Severe covid-19 pneumonia: pathogenesis and clinical management

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ABSTRACT

Severe covid-19 pneumonia has posed critical challenges for the research and medical communities. Older age, male sex, and comorbidities increase the risk for severe disease. For people hospitalized with covid-19, 15-30% will go on to develop covid-19 associated acute respiratory distress syndrome (CARDS). Autopsy studies of patients who died of severe SARS CoV-2 infection reveal presence of diffuse alveolar damage consistent with ARDS but with a higher thrombus burden in pulmonary capillaries. When used appropriately, high flow nasal cannula (HFNC) may allow CARDS patients to avoid intubation, and does not increase risk for disease transmission. During invasive mechanical ventilation, low tidal volume ventilation and positive end expiratory pressure (PEEP) titration to optimize oxygenation are recommended. Dexamethasone treatment improves mortality for the treatment of severe and critical covid-19, while remdesivir may have modest benefit in time to recovery in patients with severe disease but shows no statistically significant benefit in mortality or other clinical outcomes. Covid-19 survivors, especially patients with ARDS, are at high risk for long term physical and mental impairments, and an interdisciplinary approach is essential for critical illness recovery.

Introduction

The ongoing outbreak of the coronavirus disease 2019 (covid-19) has posed immense challenges for the research and medical communities. This review focuses on the epidemiologic and clinical features of covid-19, the pathophysiologic mechanisms, inpatient respiratory support, and the evidence to date on drug treatments. It also covers the recovery and long term management of patients with covid-19 pneumonia. The review is aimed at clinicians and intensivists caring for patients with severe covid-19 pneumonia as defined by the National Institutes of Health,¹ referring to individuals with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) testing who have SpO₂ <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.

Methods

We manually searched electronic databases PubMed and Embase for English language articles published from 1 January 2020 to 20 February 2021. We also reviewed the medRxiv preprint server to monitor the rapidly evolving information on covid-19. We used the following search terms in combination with the term “covid-19”: “pneumonia”, “ARDS”, “pathogenesis”, “epidemiology”, “survival”,

ABBREVIATIONS

RCTs (randomized controlled trials), OR (odds ratio), ECMO (extra corporeal membrane oxygenation), RR (rate ratio), HFNC (high flow nasal cannula), NIV (non-invasive ventilation), IMV (invasive mechanical ventilation), HCQ (hydroxychloroquine), CP (convalescent plasma), EUA (emergency use authorization), ED (emergency department), IV (intravenous), PICS (post-intensive care syndrome), ICU (intensive care unit), ARDS (acute respiratory distress syndrome), MoCA (Montreal Cognitive Assessment), MRI (magnetic resonance imaging), IQR (interquartile range), PEEP (positive end expiratory pressure), PPE (personal protective equipment), NMB (neuromuscular blockade), CARDS (coronavirus associated acute respiratory distress syndrome), Pplat (plateau pressure), COPD (chronic obstructive pulmonary disease), CHF (congestive heart failure), SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), NYC (New York City), IES-R (impact of event scale-revised), EQ-5D (European Quality of Life Five Dimension), HADS (Hospital Anxiety and Depression Scale), ADL (activities of daily living), IADL (instrumental activities of daily living)

“therapeutics”, and “complications”. We included articles on the basis of the quality of the study and

avored large randomized controlled trials (RCTs), high quality observational studies, systematic reviews, meta-analyses, and guidelines. Because of the evolving nature of the pandemic, the paucity of data, and the lack of RCTs, our article selection for respiratory care and post-covid complications included observational studies and case series. We excluded case reports and articles in non-peer reviewed journals.

Clinical manifestations and epidemiology

At the time of writing, covid-19 is responsible for 116 million cases globally and 2.5 million deaths.² The most striking characteristic of the disease is its heterogeneity, ranging from no symptoms to critical illness.³ Older age, male sex, race (particularly Black, Hispanic, and South Asian), and comorbidities (including hypertension, diabetes, cardiovascular disease, chronic pulmonary disease, chronic kidney disease, cancer, and chronic liver disease) have been associated with worse outcomes.³⁻⁸ Genetic factors may play a part as well, with blood type A associated with a higher risk for severe disease.⁹ A common characteristic of SARS-CoV-2 is asymptomatic transmission,¹⁰ which is likely the cause of rampant spread and transmission.¹¹ Given SARS-CoV-2 entry is primarily via the respiratory tract, upper and lower respiratory tract involvement is the most common manifestation.¹² About one third of patients hospitalized with SARS-CoV-2 infection meet criteria for acute respiratory distress syndrome.¹³ In-hospital mortality, while initially very high in certain series (60% for those intubated in a large study from New York City in April 2020¹⁴) has been declining during the course of the pandemic, with in-hospital survival improving from 74.4% (March 2020) to 92.4% (August) in a study from New York City,¹⁵ and intensive care unit (ICU) survival improving from 58% (March) to 80% (June) in a large national surveillance database from England.¹⁶

Pathophysiologic mechanisms

Structure of SARS-CoV-2

SARS-CoV-2 is a positive sense, single stranded RNA enveloped virus in the *Betacoronavirus* genus.^{12 17} Bats and pangolins may be the animal hosts of SARS-CoV-2 as there is a >90% gene homology to the SARS-CoV-2 found to infect humans.^{12 18} Currently it remains unclear if SARS-CoV-2 was directly transferred from bat/pangolins to humans or an intermediate host was required for transmission.^{12 18} In light of the current pandemic, researchers first compared SARS-CoV-2 with the previous endemic SARS-CoV (2002-03) and MERS-CoV (2012).¹⁹ SARS-CoV-2 has overlapping genetic sequences with SARS-CoV and MERS-CoV, with 79% and 50% homology, respectively.^{17 20 21}

SARS-CoV-2 is characterized by four main structural proteins that are important for infectivity and replication.²⁰ These proteins include the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins.^{22 23} The S protein, which includes two

protein subunits (S1 and S2), gives the virus its well known appearance as the S protein protrudes from the membrane.²⁴ The tip of the protruding S protein has a crown (Latin *corona*)-like shape.²⁴ The S protein is also important for binding to the angiotensin converting enzyme 2 (ACE2) receptor, which is the point of entry of the virus to the human and animal host.²⁵ Furthermore, the S protein is thought to be a major contributor to the immunogenic response; therefore the S protein is the target of most vaccines.^{25 26} The M protein is a transmembrane protein important in viral pathogenesis.²⁷ Little is understood about the E protein; however, it is known to play a role in viral replication and infectivity.^{28 29} Finally, the N protein allows for regulation of viral RNA replication, transcription, and synthesis.³⁰

SARS-CoV-2 mutations

Emerging data show distinctive mutations in the SARS-CoV-2 genome isolated from patients.³¹ SARS-CoV-2 mutated variants include B.1.1.7 (UK variant), P.1 (Brazilian variant)³², and B.1.351 (South African variant).³³ The primary region of mutation for these variants is in the spike protein. The B.1.1.7 variant has a greater rate of infectivity and spread,³² which may be related to binding affinity to the ACE2 receptor.³⁴

SARS-CoV-2 invasion and replication in cells (fig 1)

Early knowledge of the entry process of SARS-CoV-2 into host cells, via the binding of the S protein to the ACE2 receptor, was extrapolated from what was known from SARS-CoV.^{35 36} Human ACE2 (hACE) receptor is the same receptor used by SARS-CoV for viral entry.³⁷ hACE receptor is similar across animal species but with a varied binding efficiency.³⁷ Older age and male sex of the host are also determinants of S protein-ACE2 binding efficiency.³⁸ ACE2 receptors are highly expressed in the upper respiratory tract of humans.¹⁷ Proteolytic cleavage of the S protein by serine proteases including transmembrane protease serine 2 (TMPRSS2), cathepsin L, and furin, are required for binding to the ACE2 receptor.³⁵ Similar to the ACE2 receptor, protease expression varies by tissue type and location, with a high expression in the nasal and bronchial epithelium.³⁹ In addition, human epithelial cells that line mucosal surfaces and cover organs such as conjunctiva, gastrointestinal tract, liver, and kidney also express ACE2 and TMPRSS2.^{40 41} Once the virus attaches to the host cell receptors, it undergoes endocytosis, viral maturation, replication, and release of more virus within the cytoplasm of the host cell.³⁷ SARS-CoV-2 infection begins with viral replication and partially avoids host recognition during the initial infection and before the host innate response is enabled.⁴²

Host response

Limited mechanistic data are available on the innate immune response to SARS-CoV-2⁴² although expansion of in vitro studies, animal models, and covid-19 patient serum profiles has been

Fig 1 | SARS-CoV-2 S spike protein binds to the ACE2 receptor, which leads to proteolytic cleavage by TMPRSS2, cathepsin L, and furin in the epithelial cell of the respiratory tract. The virus undergoes endocytosis, viral maturation, replication, and release of more virus within the cytoplasm infecting the host cell. Consequences of infected cells include pro-inflammatory cytokine secretion, microangiopathic vasculopathy, and B cell secretion of specific SARS-CoV-2 antibodies

significant.⁴³ It is now evident that over the first few days after SARS-CoV infection, activation of toll-like receptors (TLR 3, 7, and 8) by pathogen recognition receptors (PRRs) induces transcriptional upregulation of interferons (type I and III interferons) and recruitment of leukocytes.⁴³

The magnitude of the innate antiviral response has been associated with the degree of infection, which might account for the heterogeneous viral response among those infected with covid-19.⁴² The adaptive immune response starts with IgA, IgG, and IgM specific antibody release similar to the response to SARS-CoV.⁴⁴ The timing of antibody release and the persistence of detectable levels has varied among patients.⁴⁴ Case and observational studies in patients with SARS-CoV-2 showed early detection of specific IgA and IgM antibodies (within five days) and late detection of specific IgG antibodies (after 14 days).⁴⁴ In addition, disease severity has recently been shown to drive an enhanced antibody response,^{45 46} which correlates with clinical outcomes.⁴⁷

Clinical observation of lymphopenia has been apparent since the start of the covid-19 pandemic and may be associated with worsening disease.⁴⁸ An adequate T cell response (both CD4⁺ and CD8⁺ T cells) directed toward SARS-CoV-2 has been shown to be associated with milder disease.⁴⁹ Aging is well established to be associated with failure of regeneration of naive T cells and T cell activation.⁵⁰ In covid-19, dysregulation of T cell homeostasis has been postulated as a mechanism for severe disease seen in older adults.⁴⁹ Direct anti-SARS-CoV-2 antibodies have been manufactured for treatment by Regeneron (REGN10933 and REGN 10987) and Eli Lilly (LY-CoV016) to bind to the viral receptor binding domain.³⁴ Concern is ongoing that the

mutations would give the virus the ability to escape direct binding to the specific antibodies.³⁴ More research is needed to fully identify the impact the virus mutations have on the treatment modalities available.

Early descriptions of covid-19 included development of a cytokine storm as a harbinger for clinical deterioration.⁵¹ Clinical and serologic evidence points to high levels of serum IL-6, IL-1 β , and TNF- α which are associated with clinical instability and other biomarkers of inflammation.⁵²⁻⁵⁴ More recent studies comparing serum cytokine measurements with other known cytokine mediated diseases such as sepsis and cytokine release syndrome have noted that covid-19 patients' serum cytokine levels were substantially lower.^{51 52 55} As a result, the direct role of cytokines in disease pathogenesis has been challenged.⁵⁵ Many unanswered questions related to the pathogenesis of inflammation and the mechanism of action of corticosteroids in covid-19.

