serious. Indirectness: serious.** One of three RCTs was in patients with hematologic malignancies. **Imprecision: very serious.** Number of patients is far less than would be required to meet the optimal information size (<25%). **Publication bias: no serious.**
2. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was high, with I^2: 64%. **Indirectness: serious.** One of three RCTs in patients with hematologic malignancies. **Imprecision: very serious.** Wide confidence interval that includes important benefit and harm. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, wide confidence interval that includes important benefits and harms. **Publication bias: no serious.**

Clinical Question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Face mask CPAP
Comparator: SOT

Summary

The meta-analysis for the comparison of CPAP vs SOT was informed by the results of one trial which enrolled 742

participants* (direct PICO, i.e. COVID-19 patients with AHRF) *[73]*, by 3 RCTs which enrolled a total of 168 patients* (helmet CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *[3]* and by one additional trial that enrolled 123 patients* (face mask CPAP vs SOT; indirect PICO, i.e. non-COVID patients with ARDS) *[3]*. The trial that informed the direct PICO was published. None of the trials evaluating the direct PICO included pregnant women or children. For the trials evaluating the indirect PICO, pregnant women and children were either excluded or there was no specific mention of their inclusion in methods or results sections of the trial *[3]*.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of CPAP compared with SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Note: for RECOVERY-RS (direct PICO- COVID-19 patients with AHRF), the denominator number of patients varied by outcome.

Outcome Timeframe	**Study results and measurements**	**Comparator** SOT	**Intervention** Face mask CPAP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 9 Critical	Relative risk 0.71 (CI 95% 0.38 — 1.32) Based on data from 123 participants in 1 studies. (Randomized controlled)	295 per 1000 Difference:	209 per 1000 **86 fewer per 1000** (CI 95% 183 fewer — 94 more)	Very low Due to extremely serious imprecision [1]	We are very uncertain of the impact of face mask CPAP on mortality
IMV 9 Critical	Relative risk 0.86 (CI 95% 0.54 — 1.37) Based on data from 123 participants in 1 studies. (Randomized controlled)	393 per 1000 Difference:	338 per 1000 **55 fewer per 1000** (CI 95% 181 fewer — 145 more)	Very low Due to extremely serious imprecision [2]	We are very uncertain of the impact of face mask CPAP on IMV
Hospital LOS 9 Critical	Lower better Based on data from 81 participants in 1 studies. (Randomized controlled)	16 days (Median) Difference:	14 days (Median) **MD 2 fewer** (CI 95% 17.5 fewer — 13.5 more)	Very low Due to extremely serious imprecision [3]	We are very uncertain of the impact of face mask CPAP on hospital LOS
ICU LOS 6 Important	Lower better Based on data from 81 participants in 1 studies. (Randomized controlled)	9 days (Median) Difference:	9 days (Median) **MD 0 fewer** (CI 95% 8.89 fewer — 8.89 more)	Very low Due to extremely serious imprecision [4]	We are very uncertain of the impact of face mask CPAP on ICU LOS

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence intervals that include important large benefit and harm (rated down by three). **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence intervals that include important large benefit and harm (rated down by three). **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide

confidence intervals that include important large benefit and harm (rated down by three). **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence intervals that include important large benefit and harm (rated down by three levels). **Publication bias: no serious.**

Conditional recommendation for

New

In hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation, we suggest non-invasive ventilation, rather than standard oxygen therapy (conditional recommendation).

The GDG chose not to make a recommendation regarding optimal interface for NIV, whether helmet or face mask, given the limited data. The choice between interface should be guided by clinician experience, availability, and patient comfort.

The GDG chose not to make a recommendation regarding HFNO versus CPAP versus NIV due to the uncertainty of the data. Clinicians should choose on the basis of considerations such as availability of devices and the supply of oxygen, their personal comfort and experience, and patient-specific considerations (such as claustrophobia that some patients experience with CPAP/NIV masks, and nasal discomfort that some patients experience with HFNO).

Given the likely similar direction of benefit, the GDG elected to extend this recommendation to the paediatric age range (despite the absence of randomized trial data), while emphasizing the need for more research in this population.

Practical Info

There is no specific recommendation for the initial settings to be used for non-invasive ventilation, with local experience and patient-specific factors informing decisions and manufacturer instructions. Based on clinical experience of the GDG, there is a suggestion to start with an expiratory positive airway pressure of 5–10 cmH_2O, an inspiratory positive airway pressure to achieve a tidal volume of ~6 ml/kg, titration of both settings to patient comfort and work of breathing, and titration of FiO_2 to achieve the target oxygen saturation when using facemask or oral-nasal mask. For use of helmet interfaces, additional information can be found in recent publications *[70]*.

For infection prevention precautions related to the use of these respiratory support devices, please refer to Section 5 on IPC. See also Research needs.

Resources:

1. https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit
2. https://openwho.org/courses/clinical-management-COVID-19-general-considerations
3. https://www.who.int/health-topics/oxygen#tab=tab_1

Evidence To Decision

Benefits and harms

In patients with non-COVID-19 ARDS, face mask NIV probably reduces mortality (indirect PICO, moderate certainty) and need for invasive mechanical ventilation when compared to standard oxygen therapy. Based on overall clinical experience with the device and its use among critically ill patients, the GDG was of the opinion that benefits are likely to supersede any potential harms.

Certainty of the Evidence

Comparisons with SOT:

No trials enrolling patients with COVID-19 are available. In the indirect population of hospitalized patients with ARDS not due to COVID-19 and not needing emergent intubation, moderate certainty evidence (due to serious indirectness) suggests

that face mask NIV probably reduces mortality compared with SOT, and moderate-certainty evidence (due to serious inconsistency) suggests that NIV probably reduces the need for invasive mechanical ventilation. Very low-certainty evidence (due to serious inconsistency, serious imprecision, and serious indirectness) suggests impact of NIV on hospital and ICU length of stay is uncertain

Comparisons between devices or interfaces:

Trials in patients with COVID-19 and AHRF provided very low certainty evidence for the comparison between helmet NIV and HFNO for outcomes of mortality, hospital length of stay, ICU length of stay due to extremely serious imprecision; whereas there is low certainty evidence for outcome of need for invasive ventilation due to very serious imprecision, and low certainty evidence for the outcome of device-related comfort due to serious risk of bias and serious imprecision.

Trials in patients with non-COVID-19 ARDS provided very low certainty evidence for the comparison between face mask NIV and HFNO for the outcomes of mortality and need for invasive ventilation due to serious indirectness, serious risk of bias and serious and very serious imprecision. For the outcome of ICU length of stay, the certainty of evidence is low due to very serious imprecision.

Trials in patients with non-COVID-19 ARDS provided low certainty evidence for the comparison between helmet NIV and face mask NIV for the outcomes of mortality, need for invasive mechanical ventilation and hospital length of stay due to very serious imprecision.

Values and preferences

Applying the agreed upon values and preferences, the GDG inferred that most well-informed patients with AHRF not requiring emergent intubation would choose to receive NIV rather than standard oxygen therapy.

Resources and other considerations

Studies of HFNO, CPAP, and NIV were conducted in high-resource settings with ICUs, health care workers experienced in these interventions, and resources for patient monitoring and rescue in case of clinical deterioration. The GDG emphasized that implementation of any non-invasive respiratory support intervention requires consideration of the local context of oxygen supply, training of health care providers, additional equipment for patient monitoring, considerations around maintenance of equipment, cost, and organization of service delivery. Availability of these additional resources has traditionally been restricted to areas within hospitals that provide intensive care. The GDG believed that the availability of these additional resources should be expanded to facilitate safe delivery of non-invasive respiratory support interventions globally.

Justification

When moving from evidence to the conditional recommendation for patients hospitalized for COVID-19 with acute hypoxaemic respiratory failure and not requiring emergent intubation, the panel emphasized the moderate certainty of evidence from indirect comparisons in patients without COVID-19 for the important outcomes of mortality and need for invasive mechanical ventilation.

The GDG integrated the available evidence on the risk to health care workers due to infection transmission with the use of non-invasive ventilation. There is currently insufficient evidence to inform recommendations for the outcome of health care worker transmission.

The GDG chose not to make recommendations among non-invasive respiratory support devices because of the very low or low certainty of evidence and variable contextual factors of oxygen supply, staff training, and patient monitoring that would weigh more heavily in utilization decisions, compared with evidence of clinical effectiveness.

Research Needs

Further research is needed about:

- The optimal choice of interface while delivering CPAP (helmet vs face mask, etc);

- Between-device comparisons such as between HFNO and CPAP;
- The impact of varying levels of positive pressure provided by these devices on evolving lung injury in patients with ARDS;
- The risks of aerosol generation and risk of transmission to health care workers based on choice of respiratory support device;
- Staffing requirements and skills in deploying these devices in resource-limited settings as well as on cost and oxygen requirements from the use of these devices;
- Specific populations such as children and pregnant women.

Clinical Question/ PICO

Population: Hospitalized patients with severe or critical COVID-19 and AHRF not needing emergent intubation
Intervention: Helmet NIV
Comparator: HFNO

Summary

The meta-analysis for the comparison for Helmet NIV vs HFNO was informed by the results of one trial which enrolled 110 patients (direct PICO, i.e. COVID-19 patients with AHRF) *[70]*. The trial was published and did not include children or pregnant women.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of Helmet NIV vs HFNO for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Helmet NIV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality [1] At 60 days 9 Critical	Relative risk 1.1 (CI 95% 0.55 — 2.2) Based on data from 110 participants in 1 studies. (Randomized controlled)	236 per 1000 Difference:	260 per 1000 **24 more per 1000** (CI 95% 106 fewer — 283 more)	**Very low** Due to extremely serious imprecision [2]	We are very uncertain of the impact of helmet NIV on mortality
IMV 9 Critical	Relative risk 0.54 (CI 95% 0.32 — 0.89) Based on data from 110 participants in 1 studies. (Randomized controlled)	509 per 1000 Difference:	275 per 1000 **234 fewer per 1000** (CI 95% 346 fewer — 56 fewer)	**Low** Due to very serious imprecision [3]	Helmet NIV may decrease IMV
Hospital LOS 9 Critical	Lower better Based on data from 110 participants in 1 studies. (Randomized controlled)	22 days (Median) Difference:	21 days (Median) **MD 1 fewer** (CI 95% 9.2 fewer — 7.2 more)	**Very low** Due to extremely serious imprecision [4]	We are very uncertain of the impact of helmet NIV on hospital LOS
ICU LOS 6 Important	Lower better Based on data from 110 participants in 1 studies.	10 days (Median)	9 days (Median)	**Very low** Due to extremely serious imprecision [5]	We are very uncertain of the impact of helmet NIV on ICU LOS

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Helmet NIV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	(Randomized controlled)	Difference:	**MD 1 fewer** (CI 95% 6.2 fewer — 7.3 more)		
Device-related discomfort 6 Important	Lower better Based on data from 110 participants in 1 studies. (Randomized controlled)	**1.8** VAS points (Mean) Difference:	**3.7** VAS points (Mean) **MD 1.9 higher** (CI 95% 1.4 higher — 2.5 higher)	**Low** Due to serious risk of bias and serious imprecision [6]	Helmet NIV may increase device-related discomfort

1. For this outcome, mortality is at 60d
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence intervals that include important large benefit and harm (rated down by three). **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Data from one study, large and implausible effect, number of patients does not meet the optimal information size. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence interval that includes important large benefit and harm (rated down by three). **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Data from one study, wide confidence interval that includes important large benefit and harm (rated down by three). **Publication bias: no serious.**
6. **Risk of Bias: serious.** Post hoc outcome assessment, multiple time points collected but not reported. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Data from one study, number of patients is far less than would be required to meet the optimal information size (<20%). **Publication bias: no serious.**

Clinical Question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Facemask NIV
Comparator: SOT

Summary

The meta-analysis for the comparison of face mask NIV vs SOT was informed by 11 RCTs that enrolled 1254 participants* (indirect PICO, i.e. non COVID patients with ARDS) *[3]*. All RCTs were published and trials either explicitly excluded pregnant women or children or did not mention them in their methods or results sections.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of face mask NIV vs SOT for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported on all outcomes.

