

Guideline

The Saudi Critical Care Society Clinical Practice Guidelines on the Management of COVID-19 Patients in the Intensive Care Unit

Abstract

Background: Although recent international guidelines have been published on the management of critically ill patients with the novel coronavirus disease 2019 (COVID-19), there is a vital need to develop clinical practice guidelines tailored to the context of Saudi Arabia. **Methods:** The Saudi Critical Care Society (SCCS) is the sponsor for this guideline. The expert panel consisted of 19 members. All members completed the World Health Organization Conflict of Interest Form. The expert panel formulated questions on the management of critically ill patients in the intensive care unit with COVID-19. Panel members identified relevant studies. The panel used the categories of Grading Recommendations, Assessment, Development, and Evaluation (GRADE) to assess the confidence in the evidence. **Results:** The SCCS expert panel issued 53 statements; of which 7 were strong recommendations, 9 were best practice statements, 32 were weak recommendations, and we were not able to issue recommendations in 5 instances. The statements covered different aspects of the critical illness in COVID-19 patients, including: infection control; therapeutic interventions; supportive care; and crisis management. **Conclusion:** The SCCS guidelines on the management of critically ill COVID-19 patients have been based on the best available evidence and tailored to the context of Saudi Arabia. These guidelines will be updated periodically to incorporate new evidence.

Keywords: ARDS, COV-2, COVID-19, Critical Care, Intensive Care Unit, Practice Guidelines, SARs

Introduction

The recent viral outbreak first identified in Wuhan, China has now crossed most borders and had spread into more than 224 countries.^[1] The outbreak is caused by a virus that belongs to the Coronaviridae family of viruses. Coronaviruses are RNA viruses, having RNA as their genome.^[1] The recent outbreak is caused by a novel strain of coronavirus which is very similar to the SARS-CoV that resulted in the SARS outbreak. Initially, it was named as 2019-nCoV. Recently it has been renamed by the International Committee on Taxonomy of Viruses (ICTV) as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2).^[2] The World Health Organization (WHO) has termed it coronavirus disease 2019 (COVID-19).^[3] the WHO characterized the new COVID-19 as a pandemic, the first pandemic ever caused by a coronavirus.^[4] According to the WHO, as of May 5th, 2020, there were over 3 million confirmed COVID-19 cases, causing over 100,000 deaths globally.

Saudi Arabia has commenced number of actions, including screening for travelers that were made to prevent an outbreak. The Ministry of Health and the Saudi Center for Disease Prevention and Control have published the Coronavirus Infection Guidelines along with other guidelines that should help to detect and prevent an epidemic. A decision was made to develop clinical practice guidelines for critically ill patients with COVID-19 in the intensive care unit (ICU) by the Saudi Critical Care Society, as the governing body of critical care practice in Saudi Arabia. The objectives of these guidelines were to provide guidance and recommendations to help hospitals in Saudi Arabia prepare for an outbreak of COVID-19 and standardize clinical management pathways for COVID-19 patients in the ICU.

Scope of Guidelines

The scope of the current guidelines is to provide recommendations to the critical care teams providing care to critically ill

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patients with COVID-19 in the ICU. The target users of this guideline are: intensivists; nurses; respiratory therapists; clinical psychologists, clinicians involved in the care of critically ill COVID-19 patients, and policymakers.

Panel Expertise

The Saudi Critical Care Society (SCCS) selected expert panel members in order to issue recommendations in a timely manner. The expert panel was instructed to develop the guidelines based on their expertise and evidence within a set length of time. The panel included experts in critical care, infection control, respiratory therapy, nursing, public health and clinical psychology.

Methods

Data sources and evidence assessment

Each panelist was assigned one or more guideline questions. Panelists reviewed the recently published Surviving Sepsis Campaign guidelines to structure some of the guideline questions and identify relevant evidence. They performed their own searches to identify additional relevant evidence for each question.

We relied on direct COVID-19 evidence wherever available, but we relied on indirect evidence from acute respiratory distress syndrome, sepsis, and other coronaviruses when applicable. We did not perform a systematic appraisal or grading of the evidence.

Recommendation formulation

The guideline covered three major domains related to COVID-19. These were: 1) infection control, 2) therapeutic interventions, and 3) critical care managerial strategies. Each panelist reviewed the evidence on the assigned question, drafted a preliminary recommendation, and then presented the recommendation to the panel. Consensus was reached by discussion between panel members on teleconferences and electronically. We used “we

recommend” for strong recommendations and “we suggest” for weak recommendations.

Infection control

The WHO and the United States Center for Disease Control and Prevention (CDC) have issued guidelines on infection control in hospital settings. Recently, the Surviving Sepsis Campaign COVID-19 guidelines issued recommendations related to infection control in the ICU.^[5] In this section the panel addressed pertinent infection control questions and issued evidence-based recommendations.

Recommendations

Recommendation 1

For healthcare workers performing (or in proximity to) an aerosol generating procedure (AGP) on COVID-19 patients, we recommend using fitted N95 respirators or equivalent in addition to other personal protective equipment (PPE) (best practice statement).

When fitted N95 respirators are not available or a healthcare worker fails fit-testing, we recommend using a Powered Air-Purifying Respirator (PAPR).

Rationale

A recent report from Chinese CDC stated that, among laboratory-confirmed cases, 1,716 (3.8%) were healthcare workers; among them, 14.8% had severe or critical illness and, of them, 5 died.^[6] In Italy, as of March 15, 2020, there were 2026 healthcare workers with confirmed COVID-19.^[7] These observations indicate a great burden of infection among healthcare workers. Therefore, we recommend adhering to infection control measures in the ICUs. Respirator masks can block 95 to 99% of aerosol particles and, therefore, should always be used when performing an AGP. Surgical masks are deemed to block only large particles or droplets and are less efficient in blocking small aerosol particles (<5 micrometers).^[8] Our recommendation is consistent with existing CDC, WHO, and other guidelines.

Recommendation 2

For healthcare workers performing non-aerosol generating procedures or providing care to COVID-19 patients; we **suggest** using surgical masks instead of respirator masks, in addition to other PPE (weak recommendation).

Rationale

A recent systematic review of 4 RCTs showed that N95 did not reduce the risks of laboratory-confirmed viral infection or clinical respiratory illness in healthcare workers, compared to surgical masks.^[9] The results are indirect and do not apply to the context of AGP and, therefore, should be interpreted with great caution.

A study from South Korea showed that surgical masks did not effectively filter SARS-CoV-2 during coughing by infected patients.^[10] Until more evidence is available and, given the global shortage of PPE, the panel felt that the use of surgical masks when caring for CPVOD-19 patients (who are not undergoing an AGP) in the ICU is an acceptable option.

Recommendation 3

For healthcare workers in the ICU, we suggest wearing a single surgical/medical mask when caring for known or suspected COVID-19 patients (weak recommendation).

Remarks: The masks must be changed if they become wet or contaminated. The masks are not allowed to be worn outside the clinical care areas, nor to be hung around the neck or kept in a pocket. Proper hand hygiene should be done before donning and doffing. A recent study reported the rationing of PPE to the medical staff in Singapore. They are given only 2 sets of PPE and are directed to use one set in the first half and the second set in the second half of their shift while masks are worn at all times and only changed when contaminated or at midway point in the shift.^[11]

Rationale

This recommendation follows the guideline of universal masking released by Saudi CDC, Ministry of Health, Saudi Arabia. Surgical masks are recommended to provide protection to patients and healthcare workers from exposure to infection from asymptomatic healthcare workers with COVID-19. They are also intended to provide protection for the healthcare workers from undiagnosed asymptomatic patients and patients having mild COVID-19.

Recommendation 4

For healthcare workers using an N95 respirator or surgical/medical mask, we recommend using additional PPE including gloves, gown, and eye protection; i.e., face shield or safety goggles (best practice statement).

Rationale

This recommendation is in line with the WHO guidelines for the use of PPE in healthcare and community settings while dealing with COVID-19.^[12]

Recommendation 5

For healthcare workers interacting with COVID-19 patients, we recommend maintaining hand hygiene (best practice statement).

Remark: Hands should be washed before putting on or removing masks.

Rationale

A recent report highlighted that healthcare workers are directed to use the restroom at the midpoint of their shift and use alcohol rub/gel prior to using or disposing of masks.^[11] Hand hygiene is crucial to prevent the transmission of coronaviruses. A 2015 study found that people touch their faces on an average of 23 times an hour; therefore, hand hygiene may reduce virus transmission.^[13] This recommendation is consistent with the WHO guidance.^[14]

Recommendation 6

We suggest minimizing unnecessary interaction and maintaining physical distancing in ICUs (weak recommendation).

Rationale

A recent study in Singapore described how physicians were split into teams of 4, doing 12 hour shifts alternately. These teams did not interact with each other. If a doctor in the team fell ill, the team covered him or her. Functional redundancy and rest periods are set to ensure that the physicians take enough rest.^[11] There is insufficient indirect evidence on the effect of social distancing in healthcare workers.^[15] However, due to the simplicity and lack of downsides for practicing physical distancing at work, we suggest maintaining physical distancing among healthcare workers.

Recommendation 7

We recommend performing AGPs on ICU COVID-19 patients in negative pressure rooms with at least 12 air-changes per hour and controlled direction of air flow (best practice statement).

Rationale

In negative pressure rooms, a negative pressure is created and maintained to avoid the accidental release of pathogens outside the room. Studies report that negative pressure rooms were useful in preventing cross-contamination during the SARS epidemic.^[16] The WHO also recommends performing AGPs such as bronchoscopies and non-invasive ventilation, in negative pressure rooms^[17-19]

Recommendation 8

We recommend limiting the number of healthcare workers in the room to the minimum required to provide care for COVID-19 patients (best practice statement).