Autopsy studies of patients who have died from severe SARS CoV-2 infection reveal presence of alveolar wall injury and diffuse alveolar damage consistent with ARDS.^{56 57} However, compared with classic ARDS, autopsy studies also indicate higher thrombus burden in pulmonary capillaries, which suggests a greater pathogenic role of thrombotic and microangiopathic vasculopathy in covid-19 related ARDS.^{56 57} Studies collectively show that thromboembolism occurs more frequently and is associated with a higher mortality in patients with covid-19.^{58 59} Additional studies are needed to delineate the direct clinical consequences of increased thrombosis and its association with mortality in covid-19, which have major implications for the management of respiratory failure. Current

studies are ongoing to investigate treatment with anticoagulants, which may shed light on the importance of thrombosis in covid-19 ARDS.

Respiratory care for severe covid-19 pneumonia

Severe covid-19 pneumonia as defined by NIH¹ overlaps significantly with the clinical definition of “classic” ARDS.⁶⁰ However, several unique pathophysiological processes are postulated to be at play for CARDS, such as intravascular thrombosis caused by loss of endothelial barrier, prominent loss of hypoxic pulmonary vasoconstriction resulting from endothelial dysfunction, and excessive blood flow to collapsed lung tissue.⁶¹ Further, not all case series provide a clear semantic distinction between severe covid-19 pneumonia and CARDS, which confounds interpretation. In this section, we summarize the current literature on the use of respiratory therapy equipment in patients with severe covid-19 pneumonia. To date, no controlled prospective trials inform the respiratory management of severe covid-19 pneumonia. Notwithstanding, among patients with severe covid-19 pneumonia, patient respiratory system mechanics and clinical outcomes achieved with standard ARDS management are similar to classic ARDS. Consequently, contemporary respiratory care revolves around supportive measures and is based on the management of classic ARDS. We begin by providing a general review of these concepts.

Titration of oxygen therapy to avoid hyperoxemia^{62 63} and hypoxemia⁶⁴ is strongly recommended for acute hypoxemic respiratory failure. A range of 90–96% oxygen saturation, confirmed by co-oximetry, is a reasonable target.⁶³ For patients who require invasive mechanical ventilation (IMV), the first goal is avoidance of high tidal volumes, which are associated with ventilator induced lung injury.^{65 66} Evidence suggests that similar injury could occur because of sustained high tidal volumes during spontaneous breathing, also known as patient self-induced lung injury (P-SILI).^{67–69} Although not validated in controlled clinical trials, an assessment of strain known as tidal pressure or driving pressure^{70 71} (defined as the ratio of tidal volume to tidal respiratory system compliance) allows matching of volume delivery with respiratory system mechanics and enables optimal mechanical ventilatory settings. In an observational study of non-covid ARDS trials, mediation analysis revealed that 75% of the beneficial effect of treatment group assignment was attributable to reduction in tidal pressure.⁷⁰

The second goal of mechanical ventilation in ARDS is to prevent the constant opening and closing of alveoli which may be injurious to the lung (atelectrauma). Positive end expiratory pressure (PEEP) is titrated to keep alveolar units open throughout the respiratory cycle. Several RCTs that aimed to optimize recruitment in the intervention arm showed similar clinical outcomes to controls^{72 73} and a signal for potential harm which was attributed

to recruitment maneuvers.⁷⁴ To that end, the benefits of higher PEEP are evident only when reducing tidal pressure—ie, less strain for a given tidal volume.⁷⁰ Recruitability (the ability to open and keep alveoli open) can be assessed at the bedside by calculating the recruitment/inflation (R/I) ratio.^{75 76} For patients who are proven recruitable, employing the high PEEP and F_IO₂ table⁷² may be preferable while monitoring cardiac output and respiratory mechanics to avoid concurrent hyperinflation.^{77 78}

Prone ventilation and neuromuscular blockade (NMB) are frequent adjuncts in the treatment of ARDS. Prone ventilation promotes lung recruitment and improves ventilation/perfusion matching by creating a more even distribution of transpulmonary pressure throughout the chest. A multicenter, prospective RCT showed that among patients with severe hypoxemic respiratory failure (P_aO₂/F_IO₂ <150), prone positioning >16 hours a day was associated with reduced 28 day mortality.⁷⁹ NMB in early ARDS potentially reduces lung strain by eliminating spontaneous breathing activity. Despite earlier encouraging findings, a recent meta-analysis of five RCTs showed no mortality benefit, with a modest reduction in barotrauma risk and improved oxygenation if applied after 48 hours in patients with severe ARDS.⁸⁰

The belief that respiratory care principles to treat classic ARDS should apply in CARDS was challenged when earlier series of covid-19 patients seemed to indicate two different respiratory failure phenotypes.⁸¹ A case series (n=16) noted that patients had low elastance, low ventilation/perfusion matching, low recruitability and lung weight which they named the “L type.” Conceivably, such discrepancy of ventilation/perfusion matching with relatively normal mechanics was attributed to loss of lung perfusion regulation and hypoxic vasoconstriction. The remainder of the cases were more consistent with classic ARDS (high elastance, high ventilation/perfusion ratio, high recruitability and lung weight) referred to as the “H type.” The authors suggested that patients who had the L type may not require low tidal volume ventilation and attempts at recruitment could bring harm. Further, they reasoned that patients who present with a paucity of infiltrates, low elastance, and hypoxemia should be placed on mechanical ventilation earlier to prevent spontaneous high tidal volumes generated by the patients. This proposed need for a different management has been contested on the grounds of inconclusive evidence for P-SILI and CARDS case series that revealed respiratory system mechanics similar to classic ARDS.^{82 83}

Current observational reports mirror our experience and reinforce our view that a significant proportion of patients with covid-19 pneumonia can be treated non-invasively (ie, high flow nasal cannula (HFNC) or non-invasive ventilation (NIV)) in lieu of invasive mechanical ventilation (IMV). This approach may also optimize utilization of mechanical ventilators, a scarce resource during the

pandemic. We recommend using the entire spectrum of non-invasive and invasive devices for respiratory assistance (fig 2). Figure 2 is based on our practice in treating severe covid-19 pneumonia, and draws largely from the experience in classic ARDS. Close monitoring and attention to signs of non-invasive device failure are crucial for optimal outcomes. Extra corporeal membrane oxygenation (ECMO) is available for patients who have refractory hypoxemia after these measures⁸⁴ but is infrequently needed.⁸⁵

The following sections provide an overview of the different respiratory equipment and outline the rationale for their use in severe covid-19 pneumonia.

High flow nasal cannula oxygen therapy

HFNC oxygen therapy refers to the delivery of humidified and heated oxygen at high flows, typically 20-60 L/min, which is titrated to a precise fraction of inspired oxygen (F_iO_2). The advantages of delivering oxygen in this manner include improved comfort by satisfying patient flow demand,⁸⁶ creating an oxygen reservoir in the upper airway thereby reducing physiological dead space (reduced CO_2 rebreathing),⁸⁷ and providing a modest PEEP

that could help recruit collapsed alveoli⁸⁸ with consequent reduction in work of breathing.

Recent meta-analyses suggest that application of HFNC in the setting of acute hypoxemic respiratory failure can reduce the risk of intubation and invasive mechanical ventilation by 15% compared with conventional oxygen therapy without affecting mortality.^{89,90} However, use of HFNC requires vigilant monitoring for signs of impending respiratory failure. Roca and colleagues devised and validated the ROX index (ratio of oxygen saturation by pulse oximetry/ F_iO_2 to respiratory rate) as a bedside tool for predicting HFNC failure in the setting of pneumonia and hypoxemic respiratory failure.⁹¹ Accordingly, patients with a ROX index ≥ 4.88 after 2, 6, and 12 hours of treatment had low risk of intubation, whereas a ROX index < 3.85 at the same time points was associated with a high risk of failure. Delaying intubation until the occurrence of overt desaturation, hypotension, respiratory rate > 35 breaths/min with respiratory distress, or acidosis has been associated with poor clinical outcomes.⁹²

Evidence on the use of HFNC for covid-19 pneumonia consists of case reports and case

Fig 2 | Algorithm for the respiratory management of a patient with covid-19 pneumonia. RR=respiratory rate, PEEP=positive end expiratory pressure, R/I=recruitment/inflation ratio, COPD=chronic obstructive pulmonary disease, CHF=congestive heart failure, HFNC=high flow nasal cannula, WOB=work of breathing, P/F=PaO₂/FiO₂ ratio, MAP=mean arterial pressure, NIV=non-invasive ventilation

series.⁹³⁻¹⁰² It attests to the feasibility of utilizing HFNC in this setting; however, firm conclusions regarding efficacy are difficult to draw because of the lack of control groups. Table 1 shows large case series in the English language and provides detailed patient information and outcomes. The patients in these series had respiratory failure with P_aO_2/F_iO_2 ranging from 68 to 209. The average duration of HFNC was between three and six days; however, patients who required escalation of care did so earlier in the course of treatment. HFNC was associated with successful outcomes (ie, no escalation of care) in 34% to 70% of cases. ROX index determined after 4-6 hours of treatment predicted escalation of care.^{93 95 97} Patients with $P_aO_2/F_iO_2 > 200$ before commencing HFNC and who had a reduction in respiratory rate within the first several hours had the best outcomes.¹⁰¹ Of note, HFNC treatment is feasible in conjunction with proning patients who have not been intubated (awake proning) and improves oxygenation. However, an observational study noted no difference in the rate of intubation between supine and prone patients.⁹⁴

HFNC was avoided at the beginning of the SARS CoV-2 pandemic in favor of early intubation for fear of disease transmission by exhaled aerosol. However, disease transmission has not been shown in clinical studies.¹⁰³ HFNC does not lead to aerosol generation^{104 105} and aerosol dispersion can be limited by having patients wear masks.¹⁰⁶ To that end, experts suggest clinicians utilize HFNC treatment for covid-19 patients no differently than for those without infection¹⁰⁷ with careful attention to proper use of personal protective equipment (PPE).^{98 106} Despite the lack of controlled trials in covid-19, large case series show favorable outcomes for patients who receive therapy with HFNC. A recent computer simulation study concluded that strategies incorporating HFNC for patients not urgently needing intubation could result in greater mechanical ventilator availability and fewer deaths.¹⁰⁸ Propensity score matched analyses comparing HFNC and other means of respiratory assistance suggest lesser likelihood of intubation,¹⁰² higher number of ventilator free days and reduction in ICU length of stay¹⁰⁹ with the former.

Non-invasive ventilation

Non-invasive ventilation (NIV) is delivered through a face mask or a helmet that is placed over the patient's head. The helmet interface potentially presents a safer alternative (from an infection control perspective) because it eliminates leaks. In the settings of acute congestive heart failure and acute hypercapnic respiratory failure due to COPD, NIV has been extremely effective in preventing intubation and reducing mortality.^{110 111}

Application of NIV in the setting of acute hypoxemic respiratory failure excluding COPD and cardiogenic pulmonary edema has been controversial, with mixed results.^{68 112-115} Several red flags were raised for NIV when treating ARDS patients. For instance, in the LUNG SAFE study, overall success rate for NIV in

classic ARDS was 63% with an in-hospital mortality of 36%. NIV was associated with higher intensive care unit mortality among ARDS patients with $P_aO_2/F_iO_2 < 150$ mm Hg on presentation.¹¹⁶ A prospective observational study reported failure of NIV in the presence of high expired tidal volumes (> 9.5 mL/kg predicted body weight) and poor oxygenation at baseline ($P_aO_2/F_iO_2 < 200$ mmHg).⁶⁸ Similarly, one hour after initiation of NIV, expired tidal volumes > 9 mL/kg of predicted body weight and $P_aO_2/F_iO_2 \leq 200$ mmHg independently predicted NIV failure.¹¹² A post hoc analysis reported higher risk of intubation and mortality for patients treated with NIV versus HFNC in a group of immunocompromised patients with acute respiratory failure.¹¹⁷ A recent network meta-analysis of 25 RCTs comparing standard oxygen treatment with NIV or HFNC showed lower risk of intubation (HFNC risk ratio 0.76 [95% confidence interval, 0.55 to 0.99]; NIV risk ratio 0.76 [95% confidence interval, 0.62 to 0.90]) and lower risk of mortality (NIV risk ratio 0.83 [95% confidence interval, 0.68 to 0.99]).¹¹⁸ However, mortality benefit for NIV delivered by face mask vanished for patients with severe hypoxemia ($P_aO_2/F_iO_2 \leq 200$) when excluding COPD, heart failure, or postoperative patients. In contradistinction, when helmet interface was used to facilitate NIV, the benefit on mortality was maintained, emphasizing the possible importance of how NIV is provided.