Outcome Timeframe	Study results and measurements	Comparator SOT	Intervention Facemask NIV	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 9 Critical	Relative risk 0.83 (CI 95% 0.71 — 0.96) Based on data from 1,254 participants in 11 studies. (Randomized controlled)	347 per 1000 Difference:	288 per 1000 **59 fewer per 1000** (CI 95% 101 fewer — 14 fewer)	Moderate Due to serious indirectness [1]	Face mask NIV probably decreases mortality
IMV 9 Critical	Relative risk 0.74 (CI 95% 0.64 — 0.86) Based on data from 1,166 participants in 10 studies. (Randomized controlled)	416 per 1000 Difference:	308 per 1000 **108 fewer per 1000** (CI 95% 150 fewer — 58 fewer)	Moderate Due to serious inconsistency [2]	Face mask NIV probably decreases IMV
Hospital LOS 9 Critical	Lower better Based on data from 829 participants in 6 studies. (Randomized controlled)	20.51 days (Median) Difference:	17.93 days (Median) **MD 2.02 fewer** (CI 95% 4.39 fewer — 0.35 more)	Low Due to serious inconsistency and serious imprecision [3]	Face mask NIV may decrease hospital LOS
ICU LOS 6 Important	Lower better Based on data from 1,152 participants in 10 studies. (Randomized controlled)	9.43 days (Median) Difference:	7.85 days (Median) **MD 1.61 fewer** (CI 95% 3.21 fewer — 0.03 fewer)	Low Due to serious inconsistency and serious imprecision [4]	Face mask NIV may decrease ICU LOS

1. **Inconsistency: no serious. Indirectness: serious.** RCT populations include immunocompromised, stem cell or solid organ transplant, severe thoracic trauma, mixed community-acquired pneumonia and AHRF patients. **Imprecision: no serious.** 1.4% is considered an important reduction in mortality. **Publication bias: no serious.**
2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 57%. **Indirectness: no serious.** RCT populations include immunocompromised, stem cell or solid organ transplant, mixed community-acquired pneumonia and AHRF patients. **Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:55%. **Indirectness: no serious. Imprecision: serious.** Wide confidence interval that includes benefit and harm. **Publication bias: no serious.**
4. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2: 75%. **Indirectness: no serious. Imprecision: serious.** Wide confidence interval that includes benefit and harm. **Publication bias: no serious.**

Clinical Question/ PICO

Population: Hospitalized patients with ARDS and AHRF who do not need emergent intubation
Intervention: Face mask NIV
Comparator: HFNO

Summary

The meta-analysis for the comparison of face mask NIV vs HFNO was informed by 3 RCTs that enrolled 316 participants* (indirect PICO, i.e. non COVID patients with ARDS) *[3]*. All trials were published and either explicitly excluded pregnant women and children or did not mention their inclusion in the methods and results section.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of face mask NIV compared with HFNO for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

* Not all trials reported all outcomes.

Outcome Timeframe	**Study results and measurements**	**Comparator** HFNO	**Intervention** Face mask NIV	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 9 Critical	Relative risk 1.83 (CI 95% 1.15 — 2.89) Based on data from 286 participants in 2 studies. (Randomized controlled)	**157** per 1000 Difference:	**287** per 1000 **130 more per 1000** (CI 95% 24 more — 297 more)	**Very low** Due to serious indirectness and very serious imprecision [1]	We are very uncertain of the impact of face mask NIV on mortality
IMV 9 Critical	Relative risk 1.22 (CI 95% 0.94 — 1.59) Based on data from 316 participants in 3 studies. (Randomized controlled)	**364** per 1000 Difference:	**444** per 1000 **80 more per 1000** (CI 95% 22 fewer — 215 more)	**Very low** Due to serious risk of bias, serious imprecision, and serious indirectness [2]	We are very uncertain of the impact of face mask NIV on IMV
Hospital LOS 9 Critical	Lower better		CI 95%		No studies were found that looked at hospital LOS
ICU LOS 6 Important	Lower better Based on data from 216 participants in 1 studies. (Randomized controlled)	**12.8** days (Median) Difference:	**13.35** days (Median) **MD 0.55 more** (CI 95% 3.16 fewer — 4.26 more)	**Low** Due to very serious imprecision [3]	Face mask NIV may have little or no difference on ICU LOS

1. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was moderately high, with I^2: 51%. **Indirectness: serious.** Differences between the population of interest and those studied (one of two RCTs 100% in interstitial lung disease patients, the other 100% with community-acquired pneumonia). **Imprecision: very serious.** Number of patients is far less than would be required to meet the optimal information size. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Two of three trials have unclear sequence generation and concealment of allocation during randomization process (one is a research abstract with incomplete data). **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied (one of three RCTs 100% in interstitial lung disease patients, one reports 100% with community-acquired pneumonia, and a third reports mixed acute respiratory failure and community-acquired pneumonia). **Imprecision: serious.** Wide confidence interval contains important benefit and harm. **Publication bias: no serious.**

3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals that include benefit and harm. Data from one study. **Publication bias: no serious.**

Clinical Question/ PICO

Population: Hospitalized patients with ARDS and AHRF not needing emergent intubation
Intervention: Helmet NIV
Comparator: Face mask NIV

Summary

The meta-analysis for the comparison of helmet NIV vs face mask NIV was informed by one trial that enrolled 83 participants (indirect PICO, i.e. non COVID patients with ARDS) *[3]*. The trial was published and did not include pregnant women or children.

For patients with severe or critical COVID-19, the GRADE Summary of Findings table shows the relative and absolute effects of helmet NIV compared with face mask NIV for the outcomes of interest, with certainty ratings, informed by the meta-analysis.

Outcome Timeframe	Study results and measurements	Comparator Face mask NIV	Intervention Helmet NIV	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality [1] 9 Critical	Relative risk 0.6 (CI 95% 0.37 — 0.99) Based on data from 83 participants in 1 studies. (Randomized controlled)	564 per 1000 Difference:	338 per 1000 **226 fewer per 1000** (CI 95% 355 fewer — 6 fewer)	**Low** Due to very serious imprecision [2]	Helmet NIV may decrease mortality
IMV 9 Critical	Relative risk 0.3 (CI 95% 0.15 — 0.58) Based on data from 83 participants in 1 studies.	615 per 1000 Difference:	185 per 1000 **430 fewer per 1000** (CI 95% 523 fewer — 258 fewer)	**Low** Due to very serious imprecision [3]	Helmet NIV may decrease IMV
Hospital LOS	Lower better Based on data from 83 participants in 1 studies. (Randomized controlled)	7.8 days (Median) Difference:	4.7 days (Median) **MD 5.1 fewer** (CI 95% 9.38 fewer — 0.82 fewer)	**Low** Due to very serious imprecision [4]	Helmet NIV may decrease hospital LOS
ICU LOS					No studies were found that looked at ICU LOS

1. Mortality at 90 days for this outcome. 1 year data not used based on consensus from the SR and WHO groups.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Number of patients is far less than would be required to meet the optimal information size (<10%). **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Number of patients is far less than would be required to meet the optimal information size (<10%). **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Number of patients is far less than would be required to meet the optimal information size (<10%). **Publication bias: no serious.**

Implementation tools

Additional educational modules and implementation tools for health workers:

WHO COVID-19 essential supplies forecasting tool (COVID-ESFT) assists governments, partners, and other stakeholders to forecast the necessary volume of personal protective equipment, diagnostic test equipment, consumable medical supplies, biomedical equipment for case management, and essential drugs for supportive care and treatment of COVID-19.

WHO Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation provides algorithms and practical tools for clinicians working in acute care hospitals managing adult and paediatric patients with acute respiratory infection, including severe pneumonia, acute respiratory distress syndrome, sepsis and septic shock. This includes information on screening, testing, monitoring and treatments.

WHO Openwho.org clinical management course series hosts a full course series on COVID-19 which covers a holistic pathway of care for a patient, from screening and triage to rehabilitation, testing and treatments and palliative care.

WHO Priority medical device list for the COVID-19 response and associated technical specifications describes the technical and performance characteristics of medical devices used to manage patients with COVID-19, and also includes related standards for accessories and consumables. It is intended for policy-makers and planning officers in ministries of health, procurement and regulatory agencies, intergovernmental and international agencies as well as the medical device industry. For more information see WHO website on Health products and policy standards.

Invasive ventilation and ARDS management

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 [143][144][145]. However, as with all critically ill patients, anticipate and prepare for anatomically and physiologically difficult airway.

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 [117], and is also suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria [117]. 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 [146]. The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets.

Remark 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 [147].

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

Remarks:
1. 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 [148][149].
2. 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 [117]. The main effect is to shorten the duration of ventilation. A sample protocol for implementation of this recommendation is available [150].

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:
1. 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 [151]. 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 [152]; data from RCTs of ventilation strategies that target driving pressure are not currently available.
2. 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 [153] 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 [154]. 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 [155].

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 [156], 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 [157]. 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:
1. Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).
2. Manual hyperinflation should be avoided and ventilator hyperinflation used instead, if indicated [139].

In patients with excessive secretions, or difficulty clearing secretions, consider application of airway clearance techniques. These should be performed only if deemed medically appropriate *[139]* **and appropriate IPC measures are in place.**

Remarks:

1. Active cycle of breathing techniques and positioning techniques can be used to optimize oxygenation [158][159]. 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 [159]. These techniques are only indicated for patients with mucous hypersecretion and difficulties clearing secretions, and for patients with co-existing respiratory or neuromuscular comorbidities [159].
2. All interventions inducing cough for airway clearance are potentially aerosol-generating procedures, and airborne precautions should be in place (see Section 5 on IPC) [87]; and single-patient-use disposable options are recommended (such as positive expiratory pressure device).
3. Consider use respiratory muscle training in patients recovering from critical illness with suspected respiratory muscle weakness [159].
4. 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.

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) [160]. However, ECMO was associated with a reduced risk of the composite outcome that consisted of mortality and crossover to ECMO treatment [160], and a post-hoc Bayesian analysis of this RCT showed that ECMO is very likely to reduce mortality across a range of prior assumptions [161]. In patients with MERS, ECMO vs conventional treatment was associated with reduced mortality in a cohort study [162]. 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 [163][164]. In children, ECMO can also be considered in those with severe ARDS, although high-quality evidence for benefit is lacking [147].

12. 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 *[117]*.

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 [117]. 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 [117] and children [165][118]. Alternate fluid regimens are suggested when caring for adults and children in resource-limited settings [166][167].*

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 [117]. These indices include passive leg raise, 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 [168].*
5. *Clinical trials conducted in resource-limited settings comparing aggressive versus conservative fluid regimens suggest higher mortality in patients treated with aggressive fluid regimens [166][167]. Refer to the WHO-ICRC Basic emergency care (Shock module) for an initial approach and management of shock in resource-limited settings [100].*

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 [117][169]. 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 [117].

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 boluses:

- **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** *[118]*.

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 [170] 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 [174].
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 [118].

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.

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

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).

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 *[171]*; other information available at https://www.icudelirium.org/medical-professionals/overview), preventing VAP *[178]*, treating sepsis (reviewed in http://links.lww.com/CCM/C326), preventing central venous catheter infection *[172]*, 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 *[173]*. 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.

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 can be found in the practical info tab and in the Cochrane Collaboration review of the literature published in the Web Annex. 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 *[171]*, prevent VAP *[178]*, treat sepsis (http://links.lww.com/CCM/C326), and prevent central venous catheter infection *[172]* 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.

Clinical Question/ PICO

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 Timeframe	**Study results and measurements**	**Comparator** No care bundles	**Intervention** Care bundles	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality (randomized trials) at 6 months	Relative risk 0.75 (CI 95% 0.53 — 1.06) Based on data from 180 participants in 1 studies. (Randomized controlled)	489 per 1000 Difference:	367 per 1000 **122 fewer per 1000** (CI 95% 259 fewer — 29 more)	Very low Due to very serious indirectness, Due to very serious imprecision [1]	ICU care bundles possibly reduce mortality
Mortality (observational studies) 28 days or to hospital discharge	Relative risk 0.75 (CI 95% 0.65 — 0.86) Based on data from 1,258 participants in 7 studies. (Observational (non-randomized))	359 per 1000 Difference:	269 per 1000 **90 fewer per 1000** (CI 95% 126 fewer — 50 fewer)	Very low Due to very serious indirectness, Due to very serious imprecision [2]	ICU care bundles possibly reduce mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** No care bundles	**Intervention** Care bundles	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Administrative burden	Based on data from 0 participants in 0 studies.			Very low	Care bundles may be associated with an appreciable administrative burden.
Impingement on physician autonomy	Based on data from 0 participants in 0 studies.			Very low	Care bundles may be associated with an impingement of physician autonomy.