Rationale

This approach was implemented during the MERS epidemic and was perceived to be effective in controlling the infection. Therefore, it can be implemented in COVID-19 prevention. This guideline is in accordance with the Saudi Center for Disease Management and Control.

Recommendation 9

For COVID-19 patients needing endotracheal intubation, we **recommend** that an experienced healthcare provider in airway management performs the endotracheal intubation to decrease the number of attempts and the risk of disease transmission (best practice statement).

Rationale

Endotracheal intubation is an AGP, and is associated with higher risk of disease transmission to healthcare workers.^[20] Therefore, minimizing the number of attempts and the time spent during endotracheal intubation will help reduce exposure time and possible transmission risk.

Recommendation 10

We suggest providing clean scrubs for healthcare workers to use during working hours and access to changing rooms and showering facilities, if applicable (weak recommendation).

Rationale

This would result in avoidance of cross-contamination among healthcare workers.^[19] This approach was supported by the CDC during the Ebola epidemic and by recent articles supporting healthcare workers during the COVID-19 pandemic to minimize contamination of personal clothing and disease transmission.^[21,22]

Recommendation 11

We suggest using disposable bronchoscopes when performing bronchoscopy or percutaneous tracheostomy on patients with COVID-19 (weak recommendation).

Rationale

Disposable bronchoscopes are available in Saudi Arabia and are commonly used when there are concerns about disease transmission. Although clinicians should minimize the number of AGPs on patients with COVID-19, if bronchoscopy is indicated and disposable bronchoscopes are available, clinicians may consider using them. Recent reports from Singapore showed that they used disposable bronchoscopes to perform the procedure when indicated.^[19]

Therapeutic Interventions

Antiviral therapy

Several ongoing clinical trials are investigating the potential therapeutic regimens for COVID-19. Antiviral therapy might improve clinical outcomes as critically ill patients

has a prolonged detection of SARS-CoV-2 RNA in their respiratory tract and other sites. Currently, no direct-acting antiviral agents improve the outcomes of patients with COVID-19. Many drugs approved for other indications have been anticipated as a potential treatment of COVID-19 and are undergoing clinical trials in many countries. The drugs are used either alone or in combination. They include arbidol, chloroquine, hydroxychloroquine, favipravir, interferons, ivermectin, lopinavir/ritonavir, remdesivir, ribavirin, and traditional Chinese medicines. Our recommendations are based on published literature up to April 12, 2020 and will be updated as evidence evolves.

Recommendation 12

We recommend not using high-dose hydroxychloroquine or chloroquine in critically ill adults with COVID-19 (weak recommendation).

We make no recommendation on the use of usual-dosing hydroxychloroquine or chloroquine in critically ill adults with COVID-19 outside clinical trials.

Rationale

Early *in vitro* studies showed that chloroquine and hydroxychloroquine inhibit SARS CoV-2 replication.^[23,24] Chloroquine and hydroxychloroquine can impair the replication of several viruses by interacting with the endosome-mediated viral entry or the late stages of replication of enveloped viruses,^[25] they increase the pH of intracellular vacuoles and alter protein degradation pathways through acidic hydrolases in the lysosomes, macromolecule synthesis in the endosomes, and post-translational protein modification in the Golgi apparatus.^[25]

There are several ongoing RCTs investigating the efficacy of these agents in COVID19.^[26] Currently, there are no clinical trials to support the use of chloroquine or hydroxychloroquine.

Recent news briefings from China on 10 trials that included more than 100 patients reported that “chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course”. However, the results have not yet been published.^[27] An open-label non-randomized clinical trial conducted in France reported on 42 patients with COVID-19; among these, 16 patients received usual care and were classified as “controls”, and 26 patients were treated with hydroxychloroquine; of those, 20 patients completed the study, and 6 patients received azithromycin in addition to hydroxychloroquine. Azithromycin was given as a single dose of 500 mg, then followed by 250 mg for 4 days to prevent secondary bacterial infection. Patients’ nasopharyngeal swabs were tested daily where the presence or absence of SARS CoV-2 on the 6th day was the primary end-point. Virologic clearance was achieved in all patients treated with hydroxychloroquine and azithromycin, compared with 57.1% in patients treated with hydroxychloroquine

alone, and 12.5% patients in the control arm ($P < 0.001$).^[28] Despite the small number of patients, this study has gained enormous attention worldwide. However, the study has many limitations. Unblinding and non-randomization of patients was subjected to bias as the patients were chosen to be either treated or serve as controls. In addition, the control group and treatment group were not balanced with regards to important baseline variables. Moreover, the patients in the control group were allocated at different centers to the treatment group; hence, the care was not standardized between these centers. Lastly, six patients in the treatment group were excluded due to several reasons which could have introduced attrition bias.

A recent expert consensus in China recommended using chloroquine phosphate at 500 mg twice daily for 10 days (with a minimum of 5 days) for patients with COVID-19 pneumonia.^[29] An *in vitro* study has shown hydroxychloroquine to be more potent than chloroquine against SARS-CoV-2, and based on pharmacokinetic models, hydroxychloroquine sulfate was recommended to be given orally in a loading dose of 400 mg twice daily, followed by a maintenance dose of 200 mg given twice daily for 4 days.^[3] This can serve as an alternative to chloroquine in countries with a chloroquine shortage. The results of many clinical trials are still pending; therefore, a recommendation for or against the use of chloroquine and hydroxychloroquine therapy cannot be issued.

Recently, an RCT compared high dose hydroxychloroquine (600 mg twice daily) versus a lower dose (450 mg twice daily) was stopped early for increased risk of cardiac adverse effects in the high dose arm and possible increased risk of death.^[30]

Recommendation 13

We suggest not using lopinavir/ritonavir for the treatment of critically ill adult patients with COVID-19 outside the context of clinical trials (weak recommendation).

Rationale

Lopinavir is an anti-retroviral protease inhibitor used for the treatment of human immunodeficiency virus infection, in combination with ritonavir to enhance lopinavir exposure.^[31] Lopinavir/ritonavir are recorded as having *in vitro* activity against SARS-CoV-1^[32] and MERS-CoV.^[33] A recently published randomized open-label trial included 199 hospitalized patients with laboratory-confirmed SARS-CoV-2 infection in China. In this trial, 199 patients were assigned to the lopinavir/ritonavir group, and 100 patients to the standard care group. There was no statistical difference in 28-day mortality and time to clinical improvement between the two groups.^[34] Even though this trial serves as the only available evidence for treatment of COVID-19 patients with lopinavir/ritonavir, it has several limitations. The trial was unblinded which could have introduced performance bias, and the results were imprecise due to the small number of patients. Therefore, the suggestion not to routinely use lopinavir/

ritonavir in critically ill adult patients with COVID-19 disease is reasonable. Lopinavir/ritonavir is one of the arms in a core treatment study protocol planned by WHO for COVID-19 patients,^[35] and in a trial to evaluate multiple treatment strategies for pneumonia in critically ill patients “REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) trial (NCT02735707)”. The evidence on lopinavir/ritonavir is still evolving and will help in the precision of the recommendations.

Recommendation 14

We make no recommendation on the use of other antiviral agents outside the context of clinical trials.

Rationale

Remdesivir is an investigational drug (with a development code GS-5734), undergoing clinical trials and has not yet been approved or licensed. It is considered a potential treatment for COVID-19 and recommended by WHO for research prioritization of candidate therapeutic drugs.^[35]

Remdesivir is an adenosine analog and monophosphoramidate prodrug. Remdesivir is metabolized into GS-441524, its active form, that blocks viral RNA polymerase, causing a decrease in viral RNA production.^[36] *In vitro* studies have demonstrated remdesivir's antiviral activity against SARS-CoV, MERS-CoV, and SARS-CoV-2.^[36] It was shown to be superior to lopinavir/ritonavir in animal models of MERS-CoV when combined with systemic IFN- β .^[37,38] Currently, there are several ongoing RCTs, intended to study the efficacy and safety of intravenous remdesivir versus placebo for severe COVID-19 (clinicaltrials.gov NCT04257656), and for mild/moderate COVID-19 (clinicaltrials.gov NCT04252664). Many Phase III trials to evaluate the safety and antiviral activity of remdesivir in COVID-19 patients are recruiting patients (clinicaltrials.gov NCT04292899, NCT04292730).

Another adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19 in the USA is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), and its results are currently analyzed and are expected shortly (clinicaltrials.gov NCT04280705). Of note, on the basis of data available to them NIH issued emergency authorization for the use of this drug. Until clinical evidence is available we cannot, however, issue a recommendation for or against the use of remdesivir; we can only encourage its use in the context of clinical trials.

Recommendation 15

We make no recommendation on the use of recombinant interferons, they are better used in the context of clinical trials.

Rationale

Recombinant interferons have been investigated previously in many viral infections including SARS-CoV and MERS-CoV, mainly in combination with ribavirin or antiretroviral agents due to their *in vitro* activity against these viruses.^[39-43] In a large multicenter observational study conducted in Saudi Arabia in critically ill patients with MERS-CoV, interferons in combination with ribavirin were not associated with reduction in 90-day mortality or viral clearance.^[43] Another RCT in Saudi Arabia is currently recruiting patients to study the efficacy of recombinant interferon beta 1b in combination with lopinavir/ritonavir for the treatment of MERS-CoV.^[44] Interferons might be a potential treatment option for COVID-19 as they have been prioritized for research. The current guidelines will be updated based on the development of new evidence.