A concern with respect to NIV is the higher risk for disease transmission, as noted in previous viral epidemics¹⁰³ because of mask leaks and aerosol dispersion. NIV use was limited in the US and Europe owing to concerns over disease transmission and questionable efficacy in ARDS.^{119 120} In China, on the other hand, NIV was used as the initial strategy between 57% and 85% of the time,¹²¹⁻¹²³ and to date no clear evidence shows increased disease transmission to healthcare workers.^{122 124}

The studies that report detailed patient characteristics and outcomes for the use of NIV in covid-19 pneumonia (table 1) are limited to case series.^{100 121 123 125-129} Owing to the observational nature of the studies, NIV management is not driven by protocol and no specific guidance is provided on titration of support or when to intubate. Outcome data suffer from incomplete reporting and reveal highly variable hospital survival ranging from 14% to 95%.^{125 129} Preliminary outcome data from Italy were also not as promising for the use of helmet CPAP in covid-19 as they were for non-covid respiratory failure.^{125 130} In a retrospective study¹²⁵ the patients on helmet CPAP died without intubation 54.9% of the time, attesting to the resource limited conditions under which the study was conducted. Patients with chronic illness,¹²³ severe disease on presentation,^{121 130} and increased inflammatory markers^{123 129 130} were at risk for NIV failure. A large prospective single day study from Italy indicated that NIV was successfully used outside of the ICU setting using helmet CPAP in two thirds of the cases of severe covid-19 pneumonia.¹³¹ A retrospective analysis

(n=40) of covid-19 patients who eventually required IMV found that time spent on NIV and HFNC before intubation was associated with higher mortality.¹³² More recent retrospective cohort studies, which employed multivariable risk adjustment, suggest NIV is safe¹³³ and potentially superior to early intubation¹³⁴⁻¹³⁶ strategy. Because thresholds for intubation and clinical monitoring over the course of illness were not standardized a priori, it is difficult to draw firm conclusions from these observational studies.

In the absence of concomitant COPD or pulmonary edema, the benefits of NIV are uncertain in the management of ARDS, and we prefer HFNC as the initial non-invasive support in severely hypoxemic patients with CARDS. When NIV is utilized, frequent surveillance of expired tidal volume, respiratory rate, hemodynamics, and oxygenation is critical for timely escalation of support.

Invasive mechanical ventilation

While initial case series reported high mortality rates for patients receiving IMV for covid-19 pneumonia,³⁴ these studies originated from hospitals that were overwhelmed with surges of covid-19 patients. Subsequent larger and complete series reported mortality rates consistent with classic ARDS when basic ARDS management tenets were followed.^{85 137-141} In table 1 we summarize select large case series with detailed information on baseline characteristics, ventilator settings, and outcomes for patients receiving IMV.

Similar to HFNC and NIV, studies on IMV in the setting of covid-19 pneumonia suffer from retrospective design and lack of a control group. Notwithstanding, they indicate a striking resemblance in respiratory system mechanics and outcomes to classic ARDS.

The LUNG SAFE study reported the incidence, outcome, ventilator settings, adjunctive therapies, and outcomes of 2377 patients with classic ARDS who received IMV in 459 ICUs in 50 countries.¹⁴² The median age was 61 years, with nearly 60% of patients with pneumonia as the cause for ARDS. Patients remained on IMV for a median of 8 (4-16) days. Twenty eight day mortality was 35% overall and 41% for those with severe ARDS. On presentation, median P_{aO_2}/F_{iO_2} 161 (158-163) mm Hg, mean plateau pressure (Pplat) was 23.2 (22.6-23.7) cm H₂O, delivered PEEP was 8.4 (8.3-8.6) cm H₂O, and FiO_2 0.65. Adjunctive measures included NMB (22%), prone positioning (8%), and ECMO (3%).

Compared with observations in the LUNG SAFE study, IMV duration in CARDS case series may be slightly longer^{85 137 138 140} with higher rates of NMB use and prone positioning.^{85 137 140 141} Following the preliminary retrospective analysis of respiratory physiology during IMV,⁷⁶ several larger prospective studies comparing consecutive typical ARDS and CARDS patients have been published.¹⁴³⁻¹⁴⁶ These studies essentially confirm the notion of similar respiratory mechanics and physiology between

the two conditions; however with some interesting nuances. One study¹⁴⁴ matched 30 CARDS patients with 30 typical ARDS patients based on oxygenation parameters, tidal volume, and PEEP. It confirmed similar respiratory system mechanics and demonstrated high recruitability (R/I ratio >0.5) in both CARDS (73%) and ARDS (57%) patients, in contrast to the preliminary analysis which showed low recruitability when supine. R/I ratio inversely correlated with P_aCO_2 response to PEEP titration, suggesting hyperinflation and increase in dead space when recruitability was low. A study of 301 CARDS patients¹⁴³ found similar respiratory system mechanics and lung weight as determined by computed tomography scan compared with a retrospective cohort of typical ARDS patients. The investigators identified that those with a lower respiratory system compliance (<41 mL/cm H₂O) and high D-dimer had higher mortality compared with other subgroups. Ventilatory ratio (the product of tidal volume, ventilatory rate, and $PaCO_2$, indexed for predicted body weight), which is a marker for dead space, also correlated with D-dimer levels raising suspicion for pulmonary intravascular thrombosis.

A contentious issue in IMV is when to intubate patients with CARDS. Two retrospective cohort studies of covid-19 patients have reported different conclusions, with one favoring earlier intubation¹⁴⁷ and the other finding no association of mortality with time to intubation or HFNC use.¹⁴⁸ Intensivists have struggled with this dilemma since the beginning of mechanical ventilation¹⁴⁹; triggers for initiating IMV in clinical studies and in practice are not standardized and may depend on various factors including clinical judgment, severity of illness, patient preference, and cultural norms regarding mechanical ventilation. In the case of covid-19 pneumonia, resource limitation, hypothetical concerns over P-SILI,⁸³ and expert opinion on NIV may have played a role in the adoption of early IMV. Given the favorable outcomes of HFNC trials in classic ARDS,^{89 90} we speculate that the likelihood of harm is small when standardized indices for detecting respiratory failure are applied and patients are transitioned to IMV when clinically indicated.

Tracheobronchial hygiene

Patients on mechanical ventilation for covid-19 pneumonia may develop increased mucus production with airflow obstruction. In a large cohort of covid-19 patients who underwent tracheostomy, most of the endotracheal tubes were partially occluded with sticky secretions.¹⁵⁰ This manifestation may be due to changes in mucus regulation caused by SARS-CoV2 infection.¹⁵¹ Effective humidification, monitoring airway resistance, and potentially the use of mucolytics and endotracheal tube clearing devices¹⁵² may be helpful.

Weaning and tracheostomy

We found no pertinent studies evaluating strategies for weaning from mechanical ventilation for covid-19

Table 1 | Studies on respiratory assist devices in covid-19 (HFNC, NIV, and IMV)

Study	N (HFNC)	Age median (interquartile range)	Gender (% F)	Oxygenation at baseline PaO ₂ /FiO ₂	Duration of use	Outcome	Comment
Selected studies on high flow nasal cannula							
Calligaro et al	293	52 (44-58)	44	68 (54-92)	6 (3-9) days-success 2 (1-5) days failure	47% success on HFNC alone. Overall survival to discharge 52%	ROX-6 h ≥ 3.7 , 80% success ROX-6 h ≤ 2.2 , 74% failure
Ferrando et al	199	HFNC only: 63 (55-71) HFNC+ Prone: 60 (54-70)	26	HFNC only 111 (83-144) HFNC+prone 125 (99-187)	Treatment duration not available ICU length of stay 7.5-8 days	HFNC success 58.3% +prone 60% ICU mortality 13.9% and 16.3% respectively	No difference in outcomes when proning HFNC patients. Potential delay in intubation when proning
Demoule A et al	146	60 (53-67)	21	126 (86-189)	4 (2-6)	28 day mortality 21 %	HFNC reduced intubation rate without affecting case fatality (propensity score matched analysis versus those who did not receive HFNC)
Zucman et al	62	55 (48-63)	Not reported	F _O ₂ 0.8 (0.6-1) SpO ₂ 96 (94-98) %	10 hours (7-57) for failure	34% success on HFNC alone. Overall ICU mortality 17%	ROX-4 h ≥ 3.7 , lower risk of intubation HR 0.59 (95% confidence interval 0.41 to 0.84)
Xia et al	43	64 SD 9.7	42	122.3 $\pm$ 51.3 mm Hg	4 (2-7) days 5 (3-7) days success 3.5 (1.5-6.5) days failure	53.5% success on HFNC alone. Hospital mortality 32.5% for entire cohort (65% if HFNC failure)	Male sex and lower oxygenation on admission risk factors for failure. Overall mortality 32.5%. Mortality 65% for invasive mechanical ventilation
Panadero et al	40	58.9 SD 11.8	30%	S _p O ₂ /F _i O ₂ 113.4 $\pm$ 6.6 (success) 93.7 $\pm$ 6.7 (failure)	6 (5-8) days success 2 (1-4) days failure	Not intubated at 30 days 47.5% Mortality 22.5%	ROX 2-6 $<$ 4.94 associated with high risk of intubation HR 4.03 (1.18-13.7)
Vianello et al	28	69 (42-87)	33.3	108 (52-296)	Not available	67.8% discharged alive. 17.8% required IMV 15 day mortality 11% (3 patients on IMV)	Patients with P _a O ₂ /F _i O ₂ $\leq$ 100 had failure rate of 77.8%. Among the 73 healthcare workers who took care of the patients for an average of 48 hours per person, no infections were reported
Guy et al	27	77 (77-79)	19	124 (120-158)	6 (2-10) days	70% HFNC success. 26% required invasive mechanical ventilation. Overall mortality 15%	Consecutive patients treated in a non-ICU setting
Duan et al	23	65 SD 14	48%	196 $\pm$ 46	3.6 days (1.6-8.4)	57% HFNC success. 43% transitioned to NIV 17% eventually intubated mortality 4%	Elevated C reactive protein predicted intubation
Wang et al	17	65 (56-75)	59	209 (179-376)	76 hours	59% HFNC success	If P _a O ₂ /F _i O ₂ $>$ 200, 0% failure. Reduction in respiratory rate after 1-2 h on HFNC predicted success
Studies on non-invasive ventilation							
Bellani G et al	798	68 (59-75)	26	168 (98)	Cross sectional study	62.4% were discharged alive without needing intubation	NIV outside of ICU 68% were treated with helmet CPAP. 53% NIV failure when P/F ratio $<$ 150 mm Hg
Aliberti et al	157	64 (55-75)	25.5	142.9 (96.7-203.2)	CPAP success 8 (5-14) CPAP failure 4 (3-7)	Success 55.4%. Hospital mortality 28.7%	Helmet CPAP in a respiratory unit (high dependency unit) 41.4% of patients DNI Severe pneumonia, elevated IL-6 associated with failure.
Hua et al	152	67 SD 13	46	Not provided	Length of stay 16.1 $\pm$ 9.6 days	Survival 59.2%	Higher incidence of COPD in NIV patients
Wang et al	122 (Full cohort 141)	64 (55-70) (Includes full cohort)	30	NIV 261.9 (218.6-314.3) NIV+IMV 233.3 (118-278.6)	Not reported	75% success. Mortality 17% (incomplete data)	D-dimer $>$ 1.5 mg/L increased likelihood of IMV OR 3.28 (1.07-10.1)
Duca et al	Helmet CPAP 71 BiPAP 7	70 (62-79)	16	131 (97-190) 87 (53-120)	Not reported	CPAP 14% survival BiPAP 42.9% survival	54.9% of helmet CPAP patients died before intubation.
Sivaloganathan et al	58 (NIV $\pm$ IMV) 24 (NIV only)	NIV success 50 (45-60) NIV failure 57 (50-64) NIV only 66 (54-72)	43	Not provided	17 hours (4-31) failure 72 hours (41-132) Success	Success 53% (31/58 pts). NIV+IMV group 11.1% mortality (incomplete outcome). NIV ceiling (DNI) group mortality 83.3%	Admission SOFA score predicted risk of intubation