1. **Inconsistency: no serious. Indirectness: very serious. Imprecision: very serious. Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: very serious. Imprecision: very serious. Publication bias: no serious.**

Coagulopathy is common in patients with severe COVID-19, and both venous and arterial thromboembolism have been reported *[31][32][175][176][177]*.

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.

UNDER REVIEW

Thromboprophylaxis:

This section is currently under review and will be updated in the next iteration of the guidelines.

Conditional recommendation for

In review

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).

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 12 h 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.

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.

Clinical Question/ PICO

Population: Hospitalized patients without an indication for therapeutic anticoagulation
Intervention: Anticoagulation at therapeutic or intermediate intensity
Comparator: Anticoagulation at prophylactic intensity

Summary

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

Outcome Timeframe	**Study results and measurements**	**Comparator** anticoagulation at prophylactic intensity	**Intervention** anticoagulation at therapeutic or intermediate intensity	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality at 14 days	Hazard ratio 0.86 (CI 95% 0.73 — 1.07) Based on data from 2,626 participants in 1 studies. (Observational (non-randomized))	Difference:	**19 fewer** (CI 95% 38 fewer — 3 more)	**Very low** Due to very serious risk of bias, Due to very serious imprecision [1]	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 participants in 1 studies. (Observational (non-randomized))	Difference:	**16 fewer** (CI 95% 15 fewer — 7 fewer)	**Very low** Due to very serious risk of bias, Due to very serious imprecision [2]	Therapeutic or intermediate intensity anticoagulation possibly reduces pulmonary embolism
Major bleeding at 4-12 days	(Observational (non-randomized))	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 [3]	Therapeutic or intermediate intensity anticoagulation probably increases major bleeding

1. **Risk of Bias: very serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
2. **Risk of Bias: very serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious. Upgrade: all plausible confounding would have reduced the effect.** Upgraded from low certainty evidence due to large body of relevant indirect evidence.

Info Box

Table 13.1 shows interventions to prevent complications in hospitalized and critically ill patients with COVID-19. They are based on Surviving Sepsis *[117]* or other guidelines *[178][179][180][181]*, 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 *[182]*. See the WHO *Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation* for practical tools to assist implementation *[101]*.

Table 13.1 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 • Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions • Early mobilization • 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 • Keep patient in semi-recumbent position (head of bed elevation 30–45°) • Use a closed suctioning system; periodically drain and discard condensate in tubing • 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) • 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 *[183]*	• 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.

14. Multisystem inflammatory syndrome in children (MIS-C) with COVID-19

This section outlines what information the GDG requested and used in making their recommendations for corticosteroids in hospitalized children with COVID-19 aged 0 to 18 years, who meet standardized clinical definition for MIS-C (see Annex 5 for standardized definitions).

Prioritized outcomes

For the previous recommendations, the GDG members prioritized outcomes (rating from 9 [critical] to 1 [not important]) with severe and critical COVID-19, taking a patient perspective (Table 2.1). For these new recommendations on MIS-C, the GDG concluded that the values and preferences of children and adolescents with MIS-C may differ from those used in previous recommendations. A new targeted outcomes prioritization exercise was conducted (Table 14.1). These new prioritized outcomes were used to update the meta-analysis.

Values and preferences

For these new recommendations for MIS-C, the majority of GDG members inferred that most well-informed patients, and their families, would, despite the high uncertainty of important benefit, want to receive some therapeutic agent in addition to supportive care for MIS-C, compared with no specific therapeutic agent. In doing so, patients would be placing a high value on uncertain benefit and a low value on avoiding any mild adverse effects associated with treatment.

Table 14.1. Panel outcome rating from a patient perspective and a parent perspective of MIS-C

Outcome	Median	Mean	SD	Range
Death	9	8.81	0.56	7-9
Need for invasive mechanical ventilation	8	8.07	0.94	6-9
Need for haemodynamic support	8	7.48	1.52	3-9
Severe adverse effects	7	7.23	0.93	5-9
Quality of life	7	7.19	1.28	3-9
Cardiac aneurysms at discharge	7	6.96	1.57	2-9
Change in cardiac function compared to baseline	7	6.74	1.38	3-9
Persistent symptoms at 3 months	6	6.37	1.57	3-9
Duration of hospitalization	6	6.04	1.62	2-9
Length of stay in PICU	6	6	1.36	4-8
Time to symptom resolution	6	5.74	1.55	2-8
Fever present more than 48 hours after treatment	5	4.81	1.85	1-7

PICU: Paediatric intensive care unit; SD: standard deviation.
Note: 7 to 9 – critical; 4 to 6 – important; 1 to 3 – of limited importance.

Evidence summary

The GDG's recommendations for corticosteroid use in hospitalized children who meet the standard clinical definition for MIS-C were informed by the results of systematic review and meta-analysis of the literature that pooled data from 3 studies, n = 885 *[184][185][186]*. In Annexes 3 and 4, the systematic search criteria and table of trial characteristics can be found, respectively.

From these studies, for the three comparisons: a) adding corticosteroids to IVIG compared to IVIG alone; b) corticosteroids compared to IVIG; and c) adding corticosteroids to IVIG compared to corticosteroids alone and for all prioritized outcomes including death, need for invasive mechanical ventilation two days after initiation of treatment, need for hemodynamic support two days after initiation of treatment, coronary artery dilation, acute left ventricular dysfunction 2 days after initiation of treatment, and reduction in fever 2 days after initiation of treatment, the evidence was of very low certainty.

The evidence was summarized in the summary of findings tables and presented to the GDG addressing the pre-specified PICOs and prioritized outcomes: corticosteroids + IVIG vs IVIG alone; corticosteroids alone vs IVIG alone; and corticosteroids + IVIG vs corticosteroids alone (see Research Evidence tab) below). For all three PICOs, very low certainty evidence was ascertained for all outcomes.

Subgroup analysis

Subgroup analyses were not conducted.

Conditional recommendation for

- In hospitalized children aged 0–18 who meet a standard case definition for MIS-C, we suggest using corticosteroids in addition to supportive care (rather than either IVIG plus supportive care, or supportive care alone) (conditional recommendation, very low certainty).
- In hospitalized children aged 0–18 who meet both a standard case definition for MIS-C and diagnostic criteria for Kawasaki disease, we suggest using corticosteroids in addition to standard of care for Kawasaki disease (conditional recommendation, very low certainty).

Practical Info

Practical info

There are slightly different case definitions for MIS-C (Annex 5). This guideline is applicable for any standard case definition of MIS-C. Case definitions will continue to be updated as new data emerge. Based on accessibility to corticosteroids being much wider than accessibility to IVIG, the panel suggested that most patients will receive corticosteroids before they receive IVIG, even in patients where both are prescribed.

Route: Systemic corticosteroids can be given orally or intravenously. All studies examined intravenous administration.

Dose and duration: In the three studies included in the meta-analysis, intravenous methylprednisilone was used at varying doses; one study did not report a dose. The other two reported ranges between 0.8–2.0 mg/kg/day for 5 days; or higher bolus doses of 10–30 mg/kg/day for 3 days. Both lower and higher dose options can be considered. See Annex 4 for study details.

Monitoring: It would be prudent to monitor for known complications associated with corticosteroid use, such as hyperglycemia and behavioural changes.

Supportive care: Most emphatically, the GDG emphasized the importance of high-quality supportive care to improve the outcomes of these children, apart from specific therapies. Please see the *WHO Pocket Book of Hospital Care for Children* for syndromic management guidance of severely ill children, including the importance of recognizing other conditions such leading to shock, sepsis and severe infections; as well as guidance from other organizations on supportive management of Kawasaki disease *[165]*.

Uncertainties

The GDG emphasized the need for further randomized clinical trials in this population with these agents. The panel acknowledged that results of ongoing randomized trials of therapeutic interventions for MIS-C over the next several months were highly likely to upgrade the certainty of evidence and may lead to changes in recommendations. Enrolment of patients into randomized trials should be prioritized.

Evidence To Decision

Benefits and harms

Supportive care/standard of care: The GDG emphasized the importance of optimized supportive care for children meeting the standardized case definition of MIS-C. Thus, the interpretation of these results, should consider that supportive care is the current standard of care on which these interventions are additive. See *WHO Pocket Book of Hospital Care for Children [165]*, and the *WHO Paediatric emergency triage, assessment and treatment: care of critically ill children [138]*.

Interventions:

- The effects of corticosteroids in addition to IVIG, compared with IVIG alone plus supportive care, or supportive care alone, all prioritized outcomes, including death during hospitalization, need for mechanical ventilation, coronary artery abnormalities, and cardiac dysfunction are very uncertain (very low certainty, direct evidence).
- The effects of corticosteroids alone, compared with IVIG plus supportive care, or supportive care alone on all prioritized outcomes, including death during hospitalization, need for mechanical ventilation, coronary artery abnormalities,

and cardiac dysfunction are very uncertain (very low certainty, direct evidence).
- The effects of corticosteroids in addition to IVIG compared to corticosteroids alone on all prioritized outcomes including death during hospitalization, need for mechanical ventilation, and other prioritized outcomes are very uncertain (very low certainty, direct evidence).

Based on the clinical experience of the GDG of other conditions, the possible harms of steroids were deemed to be of lesser importance than the possible benefits. However, the GDG did emphasize that for appropriate evaluation and management for undifferentiated children presenting with shock, consider other serious infections based on epidemiologic considerations (i.e., malaria, HIV, etc). Possible harms of IVIG, based on the clinical experience of the panel of other conditions, include fluid overload due to the volume of IVIG preparations. The GDG acknowledged the care of Kawasaki disease, a clinically similar condition which can be difficult to distinguish from MIS-C, includes IVIG *[165]*.

Certainty of the Evidence

Very low

For all outcomes in the three pre-specified PICOs, the GDG considered the evidence to be of very low certainty, due to risk of bias from observational designs and due to serious imprecision (confidence intervals included both important benefit and important harm). The evidence for corticosteroids and IVIG is from observational studies that compare the combination of these agents against them individually.

Values and preferences

Variability expected

The majority of GDG members inferred that most well-informed patients, and their families, would, despite the high uncertainty of important benefit, want to receive some therapeutic agent in addition to supportive care for MIS-C, compared with no specific therapeutic agent. In doing so, patients would be placing a high value on uncertain benefit and a low value on avoiding any mild adverse effects associated with treatment.

Resources

Important considerations

Corticosteroids are widely available in all regions of the world and methylprednisolone is on the WHO Model List of Essential Medicines. IVIG has important resource considerations, including higher cost, and is not readily available across all care settings and regions.

Justification

When moving from evidence to the conditional recommendations for children hospitalized with MIS-C, the panel emphasized the very low certainty evidence of reduction in mortality and the need for haemodynamic support and mechanical ventilation with the use of corticosteroids. The panel also acknowledged that some children will simultaneously meet diagnostic criteria for Kawasaki disease, and the standard of care in many parts of the world is to use IVIG, where available, in that population. The panel emphasized the practical difficulty in differentiating the two populations, leading to the emphasis on IVIG in care pathways, despite the lack of supporting direct evidence. In the absence of randomized evidence showing IVIG to be harmful, the panel expressed concern about not providing IVIG, where available, to children who meet diagnostic criteria of both Kawasaki disease and MIS-C. The panel acknowledged that ongoing randomized trials are expected to add substantially to the evidence base over the next several months.

Subgroup analyses

Given the available evidence, the panel did not find any evidence bearing on the question of subgroup effects across patients with different levels of disease severity, and therefore did not make any subgroup recommendations. In other words, the conditional recommendations are applicable across all patient subgroups. In particular, there are insufficient data to support different recommendations in the younger age ranges (given the predilection for younger age ranges in Kawasaki disease). Analyses based on dose of corticosteroid or IVIG administered were unable to be performed, given the limitations of the studies.

Applicability

Special populations

There was no special population where the panel inferred different applicability of these recommendations.