Recommendation 16

There is insufficient evidence on the use of convalescent plasma; therefore, we make no recommendation on its use in critically ill patients with COVID-19.

Rationale

Transfusing plasma obtained from COVID-19 patients who recovered from their illness has been proposed as a potential therapeutic option. A systematic review of observational studies that reported on the use of convalescent plasma in other coronaviruses and influenzas showed an association with reduced odds of death (OR 0.25; 95% CI 0.14, 0.45).^[45-47] Recent case series have showed that most patients with COVID-19 who received convalescent plasma had clinical and biochemical improvement.^[48] However, these studies lacked a control arm, and many co-interventions were administered; therefore, we cannot make any strong inferences. Given the uncertainty about the effect of convalescent plasma on COVID-19 patients' outcomes, the panel elected not to issue a recommendation until more evidence is available. Multiple RCTs are ongoing.

Recommendation 17-18

For critically ill adults with COVID-19, we suggest measuring D-dimer level (weak recommendation).

For critically ill adults with elevated D-dimer levels and no contraindication for anticoagulation, we recommend using unfractionated or low molecular weight heparin at prophylactic doses (strong recommendation).

We make no recommendation on the use of systemic anticoagulation in the absence of venous thromboembolic disease in COVID-19 patients.

Rationale

Autopsy reports of deceased patients with COVID-19 showed evidence of microvascular thrombosis and pulmonary infarction.^[49] Furthermore, several studies

have shown that patients with elevated D-dimer level are at higher risk of death. It is not clear if the elevated d-dimer level is caused by thrombosis or inflammation. Nevertheless, observational studies have showed a higher risk of thrombosis in critically ill COVID-19 patients.^[50] One observational study has showed that patients who received prophylactic dosing of heparin were at lower risk of death compared to those who did not: the results are hypothesis-generating and further high-quality studies are needed to determine the effect of anticoagulation in this population. However, because VTE prophylaxis is considered the standard of care for critically ill patients, we recommend using subcutaneous heparin, if no contraindication, at prophylactic doses.

Ventilatory support

Recommendations 19-23

We recommend starting supplemental oxygen for COVID-19 patients with SpO₂ is <90% (strong recommendation),

We suggest targeting SpO₂ of 92% to 96% when treating hypoxemic patients with COVID-19 (weak recommendation).

Supplemental oxygen for up to 5 L/minute can be given via nasal cannula or simple face mask, may use face mask with a reservoir bag (at 10-15 L/minute) if needed. Nasal prongs or a nasal cannula are preferred in young children.

If targeted SpO₂ is not achieved despite conventional oxygen therapy, we suggest using high flow nasal cannula (HFNC) over conventional oxygen therapy for adults and pediatrics with COVID-19 (weak recommendation).

We recommend using HFNC in a negative pressure room, and that healthcare workers use airborne precautions when interacting with these patients (best practice statement).

For adults with COVID-19 on HFNC, we suggest using surgical masks to cover the patient's mouth and nose and minimize aerosolization (weak recommendation).

Rationale

In a Chinese study, the prevalence of hypoxemic respiratory failure in COVID-19 patients was about 19%. Most cases were mild 81%, whereas 14% were severe and 5% were critical with complications, such as respiratory failure, septic shock, and multi-organ failure.^[6] The risk factors associated with respiratory failure requiring mechanical ventilation are not well-described. However, risk factors associated with critical illness and ICU admission were older age, male gender, and the present of pre-existing comorbidities.^[6,51]

Indirect RCTs have showed that a liberal oxygen strategy increases hospital mortality and that there was a linear association between higher SPO₂ and mortality^[52]. Furthermore, in the context of a pandemic, oxygen becomes a valuable resource that should only be used if needed. Our

recommendations are consistent with those of the Surviving Sepsis Campaign COVID-19 guidelines.^[5]

Close monitoring of patients on conventional oxygen therapy is essential for early recognition of respiratory failure and to ensure timely and safe initiation of respiratory support. In this case, HFNC can be considered over conventional oxygen therapy. Meta-analyses of RCTs in non-COVID patients showed that HFNC, compared to conventional oxygen, was associated with reduced intubation rate.^[52,53] The reduced need for intubation reported with the application of HFNC alone is very important, especially with increased demand for critical care during a pandemic.^[5]

Practical consideration

Before applying HFNC, the patient must be moved to a negative pressure room. The air exiting a negative pressure room should be filtered with a high-efficiency particulate air (HEPA) filter. Entry to the patient's room while receiving HFNC oxygen therapy should be minimized. A surgical mask applied to the patient while receiving HFNC oxygen therapy may lower the health workers' exposure overall.

Recommendations 24 – 25

If HFNC is not available or fails to provide required support, and immediate endotracheal intubation is not indicated, we suggest a trial of non-invasive positive pressure ventilation (NIPPV), with close monitoring for clinical deterioration and the need for urgent intubation (weak recommendation).

We recommend using NIPPV in a negative pressure room, and that healthcare workers use airborne precautions and PPEs when interacting with these patients (best practice statement).

Remarks: the patient interface should be selected based on institutional guidelines and tailored to achieve patient comfort and minimal leak. Infection control measures should be taken due to aerosol generation from the leak port. Commercially available filters that can be fitted to the leak port could be used.

Rationale

Critically ill adult patients with COVID-19 commonly present with acute hypoxic respiratory failure and ARDS.^[6,51] An RCT showed that NIPPV has a higher mortality rate when compared with conventional oxygen therapy and HFNC.^[60] NIPPV did not reduce mortality nor length of stay when compared with invasive mechanical ventilation.^[61] The role of NIPPV in respiratory pandemics is not clear [1]. Possible complications associated with NIPPV are high transpulmonary pressure and tidal volumes leading to ventilator induced lung injury (VILI), and delay in initiating invasive ventilation.

^[54,55] Moreover, NIPPV is an AGP which increases the risk of disease transmission.^[20] Consequently, the routine use of NIPPV in critically ill adults with COVID-19 should be avoided, but when conventional oxygen therapy or HFNC fail to provide required support then, a trial NIPPV is not unreasonable [1]; this may avoid the need for intubation and mechanical ventilation, especially with limited resources during a pandemic [1,19]. When NIPPV is used, close patient monitoring especially within the first 1-2 hours should be continued; if no improvement, then intubation and invasive mechanical ventilation should be considered.

Practical considerations

Before using HFNC or NIPPV, the patient must be moved to a negative pressure room. The air exiting a negative pressure room should be filtered with a high-efficiency particulate air (HEPA) filter. Entry to the patient's room while receiving HFNC oxygen therapy should be minimized. HFNC or NIPPV should be used selectively after balancing the risks and benefits to the patient and the risk of exposure to healthcare workers. Younger patients with no comorbidities may tolerate HFNC or NIV better than older patients with comorbidities. Patients with abnormal mental status, hemodynamically instability, and/or multiorgan failure should generally not receive HFNC or NIPPV. Patients receiving HFNC or NIPPV should be closely monitored for clinical deterioration or lack of improvement, with availability of personnel capable of endotracheal intubation if required.

Recommendation 26-27

When initiating invasive mechanical ventilation for adults with COVID-19 and moderate to severe ARDS; We recommend: using volume or pressure control modes; targeting a tidal volume of 6 ml/kg (4-8 ml/kg) of predicted body weight (PBW); and maintaining plateau pressure <30 cm H₂O (strong recommendation).

If plateau pressure is >30 cm H₂O, we suggest decreasing the tidal volume by 1 ml/kg increments to a minimum of 4 ml/kg PBW (weak recommendation).

We suggest setting the positive end expiratory pressure (PEEP) at 5 cm H₂O, then applying the PEEP/FiO₂ table from ARDS Network Protocol to adjust to appropriate PEEP level for the patient (see exception in the next recommendations) (weak recommendation).

We suggest using a higher PEEP strategy (>10 cm H₂O), over a lower PEEP strategy, only in patients with low lung compliance who are PEEP responsive (weak recommendation).

When applying a high PEEP strategy, patients should be monitored for barotrauma and worsening hemodynamics.

Rationale

Adults with COVID-19 requiring invasive ventilation due to acute respiratory failure are severely ill, and several pathology reports have showed diffuse alveolar damage and other findings commonly seen in ARDS.^[56] Therefore, the AARC recommended the ARDS Network Protocol recommendations for the initiation and management of invasive ventilation for critical patients with COVID-19^[62]. The SCCM Guideline recommendations and suggestions on invasive ventilation initiation and management were mostly based on the ARDS Network Protocol recommendations. There are no studies on mechanical ventilation strategies in patients with COVID-19 as of this time^[1]. A lung protective approach should always be applied to prevent ventilator-associated lung injury which may lead to multiorgan failure in patients with ARDS^[63].

There is insufficient evidence to confirm whether pressure-controlled ventilation (PCV) offers any advantage over volume-controlled ventilation (VCV) in acute lung injury or ARDS.^[57] Therefore, either mode is considered reasonable.

Low tidal volume ventilation strategy minimizes VILI. A multicenter RCT (861 patients) showed a lower mortality rate and more ventilator-free days with low tidal volume ventilation.^[58] A systematic review and meta-analysis of 9 RCTs (1,629 patients) showed that protocolized low tidal volume with high PEEP strategy reduced mortality.^[59]

Plateau pressure that exceeds 30 cm H₂O is associated with increased risk of VILI. A systematic review and meta-analysis of 9 RCTs (1,629 patients) showed lower risk of death with using protocolized low tidal volume, high PEEP strategy, and plateau pressure <30 cm H₂O.^[59] Several clinical practice guidelines have recommended using low tidal volume ventilation (4-8 ml/kg PBW) and maintaining plateau pressure <30 cm H₂O in patient with ARDS.^[5]

An individual patient-data meta-analysis (2,299 patients) showed that a higher PEEP strategy reduced ICU and in-hospital mortality and the need for rescue therapies in patients with ARDS, though at the expense of increased risk of pneumothorax.^[60] Clinicians should monitor their patients closely for evidence of barotrauma after increasing PEEP levels and should use the ARDS Network Protocol strategies to determine optimal PEEP level.