Table 1 | Studies on respiratory assist devices in covid-19 (HFNC, NIV, and IMV)

Study	N (HFNC)	Age median (interquartile range)	Gender (% F)	Oxygenation at baseline PaO ₂ /FiO ₂	Duration of use	Outcome	Comment
Oranger et al	38 (All CPAP) 14 controls (no CPAP)	63 (55-70)	32	P _a O ₂ 71 (63.5-88.5) On 5 (3-6) L/min O ₂	5 days	Success 77% v 43% in controls	CPAP applied in the ward. None of the intubations were emergent
Burns et al	28	81.5 (54-91)	46	Not provided	5 days (1-14)	50% survival to discharge CPAP mortality 52%, BiPAP mortality 40%	23/28 received CPAP (Average 13 cm H ₂ O) Ventilation provided in the ward
Zheng et al	19	66 (51-72)	27	Not available	Not available	95% discharged	Thrombocytopenia and high IL-6 levels more common in IMV compared with NIV
Duan et al	13	50 SD 14	8	165 ±48	7 days	85% success with NIV Mortality 8%	NIV and HFNC first strategy had comparable outcomes
Studies on invasive mechanical ventilation							
Graselli et al Lombardy, Italy	1150 (full cohort 1591)	63 (56-70)	18	P _a O ₂ /F _i O ₂ 160 (114-220) mm Hg No lung mechanics PEEP 14 (12-16) cm H ₂ O FiO ₂ 0.7 (0.5-0.8)	ICU length of stay 9 (6-13) days	ICU mortality 26% 920/1591 still in the ICU	27% were prone No data on NMB ECMO 1%
Ferrando et al 36 Spanish Andorran ICUs	742	64 (56-71)	31.9	P _a O ₂ /F _i O ₂ 120 (83-177) mm Hg Static compliance: 35 (27-45) ml/cm H ₂ O Plateau pressure 25 (22-29) cm H ₂ O Driving pressure 12 cm H ₂ O (10-16)	Ventilator length of stay 14 (7-24) days	28 day mortality 32%	Most common comorbidities HTN and obesity. <10% of cohort still in ICU Static compliance not related to outcome Lung protective ventilation, NMB (72%), proning (76%), recruitment maneuvers (79%) common
Schenck et al NY Presbyterian Hospital-Weill Cornell Medicine	267	66 (54-74)	28	P _a O ₂ /F _i O ₂ 103 (82-134) mm Hg Static compliance 28 (23-38) ml/cm H ₂ O Plateau pressure 25 (21-29) cm H ₂ O Driving pressure 14 (11-17.2) cm H ₂ O	Currently intubated 18 (14-24) Extubated 10 (6-15) Deceased 8 (4-13)	More than half of the cohort remained intubated (141 patients) 49 patients died (18.4%) 77/267 extubated 49/267 Deceased 141/267 Intubated	Longer intubation periods compared to typical ARDS NMB 60% Prone 40% 25% had static compliance >38 ml/cm H ₂ O
Cummings et al 2 NY Presbyterian hospitals (Columbia Univ.)	203 (Full cohort 257)	62 (51-72)	33	P _a O ₂ /F _i O ₂ 129 (80-203) mm Hg Driving pressure 15 (11-18) cm H ₂ O PEEP 15 (12-18) cm H ₂ O FiO ₂ 1 (0.8-1) Plateau pressure 27 (23-31) cm H ₂ O	18 (9-28) days	In-hospital mortality 39% 23% discharged alive 2% transfer to another hospital 37% remained hospitalized	25% received NMB 17% prone ECMO 3%
Auld et al Emory Healthcare acute care hospitals	165 (Full cohort 217)	64 (54-73)	45.2	P _a O ₂ /F _i O ₂ 132 (100-178) mm Hg Static lung compliance 34 (28-46) mL/cm H ₂ O	Ventilator days 9 (4-13)	Mortality for ventilated patients 33.9%	Institutional adoption of early intubation and lung protective strategy. NMB or proning data not available ECMO 1.8%
Ziehr et al MA. General Hospital and Beth Israel Deaconess Medical Center	66	58 (23-87)	35	P _a O ₂ /F _i O ₂ 182 (135-245) mm Hg Static compliance 35 (30-43) mL/cm H ₂ O Driving pressure 11 (9-12) cm H ₂ O	16 (10-21) days	Mortality 16.7% 62% extubated 21.2% received tracheostomy Length of stay 17.5 (13-25)	42% received NMB 47% prone 95% on vasopressors 5% received ECMO
Bhatraju et al 9 Seattle hospitals	18 24 patients in cohort	64 SD 8	37	P _a O ₂ /F _i O ₂ 142 (94-177) mm Hg Compliance 29 (25-36) mL/cm H ₂ O Driving pressure 13 (11-17) cm H ₂ O Plateau pressure 25 (20-28) cm H ₂ O FiO ₂ 0.9 (0.7-1)	10 (7-12) days	33% extubated 50% mortality 17% still on mechanical ventilator	NMB 39% Prone 28% 71% on vasopressors Older age associated with poor outcomes

CPAP=continuous positive airway pressure; BiPAP=bilevel positive airway pressure; SOFA=sequential organ failure score; ICU=intensive care unit

patients. Some authors recommend heightened caution because of the risk to healthcare workers during the process of extubation and reintubation following weaning failure.¹⁵³ Novel procedures such as the “mask over tube” extubation can potentially reduce exposure to droplets and aerosols.¹⁵⁴ In the absence of evidence to the contrary, we recommend no changes to the established stages to weaning from mechanical ventilation.¹⁵⁵ Extubation can be safely performed while adhering to standard PPE practices.

Tracheostomy may be necessary in approximately 13% of typical ARDS patients to facilitate continued weaning.¹⁵⁶ However, tracheostomy is considered an aerosol generating procedure. During the SARS epidemic, those involved in performing tracheostomy had >4 higher odds of contracting disease.¹⁵⁷ Hesitation to perform the procedure during the early days of the pandemic was justifiable, therefore. Several large series then show favorable outcomes and safety for tracheostomy in managing covid-19.^{150 158 159} In a national cohort study from Spain,¹⁵⁰ 1890 tracheostomies were performed within seven weeks for critically ill covid-19 patients. The investigators reported a median of 12 (4-42) days from intubation to the procedure. More than half of the patients were weaned (52%) and mortality was 24%. Open tracheostomies were preferred over percutaneous approach (81.3% versus 18.7%). No disease transmission incidents were reported among the staff performing the studies.^{150 158 159} In one study, early tracheostomy (<10 days from intubation) was associated with shorter IMV duration (mean (SD), 18 (5.4) v 22.3 (5.7) days).¹⁵⁹ The type of surgical technique (percutaneous versus open) and timing of tracheostomy were not associated with complications or mortality.¹⁵⁸ Several multidisciplinary guidelines have been put together to ensure optimal outcomes and safety.^{160 161} Tracheostomy appears feasible and safe among covid-19 patients and could facilitate earlier weaning and enhance availability of mechanical ventilators.

Covid-19 drug treatments

From a mechanistic perspective, treatments targeting viral replication could be more effective early in the disease process (eg, antiviral therapies like remdesivir, passive antibody therapies like monoclonal antibodies, and convalescent plasma). Later in the disease course, when an excess and inappropriate immune response is responsible for pathology and illness, anti-inflammatory treatments like corticosteroids could be more effective. It is important for clinicians to diagnostically classify the clinical presentation of the patient by severity of clinical disease, and consider whether a patient has mild/moderate disease (not requiring supplemental oxygen), severe (requiring low flow oxygen), or critical covid-19 (on HFNC, NIV, IMV, or ECMO) which has major implications for the choice of pharmacologic treatment and management. We have summarized the recommended treatments in table 2. Treatment with monoclonal antibodies is

currently not recommended for patients hospitalized for covid-19 and is not within the scope of our review.^{162 163}

Corticosteroids

Corticosteroids are the only therapeutic agents that have demonstrated a clear mortality benefit in the treatment of severe covid-19. Seven RCTs have evaluated treatment with steroids in critically ill patients¹⁶⁴ and one trial in severe non-critical covid-19,¹⁶⁵ including medium and high dose dexamethasone, hydrocortisone, and methylprednisolone. In the largest trial (n=2104), 28 day mortality was 22.9% in the dexamethasone arm compared with 25.7% in usual care (adjusted rate ratio 0.83, confidence interval 0.75 to 0.93). The patients with the highest mortality reduction were those on IMV compared with usual care (dexamethasone 29.3% versus usual care 41.4%; rate ratio 0.64, confidence interval 0.51 to 0.81). Those needing supplemental oxygen also had a mortality reduction but the effect size was smaller (dexamethasone 23.3% versus usual care 26.2%; rate ratio 0.82; confidence interval 0.72 to 0.94). Patients mild to moderately ill and not on supplemental oxygen had a non-significant increase in mortality rate (dexamethasone 17.8% versus usual care 14.0%; rate ratio 1.19, confidence interval 0.91 to 1.55). A meta-analysis that pooled data from all the RCTs of steroids showed a significant decrease in mortality for dexamethasone (fixed effect odds ratio 0.64, confidence interval 0.50 to 0.82 for dexamethasone from three trials, n=1282) and a non-significant decrease for hydrocortisone (odds ratio 0.69, confidence interval 0.43 to 1.12; P=0.13, n=374). No significant mortality reduction was seen with methylprednisolone but this was based on one trial with 47 patients (odds ratio 0.91, confidence interval 0.29 to 2.87; P=0.87).¹⁶⁵ We believe that, while the evidence is most robust for dexamethasone and hydrocortisone, no evidence exists at present to believe one steroid is superior to the other. Head-to-head studies comparing the different types of steroid are needed.

Remdesivir

Remdesivir is an antiviral drug that acts by inhibiting viral RNA transcription.¹⁶⁶ It has in vitro activity against many RNA viruses including SARS CoV-2. Current studies have been done in hospitalized patients with moderate or severe disease.