Clinical Question/ PICO

Population: Children aged 0–19 years meeting any standard case definition of MIS-C in hospitals in high-income countries (HIC) and low- and middle-income countries (LMIC)

Intervention: IVIG plus steroids as the initial treatment

Comparator: IVIG alone as the initial treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG alone as the initial treatment	**Intervention** IVIG plus steroids as the initial treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death during hospitalization	Odds ratio 0.32 (CI 95% 0.05 — 1.86) Based on data from 334 participants in 1 studies. [1] (Observational (non-randomized))	**16** per 1000 Difference:	**5** per 1000 **11 fewer per 1000** (CI 95% 15 fewer — 14 more)	**Very low** Due to very serious risk of bias and serious imprecision [2]	The evidence is very uncertain about the effect of adding steroids to IVIG on death during hospitalization
Ventilation support 2 days after initiation of treatment	Odds ratio 0.52 (CI 95% 0.1 — 2.76) Based on data from 429 participants in 2 studies. [3] (Observational (non-randomized))	**210** per 1000 Difference:	**109** per 1000 **101 fewer per 1000** (CI 95% 189 fewer — 370 more)	**Very low** Due to very serious risk of bias, serious inconsistency, and serious imprecision [4]	The evidence is very uncertain about the effect of adding steroids to IVIG on the need for ventilation support 2 days after initiation of treatment
Haemodynamic support 2 days after initiation of treatment	Odds ratio 0.52 (CI 95% 0.32 — 0.83) Based on data from 551 participants in 3 studies. [5] (Observational (non-randomized))	**580** per 1000 Difference:	**302** per 1000 **278 fewer per 1000** (CI 95% 395 fewer — 99 fewer)	**Very low** Due to very serious risk of bias [6]	The evidence is very uncertain about the effect of adding steroids to IVIG results in a reduction in the need for haemodynamic support 2 days after initiation of treatment
Coronary artery dilatation at discharge	Odds ratio 0.46 (CI 95% 0.05 — 4.22) Based on data from 224 participants in 1 studies. [7] (Observational (non-randomized))	**5** per 1000 Difference:	**2** per 1000 **3 fewer per 1000** (CI 95% 5 fewer — 16 more)	**Very low** Due to very serious risk of bias and serious imprecision [8]	The evidence is very uncertain about the effect of adding steroids to IVIG on coronary artery dilatation at discharge
Acute left ventricular dysfunction 2 days after initiation of treatment	Odds ratio 0.55 (CI 95% 0.18 — 1.67) Based on data from 543 participants in 3 studies. [9] (Observational (non-randomized))	**520** per 1000 Difference:	**373** per 1000 **147 fewer per 1000** (CI 95% 357 fewer — 124 more)	**Very low** Due to very serious risk of bias and serious imprecision [10]	The evidence is very uncertain about the effect of adding steroids to IVIG on acute left ventricular dysfunction 2 days after initiation of treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG alone as the initial treatment	**Intervention** IVIG plus steroids as the initial treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical improvement 2 days after initiation of treatment	Odds ratio 1.09 (CI 95% 0.53 — 2.23) Based on data from 304 participants in 1 studies. [11] (Observational (non-randomized))	268 per 1000 Difference:	292 per 1000 **24 more per 1000** (CI 95% 126 fewer — 329 more)	**Very low** Due to very serious risk of bias and serious imprecision [12]	The evidence is very uncertain about the effect of adding steroids to IVIG on clinical improvement 2 days after initiation of treatment
Fever persisting 2 days after initiation of treatment	Odds ratio 0.69 (CI 95% 0.5 — 0.95) Based on data from 661 participants in 3 studies. [13] (Observational (non-randomized))	993 per 1000 Difference:	685 per 1000 **307 fewer per 1000** (CI 95% 497 fewer — 50 fewer)	**Very low** Due to very serious risk of bias [14]	The evidence is very uncertain about the effect of adding steroids to IVIG results in a reduction in fever 2 days after initiation of treatment

1. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
3. Systematic reviewwith included studies: [185], [184]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Inconsistency: serious.** Downgraded for inconsistency as I squared > 50% or p value represented presence of statistical heterogeneity. Random effects model for pooling ORs was used. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
5. Systematic reviewwith included studies: [185], [186], [184]. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect.
7. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
9. Systematic reviewwith included studies: [186], [184], [185]. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
11. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
13. Systematic reviewwith included studies: [184], [185], [186]. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect.

Clinical Question/ PICO

Population: Children aged 0–19 years meeting any standard case definition of MIS-C in hospitals in high-income

countries (HIC) and low- and middle-income countries (LMIC)

Intervention: IVIG plus steroids as the initial treatment

Comparator: Steroids alone as the initial treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** Steroids alone as the initial treatment	**Intervention** IVIG plus steroids as the initial treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death during hospitalization	Based on data from 233 participants in 1 studies. [1] (Observational (non-randomized))	0 per 1000	24 per 1000	**Very low** Due to very serious risk of bias and serious imprecision [2]	The evidence is very uncertain about the effect of adding IVIG to steroids on death during hospitalization
Ventilation support 2 days after initiation of treatment	Odds ratio 3.7 (CI 95% 0.88 — 16.67) Based on data from 234 participants in 1 studies. [3] (Observational (non-randomized))	62 per 1000 Difference:	230 per 1000 **168 more per 1000** (CI 95% 7 fewer — 971 more)	**Very low** Due to very serious risk of bias and serious imprecision [4]	The evidence is very uncertain about the effect of adding IVIG to steroids on the need for haemodynamic support 2 days after initiation of treatment
Haemodynamic support 2 days after initiation of treatment	Odds ratio 1.75 (CI 95% 0.64 — 4.76) Based on data from 238 participants in 1 studies. [5] (Observational (non-randomized))	164 per 1000 Difference:	288 per 1000 **123 more per 1000** (CI 95% 59 fewer — 617 more)	**Very low** Due to very serious risk of bias and serious imprecision [6]	The evidence is very uncertain about the effect of adding IVIG to steroids on the need for ventilation support 2 days after initiation of treatment
Coronary artery dilatation at discharge	Odds ratio 0.61 (CI 95% 0.06 — 5.88) Based on data from 159 participants in 1 studies. [7] (Observational (non-randomized))	4 per 1000 Difference:	3 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 21 more)	**Very low** Due to very serious risk of bias and serious imprecision [8]	The evidence is very uncertain about the effect of adding IVIG to steroids on coronary artery dilatation at discharge
Acute left ventricular dysfunction 2 days after initiation of treatment	Odds ratio 2.08 (CI 95% 0.56 — 7.69) Based on data from 238 participants in 1 studies. [9] (Observational (non-randomized))	81 per 1000 Difference:	169 per 1000 **88 more per 1000** (CI 95% 36 fewer — 542 more)	**Very low** Due to very serious risk of bias and serious imprecision [10]	The evidence is very uncertain about the effect of adding IVIG to steroids on acute left ventricular dysfunction 2 days after initiation of treatment
Clinical improvement 2 days after initiation of treatment	Odds ratio 0.56 (CI 95% 0.24 — 1.32) Based on data from 212 participants in 1 studies. [11] (Observational (non-randomized))	408 per 1000 Difference:	228 per 1000 **180 fewer per 1000** (CI 95% 310 fewer — 129 more)	**Very low** Due to very serious risk of bias and serious imprecision [12]	The evidence is very uncertain about the effect of adding IVIG to steroids on clinical improvement 2 days after initiation of treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** Steroids alone as the initial treatment	**Intervention** IVIG plus steroids as the initial treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fever persisting 2 days after initiation of treatment	Odds ratio 1.3 (CI 95% 0.55 — 3.23) Based on data from 195 participants in 1 studies. [13] (Observational (non-randomized))	356 per 1000 Difference:	475 per 1000 **119 more per 1000** (CI 95% 160 fewer — 792 more)	**Very low** Due to very serious risk of bias and serious imprecision [14]	The evidence is very uncertain about the effect of adding IVIG to steroids on fever persisting two days after initiation of treatment

1. Systematic reviewwith included studies: [184]. Adjusted relative risk not available. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
3. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
5. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
7. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
9. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
11. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
13. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.

Clinical Question/ PICO

Population: Children aged 0–19 years meeting any standard case definition of MIS-C in hospitals in high-income countries (HIC) and low- and middle-income countries (LMIC)

Intervention: Steroids alone as the initial treatment

Comparator: IVIG alone as the initial treatment

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG alone as the initial treatment	**Intervention** Steroids alone as the initial treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death during hospitalization	Based on data from 239 participants in 1 studies. [1] (Observational (non-randomized))	16 per 1000	0 per 1000	Very low Due to very serious risk of bias and serious imprecision [2]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on death during hospitalization
Ventilation support 2 days after initiation of treatment	Odds ratio 0.31 (CI 95% 0.07 — 1.43) Based on data from 237 participants in 1 studies. [3] (Observational (non-randomized))	93 per 1000 Difference:	29 per 1000 **64 fewer per 1000** (CI 95% 86 fewer — 40 more)	Very low Due to very serious risk of bias and serious imprecision [4]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on the need for ventilation support 2 days after initiation of treatment
Haemodynamic support 2 days after initiation of treatment	Odds ratio 0.43 (CI 95% 0.15 — 1.22) Based on data from 241 participants in 1 studies. [5] (Observational (non-randomized))	276 per 1000 Difference:	119 per 1000 **157 fewer per 1000** (CI 95% 234 fewer — 61 more)	Very low Due to very serious risk of bias and serious imprecision [6]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on the need for haemodynamic support 2 days after initiation of treatment
Coronary artery dilatation at discharge	Odds ratio 0.75 (CI 95% 0.18 — 3.22) Based on data from 171 participants in 1 studies. [7] (Observational (non-randomized))	5 per 1000 Difference:	4 per 1000 **1 fewer per 1000** (CI 95% 4 fewer — 11 more)	Very low Due to very serious risk of bias and serious imprecision [8]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on coronary artery dilatation at discharge
Acute left ventricular dysfunction 2 days after initiation of treatment	Odds ratio 0.69 (CI 95% 0.18 — 2.62) Based on data from 243 participants in 1 studies. [9] (Observational (non-randomized))	110 per 1000 Difference:	76 per 1000 **34 fewer per 1000** (CI 95% 90 fewer — 178 more)	Very low Due to very serious risk of bias and serious imprecision [10]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on acute left ventricular dysfunction 2 days after initiation of treatment
Clinical improvement 2 days after initiation of treatment	Odds ratio 1.95 (CI 95% 0.83 — 4.6) Based on data from 212 participants in 1 studies. [11] (Observational (non-randomized))	268 per 1000 Difference:	522 per 1000 **254 more per 1000** (CI 95% 45 fewer — 965 more)	Very low Due to very serious risk of bias and serious imprecision [12]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone on clinical improvement 2 days after initiation of treatment
Fever persisting 2 days after initiation of treatment	Odds ratio 0.51 (CI 95% 0.21 — 1.2) Based on data from 208 participants in 1 studies.[13]	473 per 1000	241 per 1000	Very low Due to very serious risk of bias and serious imprecision [14]	The evidence is very uncertain about the effect of steroids alone compared with IVIG alone

Outcome Timeframe	**Study results and measurements**	**Comparator** IVIG alone as the initial treatment	**Intervention** Steroids alone as the initial treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	(Observational (non-randomized))	Difference:	**232 fewer per 1000** (CI 95% 374 fewer — 95 more)		on fever persisting 2 days after initiation of treatment

1. Systematic reviewwith included studies: [184]. Adjusted relative risk not available. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
3. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
5. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
7. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
9. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
11. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.
13. Systematic reviewwith included studies: [184]. **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: very serious.** Downgraded two levels for serious risk of confounding and selection bias in all studies which substantially lowered confidence in the certainty of the estimate of effect. **Imprecision: serious.** Downgraded for imprecision due to wide confidence intervals around the absolute effects which also crossed the line of no effect.

15. Therapeutics and COVID-19

Info Box

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

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 *[126]*, and will be based on local factors and endemic or other emerging infections *[107][133][134][183]*. 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.

UNDER REVIEW

This section is currently under review and will be updated in the next iteration of the guidelines.

In review

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 severe bacterial infections are laboratory confirmed or are clinically suspected.