Practical considerations:

For mechanically ventilated adults with COVID 19 and normal compliance and no/mild ARDS, we suggest using a lower PEEP strategy to mitigate the unwanted effects of a higher PEEP such as barotrauma and hemodynamic instability. Also, pulmonary hemorrhagic infarcts and micro-thrombosis formations have been reported in pathological biopsies of a critically ill patient with COVID 19, suggesting the importance of the meticulous use of PEEP in such patients.^[61]

Recommendation 28 and 29

We recommend not using the staircase (incremental PEEP) recruitment maneuver (SRM) (strong recommendation).

In pediatric patients, careful recruitment maneuvers (RMs) are in the attempt to improve severe oxygenation failure by slow incremental and decremental PEEP steps.

Rationale

When RMs are used in moderate to severe ARDS, the transpulmonary pressure increases enhancing recruitment of atelectatic lungs, eventually improving oxygenation, yet it may cause transient hemodynamic instability and increase the risk of barotrauma. Varying RM strategies are described and tested in clinical trials [1]. A systematic review and meta-analysis of 6 RCTs (1423) showed that conventional RMs reduced mortality and rescue interventions,^[62] but the use of incremental PEEP RM resulted in higher risk of death.

Recommendations 30-31

We recommend not routinely using inhaled nitric oxide (iNO) in adults or children with COVID-19 (strong recommendation).

In adults and children with COVID-19 and severe ARDS, we suggest using iNO only as a rescue therapy. If oxygenation does not rapidly improve, the patient should be weaned off the treatment (weak recommendation).

Rationale

The use of iNO in patients with ARDS may improve oxygenation, but does not reduce mortality, and may increase the risk of acute kidney injury (AKI).^[63]

Prone ventilation

Prone ventilation is one of the few interventions that have shown a mortality benefit in mechanically ventilated patients with moderate to severe ARDS.^[64] The prone position reduces lung compression, improves lung perfusion, and reduces the ventral-dorsal transpulmonary pressure difference, resulting in improved ventilation and oxygenation.^[65-68] Prone ventilation has recently been adopted by multiple international guidelines as a rescue management for patients with moderate to severe ARDS to reduce mortality.^[69,70]

Recommendation 32

In institutions with expertise in prone ventilation and adequate human resources, we suggest prone ventilation for at least 12 to 16 hours over no prone ventilation for mechanically ventilated adults with COVID 19 and moderate to severe ARDS (weak recommendation).

Rationale

In a large RCT of 466 patients with ARDS, prone ventilation reduced 28-day and 90-day mortality, compared

with ventilation in supine position.^[64] Several systematic reviews and meta-analyses showed that prone ventilation for 12-16 hours reduces mortality but increases the rates of endotracheal tube obstruction and pressure sores.^[71-73]

The recently released WHO interim guidance was strongly in favor of prone ventilation for patients with severe ARDS associated with COVID-19 disease, as long as sufficient human resources and expertise are available.^[74] Currently, no studies are evaluating the outcomes of prone ventilation in patients with COVID-19. Prone ventilation was utilized in 11.5% of 52 critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China^[51] and in 27% of 875 critically ill COVID-19 patients in Lombardy, Italy.^[75]

Practical considerations

Safe prone ventilation requires expertise and adequate human resources. Appropriately trained healthcare workers should take the necessary infection control precautions at the time of proning. Patients should be closely observed during prone ventilation for dislodgment of endotracheal tubes or vascular catheters, pressure sores, nerve compression, and crush injury.^[72] Clinicians should be recognizing contraindications for prone ventilation such as spinal instability, anterior burns, unstable fractures, and active bleeding.

Institutions offering prone ventilation should use a protocol for proning and should provide the necessary training. A Protocol, including a practical video, is available.^[64] (<https://www.nejm.org/doi/full/10.1056/NEJMoa1214103>).

Supportive Care (Hemodynamic Support and Fluid therapy) Management in COVID-19

Myocarditis and Shock

Problem/issue: In patients with COVID-19, the presentation of myocarditis varies from mild chest pain and dyspnea to left ventricular failure, arrhythmia and cardiogenic shock.^[76] Although the diagnosis is mainly clinical; nonspecific electrocardiogram (ECG) changes and high cardiac enzymes are common.^[77] Infection is triggered by the binding of SARS-CoV-2 spike protein to angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the heart and lungs^[78] The severity of the symptoms might be associated with increased secretion of ACE2 in these patients compared with healthy individuals.^[78]

In a retrospective study of 150 patients using the database of two hospitals in Wuhan, mortality was 45%, (68 patients). Among those, 5 (7%) of patients died with circulatory failure. Deaths were noticed mainly in elderly patients, especially more than 60 years old ($P < 0.001$); patients with cardiovascular disease have a high risk of death ($P < 0.001$).^[79] The rate of myocardial injury and

myocarditis is between 4.8-7.2%.^[80,81] Among 52 critically ill patients with COVID-19, 32 (61.5%) patients died at 28 days, and the median duration from ICU admission to death was 7 days. The APACHE II score and SOFA score at ICU admission were higher in non-survivors: 18 and 6 respectively, 23% with cardiac injury.^[51]

Recommendation 33

We suggest using dynamic parameters over static parameters to assess fluid responsiveness in patients with COVID-19 and shock (weak recommendation).

Rationale

Currently there are no studies on the assessment of fluid responsiveness in COVID-19 patients with shock. Our recommendation is based on indirect evidence on critically ill patients. The surviving sepsis campaign recommends following the dynamic parameters to judge the fluid responsiveness.^[82] A systematic review and meta-analysis including 13 RCTs found goal-directed fluid therapy based on dynamic assessment of fluid responsiveness to reduce mortality, ICU length of stay, and duration of mechanical ventilation.^[83]

Recommendations 34-36

For adults with COVID-19 and shock:

We suggest using a conservative fluid strategy (weak recommendation).

Remarks: many critically ill patients with COVID-19 are hypovolemic and have high insensible losses from ongoing fever: careful and frequent volume status assessment is warranted.

We suggest using crystalloids over colloids (weak recommendation). When crystalloids are used, we suggest using balanced crystalloids over saline (weak recommendation).

We recommend against using hydroxyethyl starches (strong recommendation).

Rationale

No studies have examined fluid resuscitation in confirmed COVID-19 patient with septic shock. Our recommendation is based on available evidence on critically ill patients. A recent meta-analysis of 9 studies published after 2015 showed no statistically significant difference between lower versus higher fluid volumes in all-cause mortality.^[84] We recommend a conservative fluid resuscitation strategy to avoid the fluid overload associated with liberal fluid.

Our recommendation is based on available evidence on critically ill patients. A meta-analysis of 14 studies, with a total of 18,916 patients, showed that patients with sepsis, resuscitation with crystalloids or albumin, compared with other fluids was associated with reduced mortality.^[85] A meta-analysis published in 2018 included

69 studies of volume resuscitation in a total of 30,020 critically ill patients. It showed no difference in mortality when using starches, dextran, albumin, FFP and gelatins versus crystalloids.^[86] Due to the availability and the low cost we recommend the use of crystalloid.

In a recent meta-analysis examining buffered intravenous fluids versus intravenous 0.9% saline in resuscitation or maintenance, a total of 21 RCTs, including 20,213 patients, adult and children in a critical care setting, showed no effect of buffered intravenous fluid on in-hospital mortality compared to 0.9% saline in critically ill patients. The effects of buffered intravenous fluids and 0.9% saline solutions on prevalence of acute kidney injury were similar.^[87] The Surviving Sepsis Guidelines on the Management of Critically ill Adults with COVID-19, suggested buffered intravenous fluids, as the point estimates for both outcomes suggest a potential for benefit from buffered crystalloid solutions in the previously mentioned meta-analysis. We recommend using buffered intravenous fluid, with 0.9% saline remaining a reasonable alternative.

Our recommendation is based on the available evidence on critically ill patients. The previously mentioned 2018 meta-analysis showed no difference in mortality with using starches, versus crystalloids in 24 studies including 11,177 patients.^[86] There were increased risk of blood transfusion and renal replacement therapy with starches. Given the risk of the side effects, and absence of benefit from the use of hydroxyethyl starches and cost, we recommend against its use for resuscitation of patients with COVID-19 and shock.

Renal Replacement Therapy

The incidence of acute kidney injury (AKI) in patients with COVID-19 ranges from 0.5% to 23% according to the most recent data.^[80,88,89] According to the studies, AKI develops at a median of 7-15 days after admission.^[90,91] AKI in COVID-19 accompanies sepsis, multiorgan failure, and shock; therefore, acute tubular necrosis (ATN) appears to be the most likely cause.^[92,93] AKI is associated with worse outcomes in patients with COVID-19. The incidence of requiring renal replacement therapy (RRT) in COVID-19 ranges from 0.8% to 5%.^[91,92,94,95] The management of AKI in this disease is probably similar to other settings.

Recommendations 37-38

For adults with COVID-19 and AKI, we recommend starting RRT if life-threatening hyperkalemia, severe acidosis, pulmonary edema, or uremic complications are present (strong recommendation).

We suggest against the early initiation of RRT in the absence of known indications (weak recommendation).