Remdesivir for moderate covid-19

SIMPLE-2¹⁶⁰ was an RCT specifically designed to evaluate remdesivir in hospitalized patients with moderate covid-19 (not needing supplemental oxygen), although ACCT-1¹⁶⁷ and SOLIDARITY¹⁶⁸ also included patients with moderate disease. SIMPLE-2 compared a course of five to 10 days of redemsivir with standard care. The 5 day group had higher odds (odds ratio 1.65; 95% confidence interval 1.09 to 2.48; P=0.02) for improved clinical status using a

Table 2 | Therapeutic considerations for acute covid-19 by clinical syndrome/disease severity

Clinical scenario	Pharmacologic interventions
Hospitalized for mild to moderate covid-19 (not hypoxemic)	<ul style="list-style-type: none"> • Supportive care • No clear benefit for remdesivir or convalescent plasma • Steroids have no demonstrated benefit and may cause harm
Hospitalized for severe covid-19, but not critical (hypoxemic needing low flow supplemental oxygen)	<ul style="list-style-type: none"> • Supportive care • Corticosteroids (dexamethasone 6 mg/day × 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone) • May consider remdesivir • May benefit from use of tocilizumab.
Hospitalized for covid-19 and critically ill (needing HFNC, NIV, IMV, or ECMO)	<ul style="list-style-type: none"> • Supportive care • Corticosteroids (dexamethasone 6 mg/day × 10 days or until discharge or an equivalent dose of hydrocortisone or methylprednisolone) • May consider remdesivir • May benefit from use of tocilizumab.

composite severity of illness score (eg, 1=discharge from hospital, 7=death). No statistically significant difference was seen between clinical status on day 11 with the 10 day course of remdesivir to standard care ($P=0.18$ by Wilcoxon rank sum test), and no significant difference in outcomes such as time to recovery, duration of treatment with supplemental oxygen, duration of hospitalization, or mortality.¹⁶⁹ Results from the other two studies that included patients with moderate covid-19 also did not show a mortality benefit.

Remdesivir for severe covid-19

Three RCTs (SIMPLE-1, ACCT-1, and SOLIDARITY) evaluated remdesivir in hospitalized patients with severe covid-19 (oxygen saturation <94% on room air requiring supplemental oxygen or more advanced respiratory support/ECMO).^{167 168 170} ACCT-1 showed earlier time to recovery and discharge from remdesivir, but no mortality benefit compared with placebo (median 10 days with remdesivir compared with 15 days with placebo; rate ratio for recovery 1.29; confidence interval 1.12 to 1.49). A post hoc sub-analysis showed the largest effect size for recovery was in patients requiring low flow oxygen who were not critically ill ($n=957$, median time to recovery 11 versus 18 days, rate ratio for recovery 1.31; confidence interval 1.12 to 1.52). The rate ratios for recovery in those critically ill (need for HFNC, NIV, IMV, or ECMO) were not statistically significant compared with placebo. Given the smaller number of patients in these subgroups it is unclear if this difference is due to an inadequate sample size or if remdesivir was not effective. Also, some of the outcomes used to create the 7-point ordinal scale for clinical improvement could have been influenced by resource limitations (ie, ventilator availability) or regional practices. SOLIDARITY ($n=2700$), the largest trial to date, showed that remdesivir was not associated with a reduction in mortality or rates of IMV (mortality rate ratio 0.95, confidence interval 0.81 to 1.11, $P=0.50$; 301/2743 remdesivir versus 303/2708 control). Despite the limitation that this was an open label study with no placebo, the outcomes for mortality or need for IMV are less prone to bias than subjective clinical outcomes. The third study (SIMPLE-1)¹⁷¹ compared five to 10 days of treatment in hospitalized patients with severe

non-critical disease. The 5 day course showed better clinical improvement at day 14, but patients in the 10 day arm had more severe disease raising the concern for confounding even after adjustment.

In summary, remdesivir may have modest benefit in time to recovery in patients with severe disease, but shows no significant benefit in mortality or other clinical outcomes.

Tocilizumab

Tocilizumab is a monoclonal antibody that blocks the IL-6 receptor and is used to treat cytokine release syndrome associated with CART cell therapy. Multiple case series and observational studies were published in the early months of the pandemic that reported improved outcomes from tocilizumab.¹⁷²⁻¹⁷⁴ Since then, eight RCTs have compared tocilizumab with placebo or standard care in severe covid-19.¹⁷⁵⁻¹⁸² Some of the largest trials have only preprints available (COVATA¹⁷⁶, REMAP-CAP¹⁸⁰ and RECOVERY).¹⁸² EMPACTA was conducted in hospitalized non-ventilated patients with covid-19 and included high risk racial and ethnic minority patients. While this RCT reported a benefit for the composite outcome of mortality and need for IMV in the tocilizumab arm, it did not show mortality benefit alone. The cumulative proportion of IMV or mortality on day 28 for tocilizumab was 12.0% versus placebo 19.3% (log rank $P=0.0360$; hazard ratio 0.56; confidence interval 0.33 to 0.97, and all cause mortality at day 28 for tocilizumab was 10.4% versus 8.6% (weighted difference 2.0%, confidence interval -5.2 to 7.8). COVACTA included patients with severe illness and critical patients and reported no differences in mortality (19.7% versus 19.4% in the placebo group at day 28; difference 0.3%, confidence interval -7.6 to 8.2) or when utilizing an ordinal scale for clinical improvement (odds ratio 1.19, confidence interval 0.81 to 1.76).

REMAP-CAP was a randomized adaptive platform open label trial ($n=353$ tocilizumab, $n=402$ usual care). Tocilizumab was administered within 24 hours of being admitted to an ICU and most also received corticosteroids. The median organ support-free days were 10 (IQR -1, 16), and 0 (IQR -1, 15) for tocilizumab and control, respectively. Hospital mortality was 28% (98/350) for tocilizumab and 35.8% (142/397) for control. The authors used bayesian statistics and

Table 3 | Post-acute covid-19 complications by system

System	Complications
Physical impairment	<ul style="list-style-type: none"> Seen in up to 80% after any critical illness and includes loss of muscle mass, neuromuscular weakness, fatigue, dyspnea, decreased exercise tolerance, joint contractures, and sexual dysfunction.¹⁹⁰⁻¹⁹² Substantial muscle wasting and neuromuscular weakness are common following non-covid ARDS and can last for months or years,¹⁹³ with major risk factors being corticosteroid use and intensive care unit length of stay¹⁹⁴ Recent study from Italy of covid-19 patients with more than half reporting 3+ persistent symptoms, including fatigue (53%), dyspnea (43%), joint pain (27%), and reductions in quality of life (44%)¹⁹⁵
Mental health impairment	<ul style="list-style-type: none"> For non-covid patients who were in intensive care unit, these include anxiety, depression, or post-traumatic stress disorder (PTSD) in 8% to 57% of cases¹⁹⁶⁻¹⁹⁸ Can also occur in family members of patients who were in intensive care units (known as PICS-family) Unique to covid-19 which increase the risk for mental health impairment include social isolation, loneliness, the stigma of the disease, limited hospital visitation policy, and the psychological effect of the pandemic itself¹⁹⁹ In a study of 402 survivors of covid-19, a significant number of patients reported PTSD (28%), depression (31%), anxiety (42%), obsessive-compulsive symptomatology (20%), and insomnia (40%)²⁰⁰
Pulmonary impairment	<ul style="list-style-type: none"> Persistent pulmonary symptoms are common after covid-19¹⁹⁵ In a 3 month follow-up study in China of covid-19 patients (n=55), 71% had radiologic abnormalities including interstitial thickening and fibrosis, and 25% had impaired diffusing capacity for carbon monoxide at three months following discharge²⁰¹ An observational study from China of 51 covid-19 patients showed that 45% had abnormal computed tomography scans four weeks after discharge²⁰²
Cardiac impairment	<ul style="list-style-type: none"> Evidence for long term sequelae from covid-19 has been noted, including evidence of myocardial inflammation on magnetic resonance imaging 12-92 days following infection^{203 204}
Neurologic impairment	<ul style="list-style-type: none"> While the occurrence of stroke due to covid-19 is relatively rare, other conditions including impairment of consciousness, encephalitis, seizure, encephalopathy, and "brain fog" have been reported 2-3 months after initial illness onset²⁰⁵⁻²⁰⁷ Cognitive impairment is typically seen in 30-80% of patients who were in intensive care and includes memory loss as well as difficulty with concentration, comprehension, and critical thinking²⁰⁸

median adjusted odds ratio for hospital survival (OR 1.64, 1.14-2.35) and assumed probability of treatment effect to be neutral, which some experts feel is too high given prior negative trials.¹⁸⁰

RECOVERY was a randomized adaptive platform open label trial (n=2022 tocilizumab, n=2094 usual care). Given the adaptive design, those who showed evidence for progressive disease (saO₂<92% on room air and C reactive protein ≥ 75 mg/L) up to 21 days after randomization were considered for tocilizumab. Twenty eight day mortality was 29% (596/2022) for tocilizumab, and 33% (694/2094) for usual care (rate ratio 0.86, confidence interval 0.77 to 0.96; p=0.007). The authors also reported a clear mortality benefit in those receiving corticosteroids in all pre-specified subgroups (27% v 33%; rate ratio 0.80; confidence interval 0.70 to 0.90). The tocilizumab arm was less likely to reach composite endpoint of need for IMV or death (33% v 38%; risk ratio 0.85, confidence interval 0.78 to 0.93; p=0.0005).¹⁸² Given the other five trials¹⁷⁵⁻¹⁷⁹ did not show a significant mortality benefit or improvement in clinical outcomes, the results from RCTs for tocilizumab have been mixed. The largest trials^{180 182} report a modest mortality benefit and improvement in outcomes; however, adaptive trials are at risk of bias that can influence non-mortality outcomes. The reason for mixed results is unclear, and possible reasons include: earlier trials had inadequate power to detect a modest benefit, the necessity for corticosteroid use, or early use in critical illness is needed for tocilizumab to be effective.

Convalescent plasma

Convalescent plasma or plasma obtained from patients who have recovered from an infection have been used historically to treat infections. Treatment is hypothesized to work best when given early in the disease process before a patient develops

an antibody response, and when it contains adequate concentrations of neutralizing antibodies.¹⁸³

One large observational study analyzed data on convalescent plasma use among hospitalized patients at 2807 acute care facilities under the US FDA Expanded Access Program.¹⁸⁴ Of the patients included, 52.3% were in intensive care and 27.5% were on mechanical ventilation. The 7 day mortality rate was 8.7% (95% confidence interval 8.3% to 9.2%) in patients transfused within three days of covid-19 diagnosis but 11.9% (11.4% to 12.2%) in those four or more days after diagnosis (P<0.001). The 30 day mortality was also lower in the patients transfused early (21.6% versus 26.7%, P<0.0001). The study reported that patients who received high IgG plasma had a lower 7 day mortality than those who received medium IgG plasma and low IgG plasma. However, the study used a semi-quantitative antibody assay, did not measure neutralizing antibody titers, and only compared early with late administration of convalescent plasma and convalescent plasma with different semi-quantitative levels of antibodies but not placebo. Eight RCTs have since evaluated convalescent plasma for the treatment of covid-19. Five of the studies had less than 100 patients in both arms and two had more than 200 patients in the convalescent plasma arm and 100 patients in the control arm.¹⁸⁵ Most of the RCTs did not show a beneficial effect for mortality or clinical status, which had been seen in the observational studies. One RCT evaluated convalescent plasma with high anti-SARS-CoV2 IgG titers in older patients within 72 hours of mild covid-19 symptoms. In the convalescent plasma arm, 16.2% (13/80) progressed to severe respiratory diseases (respiratory rate ≥30 or O₂ sat<93%)¹⁸⁶ compared with 31.2% (25/80), in a preplanned interim analysis. Early administration of high titer convalescent plasma may play a role in mild to moderate disease, but we need more data to

Table 4 | Assessment of patients in post-ICU recovery clinics adapted to post-acute covid-19 patients

Instrument	Assessment
Activities of Daily Living and Instrumental Activities of Daily Living	Functional status
Physical therapy and occupational therapy evaluation	Functional assessment, mobility, strength
European Quality of Life Five Dimension (EQ-5D)	Health related quality of life, mobility, pain
Hospital Anxiety and Depression Scale (HADS)	Anxiety, depression
Impact of Event Scale-Revised (IES-R)	Post-traumatic stress disorder
Montreal Cognitive Assessment (MoCA)	Cognition
Pulmonary function testing	Lung function
6 minute walk test	Lung function, functional status
Chest radiograph	Lung parenchyma
Echocardiogram and electrocardiogram	Cardiac function

delineate the exact role of convalescent plasma in the treatment of covid-19.