Remarks:

1. *Evidence from a living rapid review and meta-analysis of bacterial co-infection in patients who were assessed for bacterial infection presenting with COVID-19 to hospital indicates that 4.4% of patients (95%CI 3.0-6.4%; n=125 212) had coinfection identified at hospital admission and 15.5% (95% CI 10.5%-22%; n=10559) had coinfection at ICU admission [136].*
2. *The same review showed that 8.2% of the patients (95%CI 6.3-10.7%; n=30805) developed secondary bacterial infections while in the hospital while 41.9% (95%CI 29.5-55.4; n=8377) of the patients admitted to ICU developed secondary infections. Hence, estimates suggest that the likelihood of bacterial coinfection in patients with COVID-19 on presentation to hospital is low and empiric antibiotic therapy should not be given as standard of care at hospital admission, unless bacterial infections is strongly suspected, and COVID-19 diagnosis is not confirmed. In patients admitted to ICU, the frequency of bacterial secondary infections is high, therefore empiric antibiotic therapy should be considered in this population [136].*
3. *Biomarkers of infection in blood, such as C-reactive protein (CRP) and procalcitonin (PCT) are elevated in patients with severe COVID-19 and therefore cannot reliably be used to indicate bacterial coinfection [187][188].*
4. *For patients with severe disease, early and appropriate empiric antimicrobial therapy [110] can be administered and 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) [125]. 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*
5. *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.*
6. *Duration of empiric antibiotic treatment should be as short as possible; generally, 5 days is sufficient for bacterial community-acquired pneumonia.*
7. *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 [177]. Antibiotic stewardship programmes should be put into place or continue among COVID-19 patients.*

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 [94].
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 [97].

In a WHO-led study looking at outcomes for patients living with HIV and infected with the SARS-CoV2 virus, HIV increased the odds of severe presentation by 15% and the hazards for death by 38% *[190]*. The use of antiretroviral therapy reduced the risk of poor outcomes; however, HIV infection remained a risk factor for severity and mortality regardless of ART and viral load suppression status *[190]*.

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 *[36]*. Moreover, there may be potential for longer term neurological consequences such as cognitive impairment *[191]* 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 *[192][193][194][195][196][197]*. 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 *[198]*.

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 [199].
2. Maintain awareness for concurrent underlying neurological conditions such as stroke [200] or non-convulsive status epilepticus [201] which can be masked by delirium.
3. 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 [199].
4. 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 [202].
5. 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 [202]. 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 [202].
6. 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 [203].
7. 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 [203].

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.*

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 *[204]*.

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 [205].*
2. *This recommendation is consistent with the Inter-Agency Standing Committee briefing note about mental health and psychosocial aspects of COVID-19 [204], and guidance on basic psychosocial skills for COVID-19 responders [205], 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 [206].*
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 [204].*

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 [206][207].

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 [202].

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 [208]. 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 [209].

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 [209].

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 [209].

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) [210].

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 [211]. To date, there are no studies that can conclusively substantiate these theories, 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) [212] [213].*

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 *[214][215][216][217][218][219][220][221][222][223][224][225]*. 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 *[226]*. Intensive care unit-acquired weakness is ubiquitous in ARDS survivors, as it is in critically ill COVID-19 patients who required prolonged sedation *[227]*, and recovery may be incomplete at 5 years after ICU discharge *[228]*. 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 *[228]*. For ARDS survivors, a reduced exercise capacity persists in the context of relatively preserved pulmonary function at 1 year *[229]*. 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 *[230]*.

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 *[231]*. 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 *[231][232]*.

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 *[233][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 *[234]*. Not returning to usual health within 2–3 weeks of testing was reported by approximately one third of symptomatic adults in an outpatient setting *[235]*. 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 *[236]*.

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.

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 [237]. 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 [159]. Telehealth may play a role in the acute and subacute phases, in which face-to-face rehabilitation is costly, risky, and impractical [238]. Consider strategies for communication with and engagement of families during physical distancing [239].
2. Early mobilization is recommended for all patients with severe risk of functional limitations, resulting from frailty or ICU-acquired weakness [139]. 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 [159]. 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 11 (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 [214]. 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 [240].
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 [241]. 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 [159] 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 [159].

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 [242]. An example of a rapid exercise test to assess desaturation on exertion is the 1-minute sit-to-stand test [243].
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 [238] 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 [237].
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 [244][245][246]. 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 [244][245][246].

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 [247] (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% [243].

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 [247].

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 [158][242][248]. COVID-19 population needs patient-tailored supervised programmes that are flexible to adapt for patients with gas exchange abnormalities [158][242][248][249] 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 [245].

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 [247][250][251].

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 27 April 2021) (39) show that the odds of stillbirth (OR= 1.81, 95% CI 1.38 to 2.37; 25 studies, 423 477 women) and neonatal death (OR= 2.35, 95% CI 1.16 to 4.76; 21 studies, 12 416) were higher in babies born to women with Covid-19 versus those without Covid-19. Although the overall number of neonatal deaths was small (only sixteen events in the Covid-19 group), pregnant women with COVID-19 are more likely to experience any type of preterm birth (OR=1.57, 95% CI 1.36–1.81; 48 studies, 449 040 women) compared with pregnant women without the disease. Overall, 25% (95% CI 21% to 30%; 97 studies, 17 687 women) of neonates were admitted to the neonatal intensive care unit, and had higher odds of NICU admission (OR= 2.18, 95% CI 1.46 to 3.26; 29 studies, 197 196 neonates)

In another living systematic review (as of 3 August 2021) *[252]* SARS-CoV-2 positivity rates were found to be low in babies born to mothers with SARS-CoV-2 infection (1.8%, 95% CI 1.2% to 2.5%; 140 studies, 14 271 babies); the rates are lower (1%) when limited to babies with antenatal or intrapartum exposure to the virus. Evidence was found for confirmed mother-to-child transmission through in utero, intrapartum, and early postnatal exposure; but the overall risk is likely to be low. Severity of maternal Covid-19 (OR=2.36, 95% CI 1.28 to 4.36; 22 studies, 2842 mother-baby dyads) and maternal admission to an intensive care unit (3.46, 95% C 1.74 to 6.91; 19 studies, 2851 mother-baby dyads) seem to be associated with SARSCoV- 2 positivity in offspring, and not trimester of maternal infection, gestation at birth, mode of delivery, breastfeeding, or mother-baby dyad separation at birth.

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.

Pregnant or recently pregnant women with suspected or confirmed mild or moderate 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 severe or critical 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 [253][254]. 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. See the WHO Consolidated guideline on self-care interventions for health [255] and WHO Abortion Care Guideline [256]
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 [254].
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, or confirmed COVID-19, should have access to woman-centered, 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 woman'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* *[257]*.

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 [258].
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 [257].

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 quality abortion care [256].

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) *[259][260][261][262][263][264][265][266][267][268]*.

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 [269]*. 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 [103]. 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.

Info Box

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. 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. Neonates born to mothers with suspected or confirmed COVID-19 should be breastfed within 1 hour of birth. Mothers should apply appropriate IPC. 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. 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. 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. 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. 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. 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. 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. 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. Clean and disinfect surfaces with which the mother has been in contact. Wear a medical mask until symptom resolution and criteria for release from isolation have been met.

	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. 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. 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. 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. 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. 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 birthweight 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 *[270][271][272]*. 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 *[273]*. Refer to the WHO policy brief *Preventing and managing COVID-19 across long-term care services [273]* and WHO guidance *Integrated care for older people (ICOPE) [274]* 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 [275][276] (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 [277]. 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 *[274][278][279]*.

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 [274].

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 [280][281].

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 [282].

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 [93][96][97].

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 *[283]*. Palliative interventions should be integrated with curative treatment *[283]*. 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 *[283][284]*. Refer to the WHO guide Integrating palliative care and symptom relief into responses to humanitarian emergencies and crises *[283]*.

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 [283].*
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 [285]. 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 evidence is emerging about COVID-19 related persistent symptoms, which have parallels with other coronavirus diseases *[233]*.

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 *[231]*. 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 *[231][232]*.

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 *[234]*. Not returning to usual health within 2–3 weeks of testing was reported by approximately one third of symptomatic adults in an outpatient setting *[235]*. 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 *[236]*.

UNDER REVIEW

This section is currently under review and new guidance is expected shortly.

Good practice statement

In review

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 [286][287] 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, respiratory, swallow, 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. To this end, WHO has developed and released a clinical case definition of post COVID-19 condition, also known as "Long COVID-19" by a Delphi consensus, 6 October 2021 to help guide patients, caregivers, and health workers on how to identify individuals who are affected by this condition.

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 children and young people, pregnant women, and older persons (see Section 22 Caring for older people with COVID-19), and their caregivers.

Research Needs

Priority areas of research include:

- Natural history (clinical characteristics, risk factors, association with disease severity and differences between high-income and lower-middle income settings);
- Pathophysiology (viral persistence, immune dysregulation, thrombosis etc.);
- Impact of vaccination;
- Impact of treatments.

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 *[288][289]*.

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 *[1][290]*.

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 [291].

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	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. • 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. • 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. • 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 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. 2. U09 Post COVID-19 condition U09.9 Post COVID-19 condition, unspecified 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. 3. U10 Multisystem inflammatory syndrome associated with COVID-19 U10.9 Multisystem inflammatory syndrome associated with COVID-19, unspecified
ICD-11	RA02 Post COVID-19 condition RA03 Multisystem inflammatory syndrome associated with COVID-19 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* [292].

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 [292].

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 *[293]*. 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 [294].*
   - *Core CRF;*
   - *Pregnancy CRF;*
   - *Multisystem inflammatory syndrome temporally associated with COVID-19 CRF;*
   - *Post COVID-19 condition CRF.*
3. *Clinical characterization research protocols are also available [295].*

We encourage clinicians and hospitals to enroll patients in the WHO-led Solidarity PLUS trial. For more details, please refer to: https://www.who.int/news/item/11-08-2021-who-s-solidarity-clinical-trial-enters-a-new-phase-with-three-new-candidate-drugs.

O2CoV2 is a WHO-led observational study in 25 low- and middle-income countries to examine baseline practices and approaches to respiratory support for patients with COVID-19. Patient enrolment is planned to continue through October 2022. For more information, visit: https://www.who.int/news-room/articles-detail/who-respiratory-support-research-group.

Also refer to the complete WHO R&D blueprint here: https://www.who.int/teams/blueprint/covid-19.