Rationale

The timing of initiating RRT in ICU patients has been a subject of multiple recent studies. A single-center

unblinded RCT randomized 231 critically ill patients with AKI into an early start after progressing to stage 2 AKI or a delayed start when an urgent indication is present. All-cause mortality at 90 days was 39.3% in the early arm compared with 54.7% in the delayed arm (P 0.03).^[96] In contrast, a multicenter RCT randomized 619 critically ill patients with Stage 3 AKI without acute indications into an early arm starting RRT immediately or a delayed arm starting after developing emergent indications. All-cause mortality at 60 days did not differ between the two treatment arms. Furthermore, almost half of the patients in the delayed arm did not ever require any RRT.^[97] A recently completed trial looked at 488 ICU patients with sepsis and AKI and randomized them into an early RRT or a delayed start after developing an indication. Ninety-day mortality was similar in both groups.^[98] A recent meta-analysis and systematic review showed that early initiation of RRT compared with late was not associated with improved mortality (RR 0.98, 95% CI 0.85–1.13).^[99]

Recommendations 39-40

When prescribing RRT, we recommend choosing the modality based on availability, expertise, resources, and associated cost (best practice statement).

For adults with COVID-19 and shock requiring RRT, we suggest using continuous renal replacement therapy (CRRT) as opposed to intermittent hemodialysis (IHD) (weak recommendation, expert opinion).

Rationale

Patients with AKI can be treated with different RRT modalities such as intermittent hemodialysis (IHD), CRRT, and “Hybrid” modalities like sustained low-efficiency dialysis (SLED). Evidence does not support one modality over the other. A meta-analysis comparing clinical outcomes of critically ill patients with AKI treated with IHD, CRRT, and SLED found no significant difference in hospital mortality or dialysis dependence.^[100] Despite lack of high quality evidence, recent guidelines prefer using CRRT for hemodynamically unstable patients and, in COVID-19, critically ill patients with AKI.^[101]

Recommendation 41

For COVID-19 patients on CRRT, we **suggest** using an effluent flow rate of 20 to 25 ml/kg/hour over a higher flow rate (weak recommendation).

Rationale

Multiple RCTs addressed the question of the CRRT dose. A study has randomized patients on continuous veno-venous hemodiafiltration (CVVHDF) to either an effluent dose of 25 ml/kg/hour or to a 40 ml/kg/hour.^[102] Another RCT randomized patients on CVVHDF to an effluent dose of 20 ml/kg/hour or to 35 ml/kg/hour.^[103] In

both studies, intensive therapy did not improve survival or recovery of kidney function. A recent systematic review and meta-analysis found no significant difference in the 90-day mortality between high-dose and low-dose hemofiltration (OR 0.90, 95% CI 0.73, 1.11).^[104] Current guidelines recommend a minimal effluent of more than 20 to 25 ml/kg/hour to be provided. In a context of pandemic and increased disease transmission to healthcare workers, minimizing patient contact is important, therefore, a lower dialysis dose adds the extra advantage of a lesser need to interact with the CRRT machine.

Recommendations 42-43

When using CRRT for patients with COVID-19 (without coagulopathy or contraindications to anticoagulation), we recommend using anticoagulation over no anticoagulation (strong recommendation).

For anticoagulation in CRRT, we suggest using either regional citrate anticoagulation or unfractionated heparin, depending on each institution's own practice and procedure (weak recommendation).

Rationale

There are several trials comparing different anticoagulants to maximize the lifespan of the CRRT circuit. In a multicenter RCT, 212 patients with a total of 857 circuits were randomized to citrate versus heparin anticoagulation. The median lifespan of the first filter was significantly longer in the citrate group (39.2 hours; 95% CI, 32.1 to 48.0), compared with heparin anticoagulation (22.8 hours; 95% CI, 13.3 to 48.0).^[105] A subsequent meta-analysis of 14 RCTs found that regional citrate, compared to unfractionated heparin, prolongs the CRRT circuit lifespan by a mean 8.2 hours (IQR, 3.9–12.5).^[106]

Veno-venous extracorporeal membrane oxygenation

Problem: Extra-corporeal life support (ECLS) is used in mechanically ventilated patients with refractory hypoxemic respiratory failure where conventional measures and other rescue therapies and interventions fail to maintain adequate oxygenation. In experienced centers, the use of veno-venous extracorporeal membrane oxygenation (VV ECMO) may improve the outcomes of those patients.^[107] There are no RCTs on the use of VV ECMO in COVID-19 patients. A recent retrospective observational study from Italy reported that 1% of the 1591 COVID-19 patients in the ICU received VV ECMO, but the outcomes of these patients were not reported.^[75]

Recommendation 44

In mechanically ventilated adults with COVID-19 and refractory hypoxemia, despite optimizing ventilation, using rescue therapies, and proning, we suggest using VV ECMO if available, or referring the patient to an ECMO center (weak recommendation).

Rationale

The WHO interim guidelines for the management of suspected COVID-19 recommend VV ECMO for eligible patients with COVID-19 and ARDS in experienced centers.^[74] A recent systematic review and meta-analysis included two RCTs that evaluated the use of VV ECMO in non-COVID patients with severe ARDS, and three observational studies. The use of ECMO was associated with lower risk of death (RR 0.73; 95% CI 0.58, 0.92).^[71] During MERS-COV outbreak in Saudi Arabia, a before-after cohort study showed lower mortality with VV ECMO in patients with severe ARDS and MERS (65% versus 100%; $P = 0.02$).^[108] Another matched pair analyses of 75 H1N1 patients who developed severe hypoxemic respiratory failure showed survival benefits when patients were transferred to experienced ECMO centers (52.5% versus 23.7%).^[109] In the context of a pandemic, resources are valuable and healthcare systems are under continuous strain; therefore, the use of VV ECMO should only be reserved for patients who need it and are likely to survive or benefit if offered ECMO.

Timing for tracheostomy

Problem: Although trans-laryngeal intubation is the first choice for airway access in patients requiring invasive mechanical ventilation, prolonged endotracheal intubation can be associated with complications.^[110] Therefore, tracheostomy is often considered for patients who are unable to wean from invasive mechanical ventilation or when the need for invasive mechanical ventilation is expected to be prolonged.

Recommendation 45

For intubated adults with COVID-19 who are ventilated for >10 days and are unable to wean from invasive mechanical ventilation, we suggest deferring tracheostomy until SARS CoV-2 testing is negative (weak recommendation).

Rationale

The appropriate timing for tracheostomy for patients who are unable to wean from invasive mechanical ventilation is unclear.^[111,112] There are no studies on the proper timing of tracheostomy for patients with COVID 19. However, several studies have evaluated early and late timing periods for tracheostomy in the ICU population.^[113-115]

In an RCT of 1032 adult patients, tracheostomy within 4 days of ICU admission was not associated with an improvement in 30-day mortality compared with tracheostomy after 10 days.^[116] Interestingly, only 45% of the patients assigned to late tracheostomy received a tracheostomy, suggesting that the ability of clinicians to predict which patients require extended ventilatory support is limited.^[116]

A systematic review and meta-analysis of 9 studies, including 2040 patients, revealed that tracheostomy within 10 days of intubation did not significantly improve mortality compared with tracheostomy after 10 days of intubation (9 RCTs; RR = 0.88; 95% CI = 0.76-1.00; $P = 0.06$).^[117] None of the other clinical outcomes were different, except for a reduction in the duration of sedation in the early tracheostomy group (3 RCTs; MD -5.99 days; 95% CI = -11.41 to -0.57 days). Another systematic review and meta-analysis of 14 RCTs (2406 patients) reached a similar conclusion.^[118] Our recommendation for late tracheostomy places a high value on avoiding unnecessary procedures and high-risk exposure. Also, early tracheostomy is of unproven benefit and may prolong invasive ventilation in patients with COVID-19 that may otherwise be extubated.

Practical considerations

Tracheostomy is considered an AGP. Appropriate infection control measures should be taken during the procedure itself, during suctioning and care provision.

Managerial Strategies

Preparation of intensive care for expected pandemic

Pandemics are usually associated with a limited resource because of the large number of admitted patients.^[119] This should encourage health care policy makers to start preparations early when the WHO declares phase IV. One of those measures is minimizing admissions and elective surgeries while increasing intensive care (ICU) beds by transferring non COVID-19 patients to other units.^[119] At the level of hospital and intensive care, it is important to redesign the hospital and create special units with negative pressure rooms to accommodate those patients while maintaining the safety of non COVID-19 patients, protecting them from getting exposed to infectious disease.^[120] Addressing the length of stay for existing ICU patients and goals-of-care discussion for patients with overall very poor prognosis helps free some ICU beds and.^[120] We recommend using a published model that predict the course of pandemic to help in evaluating the capacity of intensive care unit (ICU) requirements over time, looking into alternative sites to provide ICU-I care within the hospital, such as operating rooms.^[121,122] These steps and planning were highlighted in recent recommendations to US hospitals to prepare for the COVID 19 pandemic.^[122]

Recommendations 46–47

We suggest grouping all critically ill COVID-19 patients in one unit (weak recommendation).

We suggest dedicating ICUs with negative pressure rooms for confirmed and suspected COVID-19 cases (weak recommendation).