Anticoagulation

Patients with severe covid-19 are at increased risk for thrombosis^{58–59}; however, no high quality evidence supports intermediate or full dose anticoagulation strategy over standard prophylactic anticoagulation. Clinical vigilance is needed in screening for thrombotic complications. D-dimers are associated with disease severity¹⁸⁷ but at present no validated algorithms exist to guide anticoagulation regimens based on D-dimers. With the results of multiple RCTs ongoing, three linked trials investigating increased levels of anticoagulation paused enrollment for critically ill patients out of concern for futility and safety,¹⁸⁸ but a recent press release suggested benefit to increased anticoagulation in the non-critically ill cohorts.¹⁸⁹ The results of these and other ongoing studies should provide guidance on whether targeting a higher anticoagulation strategy in certain populations improves outcomes.

Post-acute covid-19 complications

Current estimates are that 91.5 million patients worldwide have recovered from SARS-CoV-2 infection.² For those who survive covid-19, emerging reports have identified persistent symptoms beyond the acute phase of illness. These symptoms, which can affect multiple organ systems (table 3), are not due to persistent viral infection but instead sequelae of severe inflammation from the disease.^{209–211} “Post-acute covid-19” is defined as the presence of symptoms extending beyond three weeks, and “chronic covid-19” extends beyond 12 weeks.²⁰⁹ We know from studies before the pandemic that a high percentage of patients who require intensive care develop post-intensive care syndrome (PICS), which is the constellation of new or worsening physical and mental health and cognitive impairments that develop following critical illness.^{190–196–212} These impairments often last beyond a year and have a profound impact on quality of life.²¹³ Covid-19 patients who were in intensive care are particularly at risk¹⁹⁶ to develop PICS given the high incidence of ARDS, prolonged mechanical ventilation, higher exposure to sedatives, higher incidence of delirium, limited physical therapy owing to concern for disease transmission, and constraints on social and emotional support owing to limited visits.^{214–215}

Mitigation of post-ICU syndrome

Prevention and mitigation of PICS can be accomplished by following the “ABCDE” bundle^{216–217} and other guidelines,²¹⁸ which focus on managing pain, early ventilator liberation, assessing and treating delirium, appropriate usage of sedative agents, early mobility and exercise, and family engagement to prevent long term impairments. Early physical therapy and mobilization interventions^{208–219} are paramount, and should be continued as an outpatient with home based physical therapy.^{220–221} Other interventions include ICU diaries,^{222–223} early psychological intervention,²²⁴ animal visitation,²²⁵ peer support groups for patients and families,^{226–227} and utilizing digital technology to bridge social distance. Healthcare providers should acknowledge the difficulty of covid-19, the unique stressors covid-19 patients and families are facing, and tailor their communication and behavior accordingly.²¹⁵

Importance of post-ICU recovery programs

Patients who spent time in intensive care, especially patients with ARDS, are at high risk for PICS development. Without appropriate recognition, impairments go undiagnosed and can persist for months to years and profoundly affect quality of life. An interdisciplinary approach is essential to assist with diagnosis and management of critical illness recovery. Post-ICU recovery programs staffed by a team of providers (ie, pulmonologists, intensivists, pharmacists, advanced practice providers, nurses, physical and occupational therapists, respiratory therapists, social workers, case managers, and mental health providers) can diagnose and treat PICS impairments.^{228–230} These clinics also facilitate access to necessary subspecialties (tables 3, 4). The comprehensive approach of post-ICU clinics mirror the magnitude that critical illness affects multiple domains of a patient’s health. By bringing together various subspecialty healthcare workers, these clinics promote mind, body, social, and spiritual recovery to survivors of critical illness. The need for ongoing ambulatory care for these vulnerable patients, also known as “long-haulers,” is imperative.²³¹ Long term longitudinal observational studies and clinical trials will be critical (box 1) to clarify the durability and extent of health consequences attributable to covid-19 and define best practices for covid-19 survivors.

Box 1: Covid-19 research questions

- What are the pathophysiologic mechanisms for increased covid-19 severity in certain populations (ie, older adult populations, comorbidities, etc)?
- How does covid-19 related ARDS differ from classic ARDS?
- What is the best strategy for prevention of thrombotic complications in patients with covid-19 pneumonia?
- How does high flow nasal oxygen therapy compare with non-invasive ventilation as first line therapy for the treatment of respiratory failure in covid-19 pneumonia?
- What are the long term impacts of severe illness due to covid-19 related ARDS?
- What are the causes for persistent physical and cognitive impairments resulting from covid-19?

Guidelines

In formulating this review, we considered guidelines that provide recommendations on the management of covid-19 from the Infectious Diseases Society of America,²³² World Health Organization,²³⁴ Society of Critical Care Medicine,²³⁵ and the National Institutes of Health.²³⁶ We selected these guidelines because of their recommendations for patients with covid-19 pneumonia, which included management and molecular diagnostics. We prioritized guidelines that used explicit methodology, which stated how searches were done systematically, how synthesis (meta-analysis) was performed, and how the evidence was appraised using a priori criteria. Additionally, guidelines for management of tracheostomy¹⁶⁰ and respiratory failure¹²⁰ are included in the respiratory care section.

Conclusion

Remarkable advances have been made in a short period in the treatment of covid-19 pneumonia, including the development of drug treatments that improve mortality and recovery from illness. As more clinical and mechanistic data emerge on CARDS, tailored therapy can be designed to further improve outcomes. Management of respiratory failure is guided by principles of management for classic ARDS. Despite these promising developments, including the development of vaccines, covid-19 will continue to have an impact on healthcare systems as thousands of patients recover from critical illness. An integrated therapeutic approach to mitigate the adverse physical and mental health effects of covid-19 pneumonia is essential.

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- 1 National Institutes of Health. NIH covid-19 treatment guidelines. Clinical spectrum of SARS-CoV-2 Infection. 2020. <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum>
- 2 Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020;20:533-4. doi:10.1016/S1473-3099(20)30120-1
- 3 Grasselli G, Zangrillo A, Zanella A, et al. COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 2020;323:1574-81. doi:10.1001/jama.2020.5394
- 4 Richardson S, Hirsch JS, Narasimhan M, et al, the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with covid-19 in the New York City Area. *JAMA* 2020;323:2052-9. doi:10.1001/jama.2020.6775
- 5 Docherty AB, Harrison EM, Green CA, et al, ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985. doi:10.1136/bmj.m1985
- 6 Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—covid-NET, 14 States, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:458-64. doi:10.15585/mmwr.mm6915e3
- 7 Torres Acosta MA, Singer BD. Pathogenesis of COVID-19-induced ARDS: implications for an ageing population. *Eur Respir J* 2020;56:2002049. doi:10.1183/13993003.02049-2020
- 8 Yang Y, Zhao Y, Zhang F, Zhang L, Li L. covid-19 in elderly adults: clinical features, molecular mechanisms, and proposed strategies. *Aging Dis* 2020;11:1481-95. doi:10.14336/AD.2020.0903
- 9 Ellinghaus D, Degenhardt F, Bujanda L, et al, Severe Covid-19 GWAS Group. Genomewide association study of severe covid-19 with Respiratory Failure. *N Engl J Med* 2020;383:1522-34. doi:10.1056/NEJMoa2020283
- 10 Yang X, Yu Y, Xu J, 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. doi:10.1016/S2213-2600(20)30079-5
- 11 Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (covid-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med* 2020;172:577-82. doi:10.7326/M20-0504
- 12 Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2020;6:1-14.
- 13 Tzotzos SJ, Fischer B, Fischer H, Zeitlinger M. Incidence of ARDS and outcomes in hospitalized patients with COVID-19: a global literature survey. *Crit Care* 2020;24:516. doi:10.1186/s13054-020-03240-7
- 14 Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* 2020;369:m1966. doi:10.1136/bmj.m1966
- 15 Horwitz LI, Jones SA, Cerfolio RJ, et al. Trends in covid-19 risk-adjusted mortality rates. *J Hosp Med* 2021;16:90-2. doi:10.12788/jhm.3552
- 16 Dennis JM, McGovern AP, Vollmer SJ, Mateen BA. Improving survival of critical care patients with coronavirus disease 2019 in England: a national cohort study, March to June 2020. *Crit Care Med* 2021;49:209-14. doi:10.1097/CCM.0000000000004747
- 17 Lan J, Ge J, Yu J, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* 2020;581:215-20. doi:10.1038/s41586-020-2180-5
- 18 Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: a review of viral, host, and environmental factors. *Ann Intern Med* 2020. doi:10.7326/M20-5008
- 19 da Costa VG, Moreli ML, Saivish MV. The emergence of SARS, MERS and novel SARS-2 coronaviruses in the 21st century. *Arch Virol* 2020;165:1517-26. doi:10.1007/s00705-020-04628-0
- 20 Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. *Nature* 2020;581:221-4. doi:10.1038/s41586-020-2179-y
- 21 Zhang L, Lin D, Sun X, et al. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α -ketoamide inhibitors. *Science* 2020;368:409-12. doi:10.1126/science.abb3405
- 22 Walls AC, Park Y-J, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike