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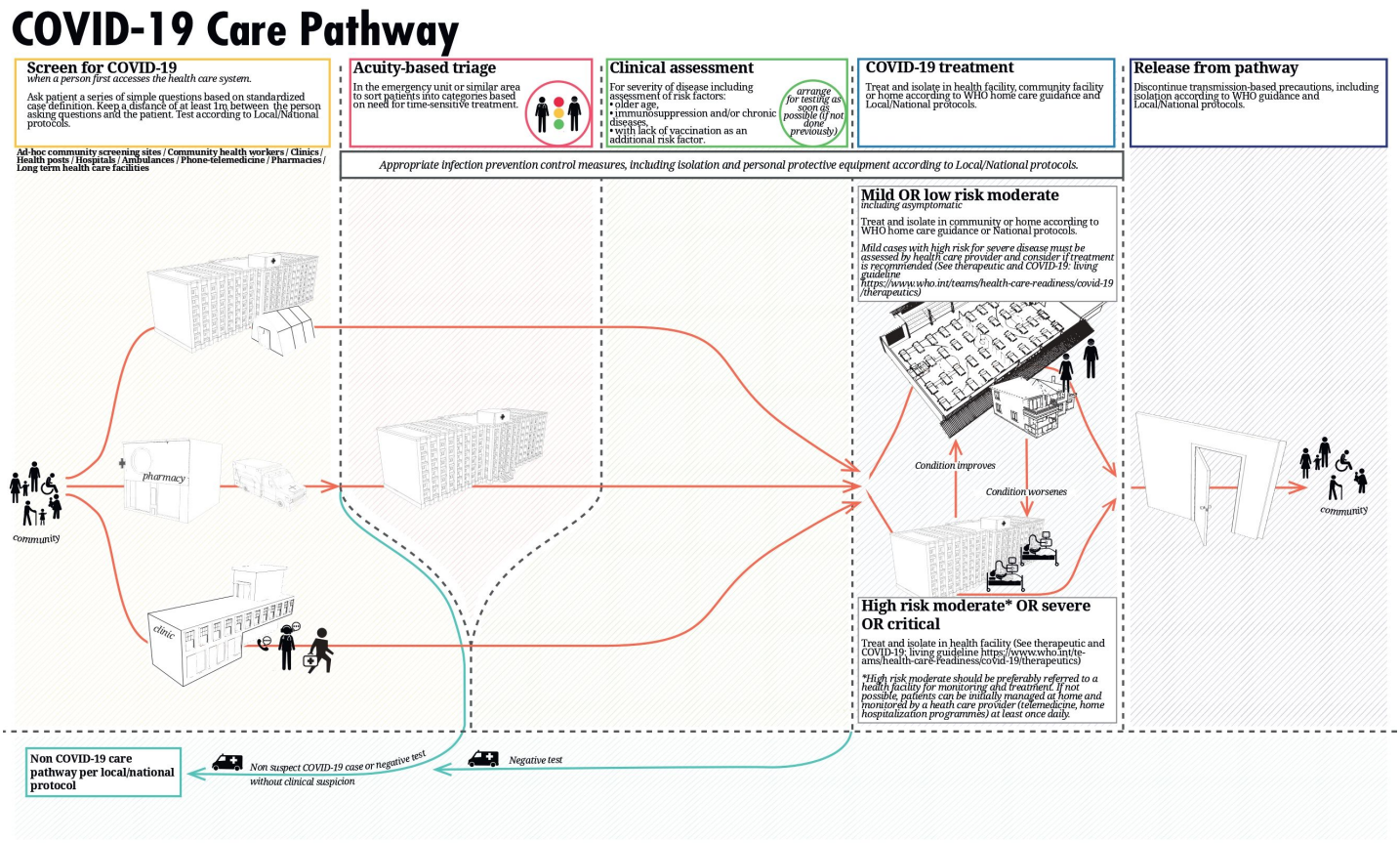
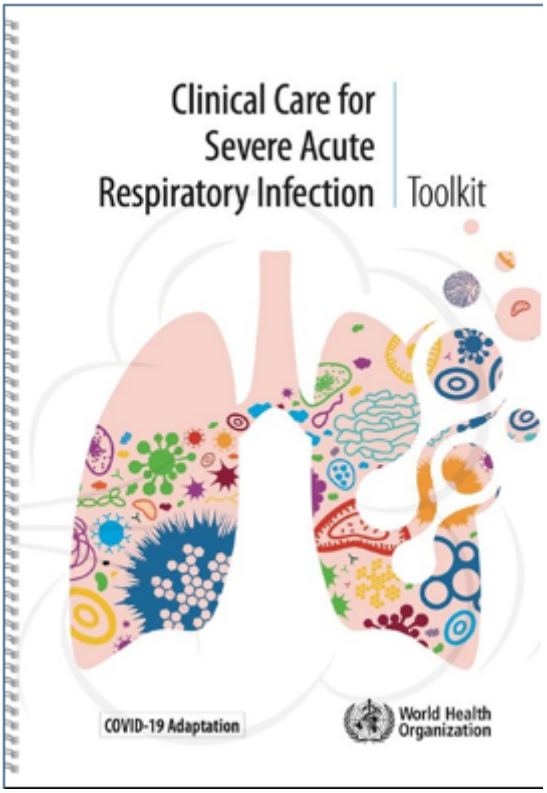
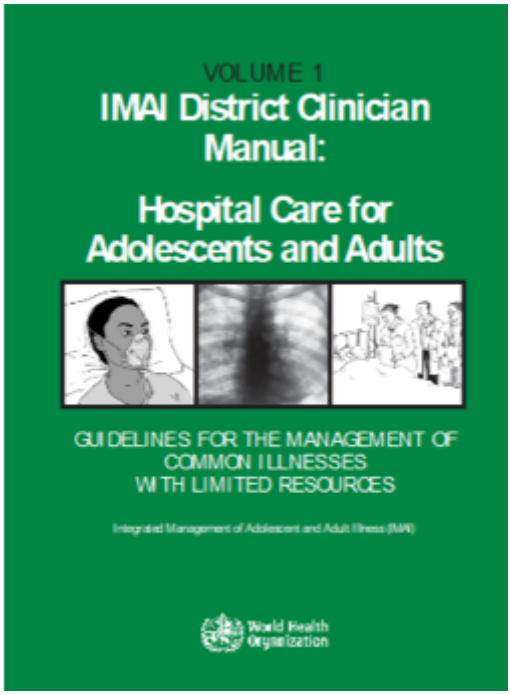
Annex 1: COVID-19 care pathway



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

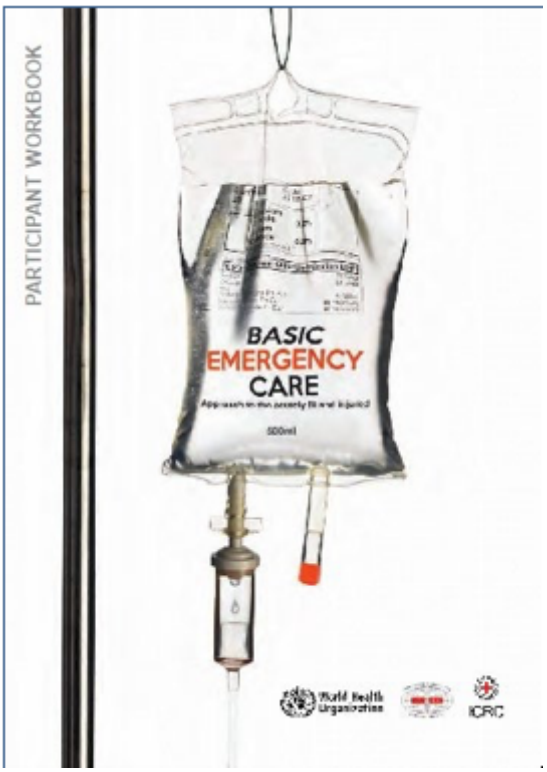


Clinical care for severe acute respiratory infection toolkit: COVID-19 adaptation (2020)
https://www.who.int/publications/i/item/clinical-care-of-severe-acute-respiratory-infections-tool-kit

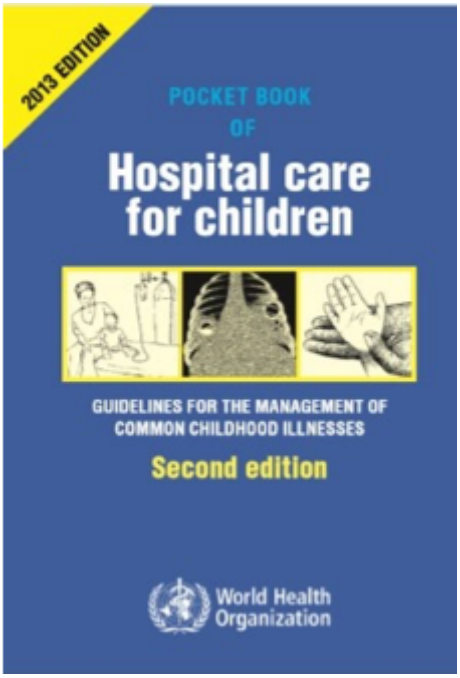


IMAI District clinician manual: hospital care for adolescents and adults. Guidelines for the management of common illnesses with limited resources (2011)
The manual is written for clinicians working at the district hospital (first-level referral care) who diagnose and manage sick adolescents and adults in resource-constrained settings. It aims to support clinical reasoning, and to provide an effective clinical approach and

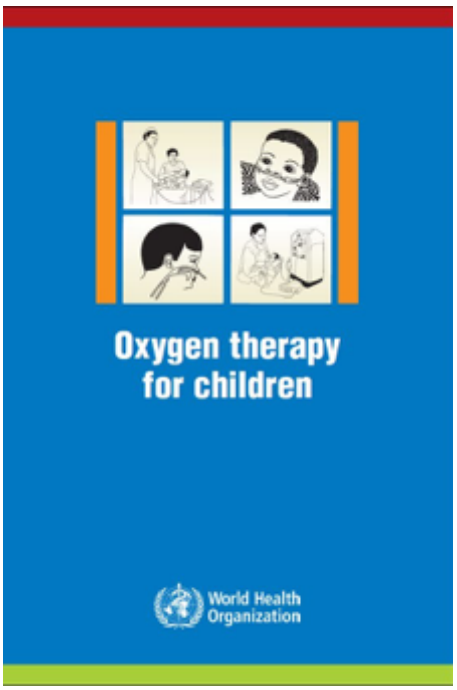
protocols for the management of common and serious or potentially life-threatening conditions at district hospitals. The target audience includes doctors, clinical officers, health officers and senior nurse practitioners. It has been designed to be applicable in both high and low HIV prevalence settings.
https://www.who.int/hiv/pub/imai/imai2011/en/



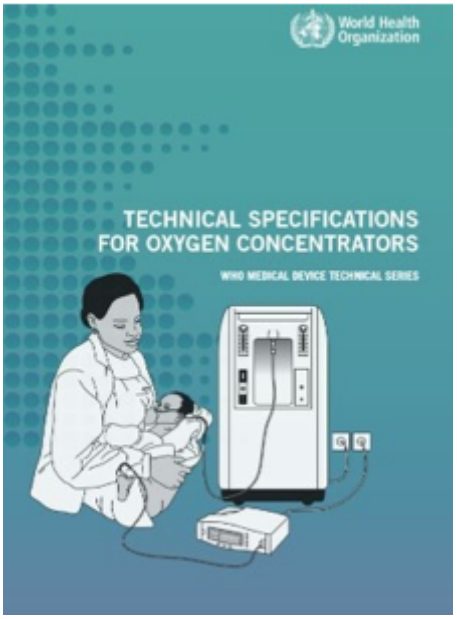
WHO-ICRC Basic emergency care: approach to the acutely ill and injured (2018)
Developed by WHO and ICRC, in collaboration with the International Federation for Emergency Medicine, Basic emergency care (BEC): approach to the acutely ill and injured is an open-access training course for frontline health 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



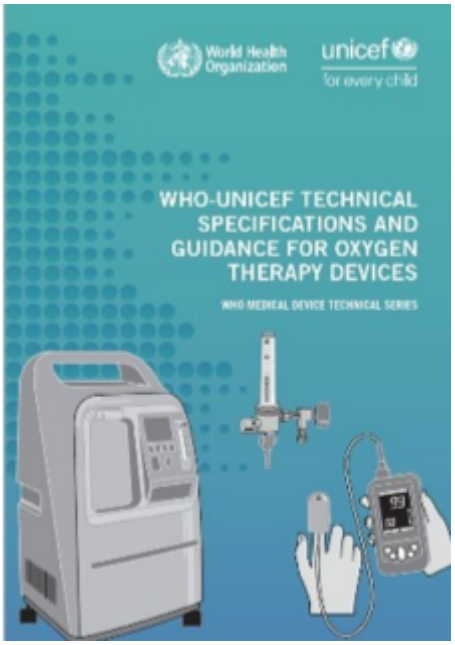
Pocket book of hospital care for children: guidelines for the management of common childhood illnesses (second edition) (2013)
For use by doctors, nurses, and other health workers caring for children at first-level referral hospitals with basic laboratory facilities and essential medicines. These guidelines 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/

WHO Priority medical devices list for the COVID-19 response and associated technical specifications (Nov 2020)
This document describes the medical devices required for the clinical management of COVID-19, selected and prioritized according to the latest available evidence and interim guidelines. This includes: oxygen therapy, pulse oximeters, patient monitors, thermometers, infusion and suction pumps, X-ray, ultrasound and CT scanners as well as personal protective equipment. In order to facilitate access to quality assured priority medical devices, the document also includes technical and performance characteristics, related standards, accessories and consumables. It is intended for policy-makers and planning officers in Ministries of Health, procurement and regulatory agencies, intergovernmental and international agencies as well as the medical device
industry.

https://www.who.int/publications/i/item/WHO-2019-nCoV-MedDev-TS-O2T.V2

Biomedical equipment for COVID-19 case management-inventory tool: Interim guidance (June 2020)
Countries can use this tool to collect in-depth facility inventories of biomedical equipment re-allocation, procurement and planning for COVID-19 case management. The survey assesses quantified availability and the causes for non-functioning of different sources of oxygen delivery and supply systems to the patient in order to determine priorities and re-allocation requirements in accordance with needs.

https://www.who.int/publications/i/item/WHO-2019-nCov-biomedical-equipment-inventory-2020.1

Annex 3: Search strategy (Section 11)