Rationale

Despite all preparations, the course of a pandemic can quickly get out of control and the demand often exceeds the current capacity of critical care and hospitals.^[123] For these reasons, policy-makers should be prepared at the national level to deal with a pandemic and direct special attention toward intensive care and areas with limited resources.^[123,124]

Strategies for ICU surge capacity

During a pandemic, hospitals often make fundamental changes and reallocate resources to accommodate a large number of critically ill patients.^[124] Planning should start before a disaster to be prepared and respond to surges at any time.^[125] Surge capacity in mass critical care refers to the ICU's ability to rapidly expand and accommodate as many patients as possible in a disaster.^[125] There are four necessary components of surge capacity: staff, supplies, space, and structure. In a pandemic, ICUs will certainly receive the sickest COVID-19 patients and will be directly affected by availability of resources and resource allocation.^[125] Planned surge and crisis preparedness expose critically ill patients to high workload staffing ratios, which is associated with reduced odds of survival.^[126]

Recommendation 48

When planning for critical care surge capacity:

We suggest adopting a phased and tiered response based on the worst-case scenarios of the COVID-19 pandemic (weak recommendation).

We suggest transferring non-acutely ill chronically ventilated patients to low-acuity ICUs (weak recommendation).

We suggest training non-ICU healthcare workers to manage critical patients outside of ICUs with supervision by ICU specialized healthcare workers (weak recommendation).

Rationale

As the demand for critical care grows, the gap between demand and supply of intensivists widens.^[126] To handle dramatic increases in the demand for essential services, hospitals must develop a mass-casualty plan with clear and practical steps.^[127] The severity of SARS-CoV-2 pneumonia poses a great strain on critical care resources.^[51] Surge plans should be at a system level in order to provide the required care for a large cohort of patients.^[125]

During a surge, the paradigm shifts away from universal and comprehensive care to providing good care on a population rather than an individual level, implementing strict ICU admission criteria, and utilizing a dynamic surge protocol.^[125] The level of response should be based on the projected number of critically ill patients, taking into account the availability of essential resources.^[125] In the context of a pandemic, all health care sectors and

governmental entities should partner to maximize capacity and offer regional consistency of care.

Tele-critical care is another commonly used method to address the shortage of critical care providers that may improve care and reduce costs.^[128,129] A phased-response, based on the impact on the capacity of the ICU to meet daily operational needs, should be implemented.

Patient Psychology and Staff Management

Psychological support for staff and patients is crucial during an epidemic. The fear of having and transmitting serious illness and being stigmatized by others can have a significant psychological impact.^[130] The WHO recommends healthcare providers take care of their psychological well-being as well as their physical health.^[130] During an epidemic, healthcare workers are at risk of developing severe anxiety, depression, delirium, and psychosis.^[130,131] Mental health services and psychological support during and after infectious diseases should not be ignored, and they are crucial for effective rehabilitation.^[132]

Recommendation 49

We suggest creating a mental health support system for patients and healthcare workers (weak recommendation).

Rationale

During the SARS epidemic, healthcare providers were prone to develop high levels of anxiety and depression.^[131] The prevalence of posttraumatic stress disorder (PTSD) after a traumatic event in the ICU is between 14 to 59%. Approximately a third of SARS-survivors developed symptoms of anxiety or depression or both within 1 month of discharge.^[130] During the 2003 epidemic, one study reported on two groups of healthcare workers. The first group included high-risk healthcare workers, who practiced respiratory medicine. The second group included low-risk healthcare workers. At one year, the high-risk group's Perceived Stress Scale (PSS-10) score differed between the two groups ($P < 0.05$). The study concluded that healthcare workers who practiced respiratory medicine were at higher risk of depression, anxiety, and PTSD [185]. Applying the mental health support system may help to assess staff and patients' needs and support them through the pandemic and after, by identifying the stressors and normalizing them through a guideline.

Possible approaches to providing psychological support may include: 1) providing insurance, accommodation, and compensation for frontline healthcare workers and administration, 2) providing an ICU psychologist for patients, 3) a confidential mental health support phone line for staff and patients, 4) post-discharge follow up, 5) outpatient psychiatrists and clinical psychologists to support healthcare workers, patients and their families.

Ethical Framework for Critically Ill Patients

During pandemics the main objectives of medical care is to minimize mortality and morbidity.^[133] But there are variables that should be taken into consideration: such as that human resources constraints and treatment options will change the nature of the ethical decisions that will be made, and this has to be adjusted continuously.^[133,134] According to assessment tools for the magnitude of the pandemic and surge capacity resilience, preset triggers with defined surge capacity levels under vigilant evaluation are crucial for justifying altered standards of care in pandemics.^[135] A higher commanding center approval is essential to call for and end an altered care ethics.^[136]

Recommendations 50-51

We recommend building ethical choices in the ICU, based on the utility and efficiency of interventions, fairness, and equity of resource distribution (weak recommendation).

We suggest using a scoring system such as Biddison's scoring system^[134] or any other acceptable rapid prognostication score, to prioritize access to scarce life-support interventions in the ICU during failure of surge plans or extreme phases of surge (weak recommendation).

Rationale

It is very difficult to develop well-structured studies in disasters and pandemics addressing ethical considerations when demand on health-care resources overcomes availability of staff, space or utilities for patients.^[134] The ethical principles used in normal situations are applicable in pandemics until the point that a health-care facility has exhausted all its surge capacity resources, leading to the likelihood of death or severe injury to patients either in the health-care facility, or coming to it. Proposed medical criteria for the patients that will benefit the most has been used, such as SOFA scoring^[134] and the Clinical Frailty Scale,^[137] honoring the "Save the greatest number of people" ethical criteria that directs us to give priority in allocation decisions to the category or categories of people that will result in the most lives saved. This usually involves allocating resources on the basis of a patient's prognosis and the amount of resources and/or personnel that will be required to sustain life.

Special Considerations for Pediatric Patients

Although COVID-19 primarily causes critical illness in adults, there have been some reports of critically ill children. All infection control recommendations are applicable to both adult and pediatric ICUs.

There are no trials on the use of chloroquine and hydroxychloroquine in critically ill children with COVID-19 in the pediatric ICU. Therefore, its routine use should be avoided and decisions regarding its use should be individualized. Similarly, there are

no trials on the use of antiviral agents in pediatric patients with severe COVID-19, therefore, we make no recommendations on the use of these agents in the pediatric population.

Illness among children appears to be mild, commonly presenting with cough, nasal congestion, rhinorrhea, sore throat, and gastrointestinal symptoms.^[138,139] As per the WHO guidance, conventional oxygen therapy should be administered only for hypoxic patients.^[74] If children are hypoxic despite conventional oxygen therapy, then HFNC can be tried with close monitoring for any sign of increased work of breathing and respiratory distress. HFNC should not routinely be used as a method of reducing the work of breathing in children who are otherwise saturating adequately. A literature review of the 26 original clinical studies including children on HFNC beyond the new-born period concluded that “until more evidence from randomized studies is available, HFNC may be used as a supplementary form of respiratory support in children, but with a critical approach regarding effect and safety, particularly when operated outside of a pediatric intensive care unit”.^[140]

When ventilating pediatric patients with COVID-19 and pediatric acute respiratory distress syndrome (PARDS), the panel issued the following recommendations:

We suggest: using volume or pressure control modes; targeting tidal volume of 6 ml/kg (4-8 ml/kg) of PBW; and maintaining plateau pressure <28 cm H₂O (weak recommendation). If plateau pressure is >28 cm H₂O, decrease tidal volume by 1 ml/kg increments to minimum of 4 ml/kg PBW. Tidal volume of (3 ml/kg ideal body weight) can be considered for patients with poor respiratory system compliance or may accept plateau pressure of up to 30 cm H₂O.

We suggest setting the PEEP at 5 cm H₂O and using a higher PEEP only in patients with clinical features of severe ARDS (weak recommendation).

Remarks: when applying a high PEEP strategy, patients should be monitored for signs of barotrauma, oxygen delivery, respiratory system compliance, and hemodynamics.

We suggest using High-Frequency Oscillatory Ventilation (HFOV) in severe pediatric PARDS and refractory hypoxemia (weak recommendation, expert opinion).

The above recommendations were developed based on the recommendations of the Pediatric Acute Lung Injury Consensus Conference.^[141]

The recommendation on iNO use also applies to children with COVID-19. Prone position is usually used early and sometimes for a longer duration in paediatric patients with ARDS.

For pediatric COVID-19 patients who develop septic shock, readers can refer to the children surviving sepsis campaign guidelines.^[142,143] In addition, the children surviving sepsis campaign suggest using VV ECMO in sever PARDS and refractory hypoxia.

All recommendations on the preparation of intensive care for an expected pandemic, ICU surge capacity, psychological support, ethical framework, and training are also applicable to the pediatric context.

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Conflict of interest

All members complete the WHO COI forms. None declared any conflict of interest related to this guideline.