- glycoprotein. *Cell* 2020;181:281-292.e6. doi:10.1016/j.cell.2020.02.058
- 23 Siu YL, Teoh KT, Lo J, et al. The M, E, and N structural proteins of the severe acute respiratory syndrome coronavirus are required for efficient assembly, trafficking, and release of virus-like particles. *J Virol* 2008;82:11318-30. doi:10.1128/JVI.01052-08
 - 24 Satarker S, Nampoothiri M. Structural proteins in severe acute respiratory syndrome coronavirus-2. *Arch Med Res* 2020;51:482-91. doi:10.1016/j.arcmed.2020.05.012
 - 25 Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antiviral drug development for COVID-19. *Acta Pharmacol Sin* 2020;41:1141-9. doi:10.1038/s41401-020-0485-4
 - 26 Duan L, Zheng Q, Zhang H, Niu Y, Lou Y, Wang H. The SARS-CoV-2 spike glycoprotein biosynthesis, structure, function, and antigenicity: implications for the design of spike-based vaccine immunogens. *Front Immunol* 2020;11:576622. doi:10.3389/fimmu.2020.576622
 - 27 Hu Y, Wen J, Tang L, et al. The M protein of SARS-CoV: basic structural and immunological properties. *Genomics Proteomics Bioinformatics* 2003;1:118-30. doi:10.1016/S1672-0229(03)01016-7
 - 28 Singh Tomar PP, Arkin IT. SARS-CoV-2 E protein is a potential ion channel that can be inhibited by Gliclazide and Memantine. *Biochem Biophys Res Commun* 2020;530:10-4. doi:10.1016/j.bbrc.2020.05.206
 - 29 Sarkar M, Saha S. Structural insight into the role of novel SARS-CoV-2 E protein: A potential target for vaccine development and other therapeutic strategies. *PLoS One* 2020;15:e0237300. doi:10.1371/journal.pone.0237300
 - 30 Dutta NK, Mazumdar K, Gordy JT. The nucleocapsid protein of SARS-CoV-2: a target for vaccine development. *J Virol* 2020;94:e00647-20. doi:10.1128/JVI.00647-20
 - 31 Lopez-Rincon A, Perez-Romero CA, Tonda A, et al. Design of specific primer sets for the detection of B.1.1.7, B.1.351 and P.1 SARS-CoV-2 variants using deep learning. *bioRxiv* [Preprint] 2021. doi:10.1101/2021.01.20.427043
 - 32 Vrancken B, Dellicour S, Smith DM, Chaillon A. Phylogenetic analyses of SARS-CoV-2 B.1.1.7 lineage suggest a single origin followed by multiple exportation events versus convergent evolution. *bioRxiv* [Preprint] 2021. doi:10.1101/2021.01.12.426373
 - 33 Centers for Disease Control and Prevention. Emerging SARS-CoV-2 variants. 2021. <https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html>
 - 34 Starr TN, Greaney AJ, Addetia A, et al. Prospective mapping of viral mutations that escape antibodies used to treat COVID-19. *Science* 2021:eabf9302. doi:10.1126/science.abf9302
 - 35 Wang Q, Zhang Y, Wu L, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell* 2020;181:894-904.e9. doi:10.1016/j.cell.2020.03.045
 - 36 Samavati L, Uhal BD. ACE2, much more than just a receptor for SARS-CoV-2. *Front Cell Infect Microbiol* 2020;10:317. doi:10.3389/fcimb.2020.00317
 - 37 Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol* 2020;215:108427. doi:10.1016/j.clim.2020.108427
 - 38 Swärd P, Edsfieldt A, Reepalu A, Jelpsson L, Rosengren BE, Karlsson MK. Age and sex differences in soluble ACE2 may give insights for COVID-19. *Crit Care* 2020;24:221. doi:10.1186/s13054-020-02942-2
 - 39 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271-280.e8. doi:10.1016/j.cell.2020.02.052
 - 40 Ma D, Chen C-B, Jhanji V, et al. Expression of SARS-CoV-2 receptor ACE2 and TMPRSS2 in human primary conjunctival and pterygium cell lines and in mouse cornea. *Eye (Lond)* 2020;34:1212-9. doi:10.1038/s41433-020-0939-4
 - 41 Bao R, Hernandez K, Huang L, Luke JJ. ACE2 and TMPRSS2 expression by clinical, HLA, immune, and microbial correlates across 34 human cancers and matched normal tissues: implications for SARS-CoV-2 COVID-19. *J Immunother Cancer* 2020;8:e001020. doi:10.1136/jitc-2020-001020
 - 42 Bergmann CC, Silverman RH. COVID-19: Coronavirus replication, pathogenesis, and therapeutic strategies. *Cleve Clin J Med* 2020;87:321-7. doi:10.3949/ccjm.87a.20047
 - 43 Blanco-Melo D, Nilsson-Payant BE, Liu W-C, et al. Imbalanced host response to SARS-CoV-2 drives development of covid-19. *Cell* 2020;181:1036-1045.e9. doi:10.1016/j.cell.2020.04.026
 - 44 Guo L, Ren L, Yang S, et al. Profiling early humoral response to diagnose novel coronavirus disease (covid-19). *Clin Infect Dis* 2020;71:778-85. doi:10.1093/cid/ciaa310
 - 45 Woodruff MC, Ramonell RP, Nguyen DC, et al. Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nat Immunol* 2020;21:1506-16. doi:10.1038/s41590-020-00814-z
 - 46 Long Q-X, Tang X-J, Shi Q-L, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med* 2020;26:1200-4. doi:10.1038/s41591-020-0965-6
 - 47 Ren L, Fan G, Wu W, et al. Antibody responses and clinical outcomes in adults hospitalized with severe coronavirus disease 2019 (covid-19): a post hoc analysis of LOTUS China trial. *Clin Infect Dis* 2020. doi:10.1093/cid/ciaa1247
 - 48 Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020;5:33. doi:10.1038/s41392-020-0148-4
 - 49 Rydzynski Moderbacher C, Ramirez SI, Dan JM, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute covid-19 and associations with age and disease severity. *Cell* 2020;183:996-1012.e19. doi:10.1016/j.cell.2020.09.038
 - 50 Goronzy JJ, Weyand CM. Mechanisms underlying T cell ageing. *Nat Rev Immunol* 2019;19:573-83. doi:10.1038/s41577-019-0180-1
 - 51 Wilk AJ, Rustagi A, Zhao NQ, et al. A single-cell atlas of the peripheral immune response in patients with severe COVID-19. *Nat Med* 2020;26:1070-6. doi:10.1038/s41591-020-0944-y
 - 52 Del Valle DM, Kim-Schulze S, Huang H-H, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020;26:1636-43. doi:10.1038/s41591-020-1051-9
 - 53 Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med* 2020;8:1233-44. doi:10.1016/S2213-2600(20)30404-5
 - 54 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med* 2020; doi:10.1056/NEJMoa2021436.
 - 55 Wilson JG, Simpson LJ, Ferreira A-M, et al. Cytokine profile in plasma of severe COVID-19 does not differ from ARDS and sepsis. *JCI Insight* 2020;5:140289. doi:10.1172/jci.insight.140289
 - 56 Maiese A, Manetti AC, La Russa R, et al. Autopsy findings in COVID-19-related deaths: a literature review. *Forensic Sci Med Pathol* 2020. doi:10.1007/s12024-020-00310-8
 - 57 Arrossi AV, Farver C. The pulmonary pathology of COVID-19. *Cleve Clin J Med* 2020. doi:10.3949/ccjm.87a.ccc063
 - 58 Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. *EclinicalMedicine* 2020;29:100639. doi:10.1016/j.eclinm.2020.100639
 - 59 Chi G, Lee JJ, Jamil A, et al. Venous thromboembolism among hospitalized patients with covid-19 undergoing thromboprophylaxis: a systematic review and meta-analysis. *J Clin Med* 2020;9:2489. doi:10.3390/jcm9082489
 - 60 Ranieri VM, Rubenfeld GD, Thompson BT, et al. ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526-33.
 - 61 Habashi NM, Camporota L, Gatto LA, Nieman GF. Functional pathophysiology of SARS-CoV-2 induced acute lung injury and clinical implications. *J Appl Physiol (1985)* 2021. doi:10.1152/japplphysiol.00742.2020
 - 62 Chu DK, Kim LHY, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018;391:1693-705. doi:10.1016/S0140-6736(18)30479-3
 - 63 Siemieniuk RAC, Chu DK, Kim LH, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ* 2018;363:k4169. doi:10.1136/bmj.k4169
 - 64 Barrot L, Asfar P, Mauny F, et al. LOCO2 Investigators and REVA Research Network. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med* 2020;382:999-1008. doi:10.1056/NEJMoa1916431
 - 65 Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Acute Respiratory Distress Syndrome Network. 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. doi:10.1056/NEJM200005043421801
 - 66 Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013;369:2126-36. doi:10.1056/NEJMra1208707
 - 67 Mascheroni D, Kolobov T, Fumagalli R, Moretti MP, Chen V, Buckhold D. Acute respiratory failure following pharmacologically induced hyperventilation: an experimental animal study. *Intensive Care Med* 1988;15:8-14. doi:10.1007/BF00255628
 - 68 Carteaux G, Millán-Guilarte T, De Prost N, et al. Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal volume. *Crit Care Med* 2016;44:282-90. doi:10.1097/CCM.0000000000001379
 - 69 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017;195:438-42. doi:10.1164/rccm.201605-1081CP

- 70 Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747-55. doi:10.1056/NEJMsa1410639
- 71 Chatburn RL, van der Staay M. Driving pressure or tidal pressure: what a difference a name makes. *Respir Care* 2019;64:1176-9. doi:10.4187/respcare.07233
- 72 Brower RG, Lanken PN, MacIntyre N, et al, National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327-36. doi:10.1056/NEJMoa032193
- 73 Meade MO, Cook DJ, Guyatt GH, et al, Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:637-45. doi:10.1001/jama.299.6.637
- 74 Cavalcanti AB, Suzumura EA, Laranjeira LN, et al, Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2017;318:1335-45. doi:10.1001/jama.2017.14171
- 75 Chen L, Del Sorbo L, Grieco DL, et al. Potential for lung recruitment estimated by the recruitment-to-inflation ratio in acute respiratory distress syndrome. A clinical trial. *Am J Respir Crit Care Med* 2020;201:178-87. doi:10.1164/rccm.201902-0334OC
- 76 Pan C, Chen L, Lu C, et al. Lung recruitability in covid-19-associated acute respiratory distress syndrome: a single-center observational study. *Am J Respir Crit Care Med* 2020;201:1294-7. doi:10.1164/rccm.202003-0527LE
- 77 Grasso S, Mirabella L, Murgolo F, et al. Effects of positive end-expiratory pressure in "high compliance" severe acute respiratory syndrome coronavirus 2 acute respiratory distress syndrome. *Crit Care Med* 2020;48:e1332-6. doi:10.1097/CCM.0000000000004640
- 78 Karbing DS, Panigada M, Bottino N, et al. Changes in shunt, ventilation/perfusion mismatch, and lung aeration with PEEP in patients with ARDS: a prospective single-arm interventional study. *Crit Care* 2020;24:111. doi:10.1186/s13054-020-2834-6
- 79 Guérin C, Reigner J, Richard J-C, et al, PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68. doi:10.1056/NEJMoa1214103
- 80 Ho ATN, Patolia S, Guervilly C. Neuromuscular blockade in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. *J Intensive Care* 2020;8:12. doi:10.1186/s40560-020-0431-z
- 81 Gattinoni L, Coppola S, Cressoni M. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;201:1299-300.
- 82 Fan E, Beitler JR, Brochard L, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *Lancet Respir Med* 2020;8:816-21. doi:10.1016/S2213-2600(20)30304-0
- 83 Tobin MJ, Laghi F, Jubran A. P-SILI is not justification for intubation of COVID-19 patients. *Ann Intensive Care* 2020;10:105. doi:10.1186/s13613-020-00724-1
- 84 Schmidt M, Hajage D, Lebreton G, et al, Groupe de Recherche Clinique en Réanimation et Soins Intensifs du Patient en Insuffisance Respiratoire aiguë (GRC-RESPIRE) Sorbonne Université, Paris-Sorbonne ECMO-COVID investigators. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med* 2020;8:1121-31. doi:10.1016/S2213-2600(20)30328-3
- 85 Ferrando C, Suarez-Sipman F, Mellado-Artigas R, et al, COVID-19 Spanish ICU Network. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. *Intensive Care Med* 2020;46:2200-11. doi:10.1007/s00134-020-06192-2
- 86 Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest* 2015;148:253-61. doi:10.1378/chest.14-2871
- 87 Möller W, Feng S, Domanski U, et al. Nasal high flow reduces dead space. *J Appl Physiol (1985)* 2017;122:191-7. doi:10.1152/japplphysiol.00584.2016
- 88 Parke RL, McGuinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. *Respir Care* 2013;58:1621-4. doi:10.4187/respcare.02358
- 89 Rochweg B, Granton D, Wang DX, 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;44:563-72. doi:10.1007/s00134-019-05658-2
- 90 Agarwal A, Basmaji J, Muttalib F, et al. High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. *Can J Anaesth* 2020;67:1217-48. doi:10.1007/s12630-020-01740-2
- 91 Roca O, Caralt B, Messika J, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. *Am J Respir Crit Care Med* 2019;199:1368-76. doi:10.1164/rccm.201803-0589OC
- 92 Kang BJ, Koh Y, Lim C-M, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med* 2015;41:623-32. doi:10.1007/s00134-015-3693-5
- 93 Calligaro GL, Lalla U, Audley G, et al. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study. *EClinicalMedicine* 2020;28:100570. doi:10.1016/j.eclinm.2020.100570
- 94 Ferrando C, Mellado-Artigas R, Gea A, et al, COVID-19 Spanish ICU Network. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. *Crit Care* 2020;24:597. doi:10.1186/s13054-020-03314-6
- 95 Zucman N, Mullaert J, Roux D, Roca O, Ricard J-D, Contributors. Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure. *Intensive Care Med* 2020;46:1924-6. doi:10.1007/s00134-020-06177-1
- 96 Xia J, Zhang Y, Ni L, et al. High-flow nasal oxygen in coronavirus disease 2019 patients with acute hypoxemic respiratory failure: a multicenter, retrospective cohort study. *Crit Care Med* 2020;48:e1079-86. doi:10.1097/CCM.0000000000004558
- 97 Panadero C, Abad-Fernández A, Rio-Ramírez MT, et al. High-flow nasal cannula for Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. *Multidiscip Respir Med* 2020;15:693. doi:10.4081/mrm.2020.693
- 98 Vianello A, Arcaro G, Molena B, et al. High-flow nasal cannula oxygen therapy to treat patients with hypoxemic acute respiratory failure consequent to SARS-CoV-2 infection. *Thorax* 2020;75:998-1000. doi:10.1136/thoraxjnl-2020-214993
- 99 Guy T, Créac'hacdec A, Ricordel C, et al. High-flow nasal oxygen: a safe, efficient treatment for COVID-19 patients not in an ICU. *Eur Respir J* 2020;56:2001154. doi:10.1183/13993003.01154-2020
- 100 Duan J, Chen B, Liu X, et al. Use of high-flow nasal cannula and noninvasive ventilation in patients with COVID-19: A multicenter observational study. *Am J Emerg Med* 2020;S0735-6757(20)30666-5. doi:10.1016/j.ajem.2020.07.071
- 101 Wang K, Zhao W, Li J, Shu W, Duan J. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. *Ann Intensive Care* 2020;10:37. doi:10.1186/s13613-020-00653-z
- 102 Demoule A, Vieillard Baron A, Darmon M, et al. High-flow nasal cannula in critically ill patients with severe covid-19. *Am J Respir Crit Care Med* 2020;202:1039-42.
- 103 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. doi:10.1371/journal.pone.0035797
- 104 Dhand R, Li J. Coughs and sneezes: their role in transmission of respiratory viral infections, including SARS-CoV-2. *Am J Respir Crit Care Med* 2020;202:651-9. doi:10.1164/rccm.202004-1263PP
- 105 Gaeckle NT, Lee J, Park Y, Kreykes G, Evans MD, Hogan CJr. Aerosol generation from the respiratory tract with various modes of oxygen delivery. *Am J Respir Crit Care Med* 2020;202:1115-24. doi:10.1164/rccm.202006-2309OC
- 106 Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high-flow nasal cannula therapy versus CPAP via different masks. *Eur Respir J* 2019;53:1802339. doi:10.1183/13993003.02339-2018
- 107 Li J, Ehrmann S. High-flow aerosol-dispersing versus aerosol-generating procedures. *Am J Respir Crit Care Med* 2020;202:1069-71. doi:10.1164/rccm.202008-3317ED
- 108 Gershengorn HB, Hu Y, Chen J-T, et al. The impact of high-flow nasal cannula use on patient mortality and the availability of mechanical ventilators in covid-19. *Ann Am Thorac Soc* 2020. doi:10.1513/AnnalsATS.202007-803OC
- 109 Mellado-Artigas R, Ferrero BL, Angriman F, et al, COVID-19 Spanish ICU Network. High-flow nasal oxygen in patients with COVID-19-associated acute respiratory failure. *Crit Care* 2021;25:58.
- 110 Berbenetz N, Wang Y, Brown J, et al. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema[CD]. *Cochrane Database Syst Rev* 2019;4:CD005351. doi:10.1002/14651858.CD005351.pub4
- 111 Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease[CD]. *Cochrane Database Syst Rev* 2017;7:CD004104. doi:10.1002/14651858.CD004104.pub4
- 112 Frat JP, Ragot S, Coudroy R, et al, REVA network. Predictors of intubation in patients with acute hypoxemic respiratory failure