Search strategy exemplars – WHO NIV PICO 1

PICO 1 – DIRECT: Systematic and rapid reviews

Database	COVID-19 Global literature on coronavirus disease
URL	https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/
Search terms	"high flow oxygen" or "high-flow oxygen" or "highflow oxygen" or "high frequency oxygen" or "high-frequency oxygen" or "high flow cannula" or "high-flow cannula" or "highflow cannula" or "high frequency cannula" or "high-frequency cannula" or "high flow cannulae" or "high-flow cannulae" or "highflow cannulae" or "high frequency cannulae" or "high-frequency cannulae" or HFNC or HFOC or "HFN oxygen" or "HFN O2" or "nasal cannula" or "nasal cannulae" OR "high flow nasal" or "high-flow nasal" or "highflow nasal" or "high frequency nasal" or "high-frequency nasal" OR NIV or FNIV or "F-NIV" or HNIV or "H-NIV" OR "controlled ventilation" OR "continuous positive airway pressure" or "continuous positive air-way pressure" or "bilevel positive airway pressure" or "bilevel positive air-way pressure" or "bi-level positive airway pressure" or "bi-level positive air-way pressure" or "biphasic positive airway pressure" or "biphasic positive air-way pressure" or "bi-phasic positive airway pressure" or "bi-phasic positive air-way pressure" OR CPAP or nCPAP or BiPAP OR Vapotherm or Vapo-therm or Optiflow or Opti-flow or "transnasal insuDlation" or "trans-nasal insuDlation" or "Ambu Res-cue mask" or "Ambu Res-cue masks" or Easyfit or Performatrack or Performax or "transnasal mask" or "transnasal masks" or "trans-nasal mask" or "trans-nasal masks" OR "mechanical ventilation" or "mechanical respiration" or "artificial ventilation" or "artificial respiration" or "artificial airway" or "artificial air-way" or "artificial airways" or "artificial air-ways" OR "high frequency ventilation" or "high-frequency ventilation" OR "invasive ventilation" or IMV OR "airway pressure release" and ventilat* OR APRV OR

"positive pressure breathing" AND inspiratory

OR

"positive pressure breathing" AND intermittent

OR

IPPB

OR

"fluoro-carbon" AND ventilat*

OR

fluorocarbon AND ventilat*

OR

"standard oxygen" or "standard O2" or "conventional oxygen" or "conventional O2" or "oxygen therapy" or "O2 therapy" or "oxygen inhalation therapy" or "O2 inhalation therapy" or "enriched air"

OR

"non-invasive" and oxygenat*

OR

noninvasive and oxygenat*

OR

"non-invasive" and ventilat*

OR

non-invasive and ventilat*

OR

Intubat*

OR

"endotracheal tube" or "endotracheal tubes" or "endotracheal tubation" or "endotracheal tubations" or "endotracheal ventilation" or "endo-tracheal tube" or "endo-tracheal tubes" or "endo-tracheal tubation" or "endo-tracheal tubations" or "endo-tracheal ventilation"

OR

tracheostom* OR tracheotom*

(tw:("high flow oxygen" or "high-flow oxygen" or "highflow oxygen" or "high frequency oxygen" or "high-frequency oxygen" or "high flow cannula" or "high-flow cannula" or "highflow cannula" or "high frequency cannula" or "high-frequency cannula" or "high flow cannulae" or "high-flow cannulae" or "highflow cannulae" or "high frequency cannulae" or "high-frequency cannulae" or HFNC or HFOC or "HFN oxygen" or "HFN O2" or "nasal cannula" or "nasal cannulae")) OR (tw:("high flow nasal" or "high-flow nasal" or "highflow nasal" or "high frequency nasal" or "high-frequency nasal")) OR (tw:(NIV or FNIV or "F-NIV" or HNIV or "H-NIV")) OR (tw:("non-invasive" and oxygenat*)) OR (tw:(noninvasive and oxygenat*)) OR (tw:("non-invasive" and ventilat*)) OR (tw:(non-invasive and ventilat*)) OR (tw:("controlled ventilation")) OR (tw:("continuous positive airway pressure" or "continuous positive air-way pressure" or "bilevel positive airway pressure" or "bilevel positive air-way pressure" or "bi-level positive airway pressure" or "bi-level positive air-way pressure" or "biphasic positive airway pressure" or "biphasic positive air-way pressure" or "bi-phasic positive airway pressure" or "bi-phasic positive air-way pressure")) OR (tw:(CPAP or nCPAP or BiPAP)) OR (tw:(Vapotherm or Vapo-therm or Optiflow or Opti-flow or "transnasal insuDlation" or "trans-

	nasal insuDlation" or "Ambu Res-cue mask" or "Ambu Res-cue masks" or Easyfit or Performatrack or Performax or "transnasal mask" or "transnasal masks" or "trans-nasal mask" or "trans-nasal masks")) OR (tw:("mechanical ventilation" or "mechanical respiration" or "artificial ventilation" or "artificial respiration" or "artificial airway" or "artificial air-way" or "artificial airways" or "artificial air-ways")) OR (tw:("high frequency ventilation" or "high-frequency ventilation")) OR (tw:("invasive ventilation" or IMV)) OR (tw:("airway pressure release" and ventilat*)) OR (tw:(APRV)) OR (tw:("positive pressure breathing" AND inspiratory)) OR (tw:("positive pressure breathing" AND intermittent)) OR (tw:(IPPB)) OR (tw:("fluoro-carbon" AND ventilat*)) OR (tw:(fluorocarbon AND ventilat*)) OR (tw:("standard oxygen" or "standard O2" or "conventional oxygen" or "conventional O2" or "oxygen therapy" or "O2 therapy" or "oxygen inhalation therapy" or "O2 inhalation therapy" or "enriched air")) OR (tw:(intubat*)) OR (tw:("endotracheal tube" or "endotracheal tubes" or "endotracheal tubation" or "endotracheal tubations" or "endotracheal ventilation" or "endo-tracheal tube" or "endo-tracheal tubes" or "endo-tracheal tubation" or "endo-tracheal tubations" or "endo-tracheal ventilation")) OR (tw:(tracheostom* OR tracheotom*)) Refined by: Systematic Review, Evidence Synthesis, Broad Synthesis TOTAL: 287 records
Study types	Systematic or rapid reviews
Search date	3 May 2021

PICO 1 – DIRECT: Top-up of RCTs since last SR search date

Database	COVID-19 Global literature on coronavirus disease
URL	https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/
Search terms	"high flow oxygen" or "high-flow oxygen" or "highflow oxygen" or "high frequency oxygen" or "high-frequency oxygen" or "high flow cannula" or "high-flow cannula" or "highflow cannula" or "high frequency cannula" or "high-frequency cannula" or "high flow cannulae" or "high-flow cannulae" or "highflow cannulae" or "high frequency cannulae" or "high-frequency cannulae" or HFNC or HFOC or "HFN oxygen" or "HFN O2" or "nasal cannula" or "nasal cannulae" OR "high flow nasal" or "high-flow nasal" or "highflow nasal" or "high frequency nasal" or "high-frequency nasal" OR NIV or FNIV or "F-NIV" or HNIV or "H-NIV" OR "controlled ventilation" OR "continuous positive airway pressure" or "continuous positive air-way pressure" or "bilevel positive airway pressure" or "bilevel positive air-way pressure" or "bi-level positive airway pressure" or "bi-level positive air-way pressure" or "biphasic positive airway pressure" or "biphasic positive air-way pressure" or "bi-phasic positive airway pressure" or "bi-phasic positive air-way pressure" OR CPAP or nCPAP or BiPAP OR Vapotherm or Vapo-therm or Optiflow or Opti-flow or "transnasal insuDlation" or "trans-nasal insuDlation" or "Ambu Res-cue mask" or "Ambu Res-cue masks" or Easyfit or Performatrack or Performax or "transnasal

	mask" or "transnasal masks" or "trans-nasal mask" or "trans-nasal masks" OR "mechanical ventilation" or "mechanical respiration" or "artificial ventilation" or "artificial respiration" or "artificial airway" or "artificial air-way" or "artificial airways" or "artificial air-ways" OR "high frequency ventilation" or "high-frequency ventilation" OR "invasive ventilation" or IMV OR "airway pressure release" and ventilat* OR APRV OR "positive pressure breathing" AND inspiratory OR "positive pressure breathing" AND intermittent OR IPPB OR "fluoro-carbon" AND ventilat* OR fluorocarbon AND ventilat* OR "standard oxygen" or "standard O2" or "conventional oxygen" or "conventional O2" or "oxygen therapy" or "O2 therapy" or "oxygen inhalation therapy" or "O2 inhalation therapy" or "enriched air" OR "non-invasive" and oxygenat* OR noninvasive and oxygenat* OR "non-invasive" and ventilat* OR non-invasive and ventilat* OR Intubat*

	OR "endotracheal tube" or "endotracheal tubes" or "endotracheal tubation" or "endotracheal tubations" or "endotracheal ventilation" or "endo-tracheal tube" or "endo-tracheal tubes" or "endo-tracheal tubation" or "endo-tracheal tubations" or "endo-tracheal ventilation" OR tracheostom* OR tracheotom* (tw:("high flow oxygen" or "high-flow oxygen" or "highflow oxygen" or "high frequency oxygen" or "high-frequency oxygen" or "high flow cannula" or "high-flow cannula" or "highflow cannula" or "high frequency cannula" or "high-frequency cannula" or "high flow cannulae" or "high-flow cannulae" or "highflow cannulae" or "high frequency cannulae" or "high-frequency cannulae" or HFNC or HFOC or "HFN oxygen" or "HFN O2" or "nasal cannula" or "nasal cannulae")) OR (tw:("high flow nasal" or "high-flow nasal" or "highflow nasal" or "high frequency nasal" or "high-frequency nasal")) OR (tw:(NIV or FNIV or "F-NIV" or HNIV or "H-NIV")) OR (tw:("non-invasive" and oxygenat*)) OR (tw:(noninvasive and oxygenat*)) OR (tw:("non-invasive" and ventilat*)) OR (tw:(non-invasive and ventilat*)) OR (tw:("controlled ventilation")) OR (tw:("continuous positive airway pressure" or "continuous positive air-way pressure" or "bilevel positive airway pressure" or "bilevel positive air-way pressure" or "bi-level positive airway pressure" or "bi-level positive air-way pressure" or "biphasic positive airway pressure" or "biphasic positive air-way pressure" or "bi-phasic positive airway pressure" or "bi-phasic positive air-way pressure")) OR (tw:(CPAP or nCPAP or BiPAP)) OR (tw:(Vapotherm or Vapo-therm or Optiflow or Opti-flow or "transnasal insuDlation" or "trans-nasal insuDlation" or "Ambu Res-cue mask" or "Ambu Res-cue masks" or Easyfit or Performatrack or Performax or "transnasal mask" or "transnasal masks" or "trans-nasal mask" or "trans-nasal masks")) OR (tw:("mechanical ventilation" or "mechanical respiration" or "artificial ventilation" or "artificial respiration" or "artificial airway" or "artificial air-way" or "artificial airways" or "artificial air-ways")) OR (tw:("high frequency ventilation" or "high-frequency ventilation")) OR (tw:("invasive ventilation" or IMV)) OR (tw:("airway pressure release" and ventilat*)) OR (tw:(APRV)) OR (tw:("positive pressure breathing" AND inspiratory)) OR (tw:("positive pressure breathing" AND intermittent)) OR (tw:(IPPB)) OR (tw:("fluoro-carbon" AND ventilat*)) OR (tw:(fluorocarbon AND ventilat*)) OR (tw:("standard oxygen" or "standard O2" or "conventional oxygen" or "conventional O2" or "oxygen therapy" or "O2 therapy" or "oxygen inhalation therapy" or "O2 inhalation therapy" or "enriched air")) OR (tw:(intubat*)) OR (tw:("endotracheal tube" or "endotracheal tubes" or "endotracheal tubation" or "endotracheal tubations" or "endotracheal ventilation" or "endo-tracheal tube" or "endo-tracheal tubes" or "endo-tracheal tubation" or "endo-tracheal tubations" or "endo-tracheal ventilation")) OR (tw:(tracheostom* OR tracheotom*)) Refined by: Controlled Clinical Trial, Year 2020-2021 504 results
Study types	Randomized and non-randomized studies of interventions
Search date	17 June 2021 (alerts continued to Dec 2021, ongoing studies were all checked for results or status changes to same date)