References

1. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* 2020;395:565-74.
2. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020;5:536-44.
3. WHO. Naming the coronavirus disease (COVID-19) and the virus that causes it. 2020.
4. Organization WH. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. 2020.
5. Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, *et al.* Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med* 2020;46:854-87.
6. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the chinese center for disease control and prevention. *JAMA* 2020. doi: 10.1001/jama. 2020.2648.
7. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. *JAMA* 2020. doi: 10.1001/jama. 2020.4344.
8. Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: Particle size, culturability, and effect of surgical masks. *PLoS Pathog* 2013;9:e1003205.
9. Radonovich LJ Jr, Simberkoff MS, Bessesen MT, Brown AC, Cummings DAT, Gaydos CA, *et al.* N95 Respirators vs medical masks for preventing influenza among health care personnel: A randomized clinical trial. *JAMA* 2019;322:824-33.
10. Bae S, Kim MC, Kim JY, Cha HH, Lim JS, Jung J, *et al.* Effectiveness of surgical and cotton masks in blocking SARS-CoV-2: A controlled comparison in 4 patients. *Ann Intern Med* 2020. doi: 10.7326/M20-1342.
11. Xinghui K. Why are there so few coronavirus infections in Singapore's health workers? *This Week in Asia* 2020.
12. WHO. Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19) 2020.
13. Kwok YL, Gralton J, McLaws ML. Face touching: A frequent habit that has implications for hand hygiene. *Am J Infect Control*

- 2015;43:112-4.
14. WHO. Coronavirus disease (COVID-19) advice for the public. 2020.
15. Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, *et al.* Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database Syst Rev* 2011;CD006207. doi: 10.1002/14651858.CD006207.pub4.
16. Twu SJ, Chen TJ, Chen CJ, Olsen SJ, Lee LT, Fisk T, *et al.* Control measures for severe acute respiratory syndrome (SARS) in Taiwan. *Emerg Infect Dis* 2003;9:718-20.
17. Cabrini L, Landoni G, Zangrillo A. Minimise nosocomial spread of 2019-nCoV when treating acute respiratory failure. *Lancet* 2020;395:685.
18. Yam LY, Chen RC, Zhong NS. SARS: Ventilatory and intensive care. *Respirology* 2003;8(Suppl):S31-5.
19. Liew MF, Siow WT, MacLaren G, See KC. Preparing for COVID-19: Early experience from an intensive care unit in Singapore. *Crit Care* 2020;24:83.
20. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: A systematic review. *PLoS One* 2012;7:e35797.
21. CDC. Guidance on Personal Protective Equipment (PPE) To Be Used By Healthcare Workers during Management of Patients with Confirmed Ebola or Persons under Investigation (PUIs) for Ebola who are Clinically Unstable or Have Bleeding, Vomiting, or Diarrhea in U.S. Hospitals, Including Procedures for Donning and Doffing PPE. 2018.
22. Adams JG, Walls RM. Supporting the health care workforce during the COVID-19 global epidemic. *JAMA* 2020. doi: 10.1001/jama. 2020.3972.
23. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, *et al.* *In Vitro* antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020. doi: 10.1093/cid/ciaa237.
24. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: An old drug against today's diseases? *Lancet Infect Dis* 2003;3:722-7.
25. Plantone D, Koudriavtseva T. Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic, and neurological diseases: A mini-review. *Clin Drug Investig* 2018;38:653-71.
26. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care* 2020. doi: 10.1016/j.jcrc. 2020.03.005.
27. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020;14:72-3.
28. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020;105949. doi: 10.1016/j.ijantimicag. 2020.105949
29. multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. [Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]. *Zhonghua Jie He He Hu Xi Za Zhi* 2020;43:185-8.
30. Borba MG, Val FF, Sampaio VS, Alexandre MA, Melo GC, Brito M, *et al.* Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). *medRxiv*; 2020. doi: 10.1101/2020.04.07.20056424.
31. Srinivas NR. Prediction of area under the concentration-time curve for lopinavir from peak or trough lopinavir concentrations in patients receiving lopinavir-ritonavir therapy. *Am J Health Syst Pharm* 2016;73:376-85.
32. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, *et al.* Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. *Thorax* 2004;59:252-6.
33. de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, *et al.* Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother* 2014;58:4875-84.
34. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al.* A Trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382:1787-99.
35. Organization WH. WHO R and D Blueprint: Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection, Geneva, Switzerland, 24 January 2020. World Health Organization. 2020.
36. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. *Travel Med Infect Dis* 2020;101615. doi: 10.1016/j.tmaid. 2020.101615.
37. Sheahan TP, Sims AC, Leist SR, Schafer A, Won J, Brown AJ, *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020;11:222.
38. de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T, *et al.* Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A* 2020;117:6771-6.
39. Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ, Feldmann H. Inhibition of novel beta coronavirus replication by a combination of interferon-alpha2b and ribavirin. *Sci Rep* 2013;3:1686.
40. Falzarano D, de Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, *et al.* Treatment with interferon-alpha2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. *Nat Med* 2013;19:1313-7.
41. Momattin H, Mohammed K, Zumla A, Memish ZA, Al-Tawfiq JA. Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)--possible lessons from a systematic review of SARS-CoV therapy. *Int J Infect Dis* 2013;17:e792-8.
42. Hart BJ, Dyal J, Postnikova E, Zhou H, Kindrachuk J, Johnson RF, *et al.* Interferon-beta and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. *J Gen Virol* 2014;95(Pt 3):571-7.
43. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, *et al.* Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: A multicenter observational study. *Clin Infect Dis* 2020;70:1837-44.
44. Arabi YM, Alotman A, Balkhy HH, Al-Dawood A, AlJohani S, Al Harbi S, *et al.* Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-beta1b (MIRACLE trial): Study protocol for a randomized controlled trial. *Trials* 2018;19:81.

45. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, *et al.* The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis. *J Infect Dis* 2015;211:80-90.
46. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, *et al.* Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020. doi: 10.1001/jama.2020.4783.
47. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, *et al.* Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *Chest* 2020. doi: 10.1016/j.chest.2020.03.039.
48. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, *et al.* Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A* 2020;117:9490-6.
49. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in Covid-19: The first autopsy series from New Orleans. *medRxiv* 2020. doi: 10.1101/2020.04.06.20050575.
50. Tavazzi G, Civardi L, Caneva L, Mongodi S, Mojoli F. Thrombotic events in SARS-CoV-2 patients: An urgent call for ultrasound screening. *Intensive Care Medicine* 2020. doi: 10.1007/s00134-020-06040-3.
51. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al.* Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475-81.
52. Ni YN, Luo J, Yu H, Liu D, Liang BM, Liang ZA. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. *Am J Emerg Med* 2018;36:226-33.
53. Rochwerg B, Granton D, Wang DX, Helviz Y, Einav S, Frat JP, *et al.* High flow nasal cannula compared with conventional oxygen therapy for acute hypoxemic respiratory failure: A systematic review and meta-analysis. *Intensive Care Med* 2019;45:563-72.
54. Brochard L, Lefebvre JC, Cordoli RL, Akoumianaki E, Richard JC. Noninvasive ventilation for patients with hypoxemic acute respiratory failure. *Semin Respir Crit Care Med* 2014;35:492-500.
55. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013;369:2126-36.
56. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al.* Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:420-2.
57. Chacko B, Peter JV, Tharyan P, John G, Jeyaseelan L. Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). *Cochrane Database Syst Rev* 2015;1:CD008807.
58. Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301-8.
59. Walkey AJ, Goligher EC, Del Sorbo L, Hodgson CL, Adhikari NKJ, Wunsch H, *et al.* Low tidal volume versus non-volume-limited strategies for patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017;14(Supplement_4):S271-9.
60. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, *et al.* Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA* 2010;303:865-73.
61. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, *et al.* Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res* 2020. doi: 10.1016/j.trsl.2020.04.007.
62. Goligher EC, Hodgson CL, Adhikari NKJ, Meade MO, Wunsch H, Uleryk E, *et al.* Lung recruitment maneuvers for adult patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017;14(Supplement_4):S304-11.
63. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev* 2016;CD002787. doi: 10.1002/14651858.CD002787.pub2.
64. Guerin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, *et al.* Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68.
65. Kraye S, Rehder K, Vettermann J, Didier EP, Ritman EL. Position and motion of the human diaphragm during anesthesia-paralysis. *Anesthesiology* 1989;70:891-8.
66. Rehder K, Knopp TJ, Sessler AD. Regional intrapulmonary gas distribution in awake and anesthetized-paralyzed prone man. *J Appl Physiol Respir Environ Exerc Physiol* 1978;45:528-35.
67. Albert RK, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. *Am J Respir Crit Care Med* 2000;161:1660-5.
68. Lamm WJ, Starr IR, Neradilek B, Polissar NL, Glenny RW, Hlastala MP. Hypoxic pulmonary vasoconstriction is heterogeneously distributed in the prone dog. *Respir Physiol Neurobiol* 2004;144:281-94.
69. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, *et al.* An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;195:1253-63.
70. Griffiths MJD, McAuley DF, Perkins GD, Barrett N, Blackwood B, Boyle A, *et al.* Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respir Res* 2019;6:e000420.
71. Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, *et al.* Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2017;14(Supplement_4):S280-8.
72. Park SY, Kim HJ, Yoo KH, Park YB, Kim SW, Lee SJ, *et al.* The efficacy and safety of prone positioning in adults patients with acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. *J Thorac Dis* 2015;7:356-67.
73. Hu SL, He HL, Pan C, Liu AR, Liu SQ, Liu L, *et al.* The effect of prone positioning on mortality in patients with acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. *Crit Care* 2014;18:R109.
74. WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected. Interim guidance. 2020.
75. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al.* Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020. doi: 10.1001/jama.2020.5394.