PICO 1 – INDIRECT: Systematic and rapid reviews

Database	Epistemonikos
URL	https://www.epistemonikos.org/
Search terms	(advanced_title_en:(ventilat* OR cannula* OR HFNC OR HFOC OR "HFN oxygen" OR "HFN O2" OR NIV OR FNIV OR "F-NIV" OR HNIV OR "H-NIV" OR "positive airway pressure" OR ""positive air-way pressure" OR CPAP OR nCPAP OR BiPAP OR "high flow oxygen" OR "highflow oxygen" OR "high frequency oxygen" OR oxygenat* OR "high flow nasal" OR "high-flow nasal" OR "highflow nasal" OR "high frequency nasal" OR "transnasal mask" OR "transnasal masks" OR "trans-nasal mask" OR "trans-nasal masks" OR IMV OR "mechanical respiration" OR "artificial respiration" OR "artificial airway" OR "artificial air-way" OR "artificial airways" OR "artificial air-ways" OR "airway pressure release" OR APRV OR "positive pressure breathing" OR "standard oxygen" OR "standard O2" OR "conventional oxygen" OR "conventional O2" OR "oxygen therapy" OR "O2 therapy" OR "oxygen inhalation therapy" OR "O2 inhalation therapy" OR "enriched air" OR intubat* OR tubation* OR tube OR tubes OR tracheostom* OR tracheotom*) OR

	advanced_abstract_en:(ventilat* OR cannula* OR HFNC OR HFOC OR "HFN oxygen" OR "HFN O2" OR NIV OR FNIV OR "F-NIV" OR HNIV OR "H-NIV" OR "positive airway pressure" OR ""positive air-way pressure" OR CPAP OR nCPAP OR BiPAP OR "high flow oxygen" OR "highflow oxygen" OR "high frequency oxygen" OR oxygenat* OR "high flow nasal" OR "high-flow nasal" OR "highflow nasal" OR "high frequency nasal" OR "transnasal mask" OR "transnasal masks" OR "trans-nasal mask" OR "trans-nasal masks" OR IMV OR "mechanical respiration" OR "artificial respiration" OR "artificial airway" OR "artificial air-way" OR "artificial airways" OR "artificial air-ways" OR "airway pressure release" OR APRV OR "positive pressure breathing" OR "standard oxygen" OR "standard O2" OR "conventional oxygen" OR "conventional O2" OR "oxygen therapy" OR "O2 therapy" OR "oxygen inhalation therapy" OR "O2 inhalation therapy" OR "enriched air" OR intubat* OR tubation* OR tube OR tubes OR tracheostom* OR tracheotom*)) AND (advanced_title_en:((advanced_title_en:(acute respiratory distress) OR advanced_abstract_en:(acute respiratory distress)) OR (advanced_title_en:(ards) OR advanced_abstract_en:(ards)) OR (advanced_title_en:(acute hypoxemic respiratory failure) OR advanced_abstract_en:(acute hypoxemic respiratory failure)) OR (advanced_title_en:(acute hypoxaemic respiratory failure) OR advanced_abstract_en:(acute hypoxaemic respiratory failure)) OR (advanced_title_en:(AHRF) OR advanced_abstract_en:(AHRF)) OR (advanced_title_en:(shock lung) OR advanced_abstract_en:(shock lung))) OR advanced_abstract_en:((advanced_title_en:(acute respiratory distress) OR advanced_abstract_en:(acute respiratory distress)) OR (advanced_title_en:(ards) OR advanced_abstract_en:(ards)) OR (advanced_title_en:(acute hypoxemic respiratory failure) OR advanced_abstract_en:(acute hypoxemic respiratory failure)) OR (advanced_title_en:(acute hypoxaemic respiratory failure) OR advanced_abstract_en:(acute hypoxaemic respiratory failure)) OR (advanced_title_en:(AHRF) OR advanced_abstract_en:(AHRF)) OR (advanced_title_en:(shock lung) OR advanced_abstract_en:(shock lung)))) [Filters: protocol=no, classification=systematic-review]
Study types	Systematic or rapid reviews
Search date	18 May 2021

PICO 1 – INDIRECT: Top-up of RCTs since last SR search date

Database	EBM Reviews - Cochrane Central Register of Controlled Trials
URL	https://www.wolterskluwer.com/en/solutions/ovid/evidencebased-medicine-reviews-ebmr-904
Search terms	1 respiratory distress syndrome, adult/ (37) 2 ((respiratory or respiration or lung or ventilatory) adj2 (depress* or insufficien* or fail* or deficien* or disturb* or dysfunction* or compromis*) adj3 (acute or adult)).ti,ab,kw. (1910) 3 (lung adj1 shock).ti,ab,kw. (10) 4 ARDS.ti,ab,kw. (2155) 5 ARDSS.ti,ab,kw. (0) 6 exp Respiratory Insufficiency/ (2829) 7 (respiratory failure adj3 hypox?emi*).ti,ab,kw. (404) 8 (respiratory failure adj3 hypercapni*).ti,ab,kw. (327) 9 AHRF.ti,ab,kw. (90) 10 (acute adj2 (hypoxia or hypox?emi*)).ti,ab,kw. (670) 11 or/1-10 [ARDS/AHRF] (6797) 12 Cannula/ (113) 13 Oxygen/ (5200) 14 Oxygen Inhalation Therapy/ (1164) 15 11 and (13 or 14) (456) 16 ((high-flow or highflow or high-frequency or prolong*) adj3 cannula*).ti,ab,kw. (908)

	17 ((high-flow or highflow or high-frequency or prolong*) adj3 nasal*).ti,ab,kw. (1332) 18 ((high-flow or highflow or high-frequency or prolong*) adj3 (oxygen* or O2)).ti,ab,kw. (1097) 19 (HFNC or HFNO or HFNP or HFOC).ti,ab,kw. (561) 20 (("positive pressure" or "positive end-expiratory pressure") adj3 (respirat* or ventilat*)).ti,ab,kw. (2211) 21 continuous positive airway pressure.ti,ab,kw. (3829) 22 (CPAP or nCPAP).ti,ab,kw. (5110) 23 (airway pressure release adj3 ventilat*).ti,ab,kw. (80) 24 APRV.ti,ab,kw. (69) 25 ((inspiratory or intermittent) adj3 positive pressure breathing).ti,ab,kw. (75) 26 IPPB.ti,ab,kw. (69) 27 ((non-invasive or noninvasive) adj3 (oxygen* or ventilat*)).ti,ab,kw. (3456) 28 controlled ventilation.ti,ab,kw. (849) 29 (bi level positive airway pressure or bilevel positive airway pressure or bi-level positive airway pressure or BiPaP or NIV).ti,ab,kw. (1635) 30 (FNIV or F-NIV or H-NIV or HNIV).ti,ab,kw. (20) 31 standard oxygen.ti,ab,kw. (206) 32 ((low flow or low-flow or lowflow) adj2 oxygen*).ti,ab,kw. (206) 33 ((mask* or helmet*) adj1 (face or oxygen)).ti,ab,kw. (1826) 34 (Ambu Res-cue mask* or Easyfit or Performatrack or Performax or transnasal mask* or facemask* or face-mask*).ti,ab,kw. (2042) 35 controlled ventilation.ti,ab,kw. (849) 36 exp Respiration, Artificial/ (6241) 37 exp Ventilators, Mechanical/ (268) 38 ((artificial* or mechanical*) adj3 (respirat* or ventilat*)).ti,ab,kw. (15417) 39 artificial airway?.ti,ab,kw. (98) 40 ((assist* or depend* or support*) adj3 (respirat* or ventilat*)).ti,ab,kw. (5925) 41 ((liquid or fluorocarbon or fluoro-carbon) adj3 ventilat*).ti,ab,kw. (42) 42 (high-frequency adj3 ventilat*).ti,ab,kw. (569) 43 (invasive* adj3 (oxygen* or ventilat*)).ti,ab,kw. (3149) 44 [IMV.tw,kf.] (0) 45 or/15-44 [VENTILATION OPTIONS] (30378) 46 11 and 45 [ARDS/AHRF - VENTILATION OPTIONS] (3698) 47 (202012* or 2021*).up. (642312) 48 46 and 47 [UPDATE PERIOD] (1817)
Study types	Randomized studies published after the date of the last indirect PICO SR or RR search (December 1, 2020 based on included SR)

Search date	Dec 1 2020 to 1 Jun 2021 (alerts continued to Dec 2021)

Annex 4: Description of included studies (Section 11)

Direct PICO: Severe or critical COVID-19 patients with acute hypoxaemic respiratory failure and not requiring emergent intubation:

Five randomized controlled trials (RCTs) of non-invasive ventilation strategies in hospitalized patients with severe or critical COVID-19 and acute hypoxaemic respiratory failure not requiring emergent intubation were identified *[69][70][71][72][73]*. This evidence was collected using the included study lists of **three relevant systematic reviews, four rapid reviews, and a top-up search** of bibliographic databases for more recent RCTs (with alerts until December 2021) *[3]*.

Summary of included RCTs:

Study/ Design	Population	Country/ Setting	Interventions	Outcomes reported
Li et al. 2020 *[72]* two-arm, parallel RCT N=72	Patients with severe coronavirus pneumonia complicated with acute respiratory failure	China, isolation ward of a single centre	HFNO [n=37] Standard oxygen therapy [n=35]	Mechanical ventilation at 12 h No patient-reported outcomes
Grieco et al. 2021 *[70]* HENIVOT two-arm, parallel RCT N=109	Patients admitted to the intensive care unit with COVID-19–induced moderate to severe hypoxaemic respiratory failure	Italy, ICUs in four centres	Helmet NIV [n=55] HFNO [n=54]	Intubation, 28 d Hospital LOS ICU LOS Patient-reported: Device-related discomfort
Perkins et al. 2021 *[73]* RECOVERY-RS three-arm, adaptive RCT N=1272	Hospitalized adults with acute respiratory failure due to COVID-19 were deemed suitable for tracheal intubation if treatment escalation was required	United Kingdom, 75 hospitals	CPAP [n=380] HFNO [n=417] Standard oxygen therapy [n=475] (primary comparisons were CPAP to standard oxygen and HFNO to standard oxygen)	Mortality, 30 d Intubation, 30 d Tracheal intubation during the study period Critical care

Study/ Design	Population	Country/ Setting	Interventions	Outcomes reported
				(ICU) LOS Hospital LOS No patient-reported outcomes
Teng et al. 2021 *[69]* two-arm, parallel RCT N= 22	Patients diagnosed with severe COVID-19.	China, single centre	HFNO [n=12] Standard oxygen therapy [n=10]	Mortality (indirect) Hospital LOS ICU LOS No patient-reported outcomes
Ospina-Tascón et al. 2021 *[71]* Two-arm, open-label parallel RCT N=199	Adult patients admitted to the emergency department, general ward, or intensive care unit with acute respiratory failure and COVID-19	Colombia, three centres	HFNO [n=99] Standard oxygen therapy [n=100]	Mortality, 28 d Intubation, 28 d Hospital LOS ICU LOS No patient-reported outcomes

d=days; h=hours; HFNO=high flow nasal oxygen; ICU=intensive care unit; LOS=length of stay; RCT=randomized controlled trial; QoL=quality of life.

Indirect PICO: Non-COVID-19 ARDS patients with acute hypoxaemic respiratory failure not requiring emergent intubation

22 completed randomized controlled trials (RCTs) from 24 reports of non-invasive ventilation support in hospitalized patients with acute respiratory distress syndrome (ARDS) and acute hypoxaemic respiratory failure (AHRF) not requiring emergent intubation were identified *[3]*.

This evidence was collected using the included study lists of **four systematic reviews (SRs)** *[3]*. **A top-up search** of study registry databases found no additional eligible RCTs. None of the included SRs included RCTs relevant to the indirect PICO with patient-reported outcomes such as comfort or satisfaction with care.

Annex 5: Case definitions of MIS-C (Section 14)

Organization	Case definition
World Health Organization	1. Age 0 to 19 years; AND 2. Fever for ≥ 3 days; AND 3. Clinical signs of multisystem involvement (at least two of the following): • rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet); • hypotension or shock; • cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP); • evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer); • acute gastrointestinal symptoms (diarrhoea, vomiting, or abdominal pain); AND 4. Elevated markers of inflammation (e.g. ESR, CRP, or procalcitonin); AND 5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/ streptococcal toxic shock syndromes; AND 6. Evidence of SARS-CoV-2 infection with ANY of the following: positive SARS-CoV-2 RT-PCR; positive serology; positive antigen test; contact with an individual with COVID-19.
US CDC	1. Individual < 21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, haematologic, gastrointestinal, dermatologic or neurological); AND 2. No alternative plausible diagnoses; AND 3. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.
Royal College of Paediatrics and Child Health (RCPCR)	1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single- or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease. 2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus. 3. SARS-CoV-2 PCR testing may be positive or negative.

Web annex: GRADE recommendations - additional information

The web annex for the Clinical management of COVID-19 patients: living guidance (second version, 25 January 2021) PDF can be found here: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2.

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