76. Wang D, Li S, Jiang J, Yan J, Zhao C, Wang Y, *et al.* Chinese society of cardiology expert consensus statement on the diagnosis and treatment of adult fulminant myocarditis. *Sci China Life Sci* 2019;62:187-202.
77. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 2020;17:259-60.
78. Turner AJ, Hiscox JA, Hooper NM. ACE2: From vasoepitaxide to SARS virus receptor. *Trends Pharmacol Sci* 2004;25:291-4.
79. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46:846-8.
80. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020. doi: 10.1001/jama.2020.1585.
81. Basu-Ray I, Soos MP. Cardiac Manifestations Of Coronavirus (COVID-19). Treasure Island (FL): StatPearls; 2020.
82. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al.* Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017;45:486-552.
83. Bednarczyk JM, Fridfinnson JA, Kumar A, Blanchard L, Rabbani R, Bell D, *et al.* Incorporating dynamic assessment of fluid responsiveness into goal-directed therapy: A systematic review and meta-analysis. *Crit Care Med* 2017;45:1538-45.
84. Meyhoff TS, Moller MH, Hjortrup PB, Cronhjort M, Perner A, Wetterslev J. Lower vs higher fluid volumes during initial management of sepsis: A systematic review with meta-analysis and trial sequential analysis. *Chest* 2020. doi: 10.1016/j.chest.2019.11.050.
85. Rochwerf B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, *et al.* Fluid resuscitation in sepsis: A systematic review and network meta-analysis. *Ann Intern Med* 2014;161:347-55.
86. Lewis SR, Pritchard MW, Evans DJ, Butler AR, Alderson P, Smith AF, *et al.* Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev* 2018;8:CD000567.
87. Antequera Martin AM, Barea Mendoza JA, Muriel A, Saez I, Chico-Fernandez M, Estrada-Lorenzo JM, *et al.* Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. *Cochrane Database Syst Rev* 2019;7:CD012247.
88. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-20.
89. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
90. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020;395:507-13.
91. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 2020;395:1054-62.
92. Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, *et al.* Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *medRxiv* 2020. doi: 10.1101/2020.03.04.20031120.
93. Xu D, Zhang H, Gong H, Chen J, Ye J, Meng T, *et al.* Identification of a potential mechanism of acute kidney injury during the covid-19 outbreak: A study based on single-cell transcriptome analysis. Preprints 2020, 2020020331.
94. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, *et al.* Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020. doi: 10.1001/jama.2020.4326.
95. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, *et al.* Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020;97:829-38.
96. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstadt H, *et al.* Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. *JAMA* 2016;315:2190-9.
97. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, *et al.* Initiation Strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016;375:122-33.
98. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyere R, *et al.* Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018;379:1431-42.
99. Xiao L, Jia L, Li R, Zhang Y, Ji H, Faramand A. Early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: A systematic review and meta-analysis. *PLoS One* 2019;14:e0223493.
100. Nash DM, Przech S, Wald R, O'Reilly D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. *J Crit Care* 2017;41:138-44.
101. Durvasula R, Wellington T, McNamara E, Watnick S. COVID-19 and kidney failure in the acute care setting: Our experience from seattle. *Am J Kidney Dis* 2020. doi: 10.1053/j.ajkd.2020.04.001.
102. Investigators RRTS, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, *et al.* Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009;361:1627-38.
103. Network VNARFT, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, *et al.* Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008;359:7-20.
104. Li P, Qu LP, Qi D, Shen B, Wang YM, Xu JR, *et al.* High-dose versus low-dose haemofiltration for the treatment of critically ill patients with acute kidney injury: An updated systematic review and meta-analysis. *BMJ Open* 2017;7:e014171.
105. Gattas DJ, Rajbhandari D, Bradford C, Buhr H, Lo S, Bellomo R. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults. *Crit Care Med* 2015;43:1622-9.
106. Liu C, Mao Z, Kang H, Hu J, Zhou F. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: A meta-analysis with trial sequential analysis of randomized controlled trials. *Crit Care* 2016;20:144.
107. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: A systematic review and meta-analysis. *Lancet Respir Med* 2019;7:163-72.
108. Alshahrani MS, Sindi A, Alshamsi F, Al-Omari A, El Tahan M, Alahmadi B, *et al.* Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. *Ann Intensive Care* 2018;8:3.
109. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, *et al.* Referral to an extracorporeal membrane

- oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). *JAMA* 2011;306:1659-68.
110. Plummer AL, Gracey DR. Consensus conference on artificial airways in patients receiving mechanical ventilation. *Chest* 1989;96:178-80.
111. Gomes Silva BN, Andriolo RB, Saconato H, Atallah AN, Valente O. Early versus late tracheostomy for critically ill patients. *Cochrane Database Syst Rev* 2012;CD007271. doi: 10.1002/14651858.CD007271.pub2.
112. Wang F, Wu Y, Bo L, Lou J, Zhu J, Chen F, *et al.* The timing of tracheotomy in critically ill patients undergoing mechanical ventilation: A systematic review and meta-analysis of randomized controlled trials. *Chest* 2011;140:1456-65.
113. Terragni PP, Antonelli M, Fumagalli R, Faggiano C, Berardino M, Pallavicini FB, *et al.* Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: A randomized controlled trial. *JAMA* 2010;303:1483-9.
114. Blot F, Similowski T, Trouillet JL, Chardon P, Korach JM, Costa MA, *et al.* Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med* 2008;34:1779-87.
115. Cinotti R, Voicu S, Jaber S, Chousterman B, Paugam-Burtz C, Oueslati H, *et al.* Tracheostomy and long-term mortality in ICU patients undergoing prolonged mechanical ventilation. *PLoS One* 2019;14:e0220399.
116. Young D, Harrison DA, Cuthbertson BH, Rowan K, TracMan C. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: The TracMan randomized trial. *JAMA* 2013;309:2121-9.
117. Meng L, Wang C, Li J, Zhang J. Early vs late tracheostomy in critically ill patients: A systematic review and meta-analysis. *Clin Respir J* 2016;10:684-92.
118. Szakmany T, Russell P, Wilkes AR, Hall JE. Effect of early tracheostomy on resource utilization and clinical outcomes in critically ill patients: Meta-analysis of randomized controlled trials. *Br J Anaesth* 2015;114:396-405.
119. Nap RE, Andriessen MP, Meessen NE, Miranda Ddos R, van der Werf TS. Pandemic influenza and excess intensive-care workload. *Emerg Infect Dis* 2008;14:1518-25.
120. Lateef F. Hospital design for better infection control. *J Emerg Trauma Shock* 2009;2:175-9.
121. Nap RE, Andriessen MP, Meessen NE, van der Werf TS. Pandemic influenza and hospital resources. *Emerg Infect Dis* 2007;13:1714-9.
122. Toner E, Waldhorn R. What hospitals should do to prepare for an influenza pandemic. *Biosecur Bioterror* 2006;4:397-402.
123. Kain T, Fowler R. Preparing intensive care for the next pandemic influenza. *Crit Care* 2019;23:337.
124. Dichter JR, Kanter RK, Dries D, Luyckx V, Lim ML, Wilgis J, *et al.* System-level planning, coordination, and communication: Care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest* 2014;146 (4 Suppl):e87S-102S.
125. Hick JL, Einav S, Hanfling D, Kissoon N, Dichter JR, Devereaux AV, *et al.* Surge capacity principles: Care of the critically ill and injured during pandemics and disasters: CHEST consensus statement. *Chest* 2014;146 (4 Suppl):e1S-16S.
126. Courtright KR, Kerlin MP. Intensive care unit staffing and quality of care: Challenges in times of an intensivist shortage. *Rev Bras Ter Intensiva* 2014;26:205-7.
127. Seda G, Parrish JS. Augmenting critical care capacity in a disaster. *Crit Care Clin* 2019;35:563-73.
128. Rolston DM, Meltzer JS. Telemedicine in the intensive care unit: Its role in emergencies and disaster management. *Crit Care Clin* 2015;31:239-55.
129. Kadar RB, Amici DR, Hesse K, Bonder A, Ries M. Impact of telemonitoring of critically ill emergency department patients awaiting ICU transfer. *Crit Care Med* 2019;47:1201-7.
130. Lee AM, Wong JG, McAlonan GM, Cheung V, Cheung C, Sham PC, *et al.* Stress and psychological distress among SARS survivors 1 year after the outbreak. *Can J Psychiatry* 2007;52:233-40.
131. Maunder R, Hunter J, Vincent L, Bennett J, Peladeau N, Leszcz M, *et al.* The immediate psychological and occupational impact of the 2003 SARS outbreak in a teaching hospital. *CMAJ* 2003;168:1245-51.
132. Wu KK, Chan SK, Ma TM. Posttraumatic stress after SARS. *Emerg Infect Dis* 2005;11:1297-300.
133. Prevention CfDca. Ethical Considerations for Decision Making Regarding Allocation of Mechanical Ventilators during a Severe Influenza Pandemic or Other Public Health Emergency. 2011.
134. Daugherty Biddison EL, Faden R, Gwon HS, Mareiniss DP, Regenber AC, Schoch-Spana M, *et al.* Too many patients. A framework to guide statewide allocation of scarce mechanical ventilation during disasters. *Chest* 2019;155:848-54.
135. Crisis Standards of Care: A Systems Framework for Catastrophic Disaster Response. Washington (DC): National Academies Press (US); 2012.
136. Thompson AK, Faith K, Gibson JL, Upshur RE. Pandemic influenza preparedness: An ethical framework to guide decision-making. *BMC Med Ethics* 2006;7:E12.
137. Borenskie KF, Borenskie PE, Melady D. Age is just a number-and so is frailty: Strategies to inform resource allocation during the COVID-19 pandemic. *CJEM* 2020;1-3. doi: 10.1017/cem.2020.358.
138. Prevention CfDC. Information for Pediatric Healthcare Providers. 2020.
139. Streng A, Hartmann K, Armann J, Berner R, Liese JG. [COVID-19 in hospitalized children and adolescents]. *Monatsschr Kinderheilkd* 2020;1-12. doi: 10.1007/s00112-020-00919-7
140. Mikalsen IB, Davis P, Oymar K. High flow nasal cannula in children: A literature review. *Scand J Trauma Resusc Emerg Med* 2016;24:93.
141. Rimensberger PC, Cheifetz IM; Pediatric Acute Lung Injury Consensus Conference Group. Ventilatory support in children with pediatric acute respiratory distress syndrome: Proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015;16 (5 Suppl 1):S51-60.
142. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, *et al.* Surviving Sepsis Campaign International Guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med* 2020;21:e52-106.
143. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, *et al.* Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Intensive Care Med* 2020;46(Suppl 1):10-67.