- treated with a noninvasive oxygenation strategy. *Crit Care Med* 2018;46:208-15. doi:10.1097/CCM.0000000000002818
- 113 Xu XP, Zhang XC, Hu SL, et al. Noninvasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis. *Crit Care Med* 2017;45:e727-33. doi:10.1097/CCM.0000000000002361
 - 114 Kondo Y, Kumasawa J, Kawaguchi A, Seo R, Nango E, Hashimoto S. Effects of non-invasive ventilation in patients with acute respiratory failure excluding post-extubation respiratory failure, cardiogenic pulmonary edema and exacerbation of COPD: a systematic review and meta-analysis. *J Anesth* 2017;31:714-25. doi:10.1007/s00540-017-2389-0
 - 115 David-João PG, Guedes MH, Réa-Neto Á, Chaibem VBO, Baena CP. Noninvasive ventilation in acute hypoxemic respiratory failure: A systematic review and meta-analysis. *J Crit Care* 2019;49:84-91. doi:10.1016/j.jccr.2018.10.012
 - 116 Bellani G, Laffey JG, Pham T, et al, LUNG SAFE Investigators, ESICM Trials Group. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am J Respir Crit Care Med* 2017;195:67-77. doi:10.1164/rccm.201606-1306OC
 - 117 Frat J-P, Ragot S, Girault C, et al, REVA network. Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: a post-hoc analysis of a randomised trial. *Lancet Respir Med* 2016;4:646-52. doi:10.1016/S2213-2600(16)30093-5
 - 118 Ferreyro BL, Angriman F, Munshi L, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *JAMA* 2020;324:57-67. doi:10.1001/jama.2020.9524
 - 119 Alhazzani W, Möller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (covid-19). *Crit Care Med* 2020;48:e440-69. doi:10.1097/CCM.0000000000004363
 - 120 Pfeifer M, Ewig S, Voshaar T, et al, German Respiratory Society. Position paper for the state of the art application of respiratory support in patients with covid-19. *Pneumologie* 2020;74:337-57.
 - 121 Hua J, Qian C, Luo Z, Li Q, Wang F. Invasive mechanical ventilation in COVID-19 patient management: the experience with 469 patients in Wuhan. *Crit Care* 2020;24:348. doi:10.1186/s13054-020-03044-9
 - 122 Guan W-J, Ni Z-Y, Hu Y, et al, China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708-20. doi:10.1056/NEJMoa2002032
 - 123 Wang T, Tang C, Chen R, et al. Clinical features of coronavirus disease 2019 patients with mechanical ventilation: a nationwide study in China. *Crit Care Med* 2020;48:e809-12.
 - 124 Guan L, Zhou L, Le Grange JM, Zheng Z, Chen R. Non-invasive ventilation in the treatment of early hypoxemic respiratory failure caused by COVID-19: considering nasal CPAP as the first choice. *Crit Care* 2020;24:333. doi:10.1186/s13054-020-03054-7
 - 125 Duca A, Memaj I, Zanardi F, et al. Severity of respiratory failure and outcome of patients needing a ventilatory support in the Emergency Department during Italian novel coronavirus SARS-CoV2 outbreak: Preliminary data on the role of Helmet CPAP and Non-Invasive Positive Pressure Ventilation. *EclinicalMedicine* 2020;24:100419. doi:10.1016/j.eclinm.2020.100419
 - 126 Sivaloganathan AA, Nasim-Mohi M, Brown MM, et al, University Hospital Southampton Critical Care and Respiratory Medicine Teams and the REACT investigators, UHS Critical Care Clinical Team, UHS Respiratory Clinical Team, REACT Investigators. Noninvasive ventilation for COVID-19-associated acute hypoxaemic respiratory failure: experience from a single centre. *Br J Anaesth* 2020;125:e368-71. doi:10.1016/j.bja.2020.07.008
 - 127 Oranger M, Gonzalez-Bermejo J, Dacosta-Noble P, et al. Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study. *Eur Respir J* 2020;56:2001692. doi:10.1183/13993003.01692-2020
 - 128 Burns GP, Lane ND, Tedd HM, et al. Improved survival following ward-based non-invasive pressure support for severe hypoxia in a cohort of frail patients with COVID-19: retrospective analysis from a UK teaching hospital. *BMJ Open Respir Res* 2020;7:e000621. doi:10.1136/bmjresp-2020-000621
 - 129 Zheng Y, Sun L-J, Xu M, et al. Clinical characteristics of 34 COVID-19 patients admitted to intensive care unit in Hangzhou, China. *J Zhejiang Univ Sci B* 2020;21:378-87. doi:10.1631/jzus.B2000174
 - 130 Aliberti S, Radovanovic D, Billi F, et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study. *Eur Respir J* 2020;56:2001935. doi:10.1183/13993003.01935-2020
 - 131 Bellani G, Grasselli G, Cecconi M, et al. COVID-19 Lombardy ICU Network. Noninvasive Ventilatory Support of COVID-19 Patients Outside the Intensive Care Units (WARD-COVID). *Ann Am Thorac Soc* 2021; doi:10.1513/AnnalsATS.202008-1080OC
 - 132 Zhang Q, Shen J, Chen L, et al. Timing of invasive mechanical ventilation in critically ill patients with coronavirus disease 2019. *J Trauma Acute Care Surg* 2020;89:1092-8.
 - 133 Potalivo A, Montomoli J, Facondini F, et al. Sixty-day mortality among 520 Italian hospitalized COVID-19 patients according to the adopted ventilatory strategy in the context of an integrated multidisciplinary clinical organization: a population-based cohort study. *Clin Epidemiol* 2020;12:1421-31.
 - 134 Diaz de Teran T, Gonzalez Martinez M, Banfi P, et al. Management of patients with severe acute respiratory failure due to SARS-CoV-2 pneumonia with non-invasive ventilatory support outside intensive care unit. *Minerva Med* 2021; doi:10.23736/S0026-4806.21.07134-2.
 - 135 Dupuis C, Bouadma L, de Montmollin E, et al. Association between early invasive mechanical ventilation and day-60 mortality in acute hypoxemic respiratory failure related to coronavirus disease-2019 pneumonia. *Crit Care Explor* 2021;3:e0329.
 - 136 Daniel P, Mecklenburg M, Massiah C, et al. Non-invasive positive pressure ventilation versus endotracheal intubation in treatment of COVID-19 patients requiring ventilatory support. *Am J Emerg Med* 2021;43:103-8.
 - 137 Schenck EJ, Hoffman K, Goyal P, et al. Respiratory mechanics and gas exchange in covid-19-associated respiratory failure. *Ann Am Thorac Soc* 2020;17:1158-61. doi:10.1513/AnnalsATS.202005-427RL
 - 138 Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 2020;395:1763-70. doi:10.1016/S0140-6736(20)31189-2
 - 139 Auld SC, Caridi-Scheible M, Blum JM, et al, Emory COVID-19 Quality and Clinical Research Collaborative. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. *Crit Care Med* 2020;48:e799-804. doi:10.1097/CCM.0000000000004687
 - 140 Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with covid-19: a cohort study. *Am J Respir Crit Care Med* 2020;201:1560-4. doi:10.1164/rccm.202004-1163LE
 - 141 Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region—case series. *N Engl J Med* 2020;382:2012-22. doi:10.1056/NEJMoa2004500
 - 142 Bellani G, Laffey JG, Pham T, et al, LUNG SAFE Investigators, ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016;315:788-800. doi:10.1001/jama.2016.0291
 - 143 Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med* 2020;8:1201-8.
 - 144 Grieco DL, Bongiovanni F, Chen L, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. *Crit Care* 2020;24:529. doi:10.1186/s13054-020-03253-2
 - 145 Haudebourg A-F, Perier F, Tuffet S, et al. Respiratory mechanics of covid-19- versus non-covid-19-associated acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;202:287-90. doi:10.1164/rccm.202004-1226LE
 - 146 Brault C, Zerbib Y, Kontar L, et al. covid-19- versus non-covid-19-related acute respiratory distress syndrome: differences and similarities. *Am J Respir Crit Care Med* 2020;202:1301-4. doi:10.1164/rccm.202005-2025LE
 - 147 Hyman JB, Leibner ES, Tandon P, et al. Timing of intubation and in-hospital mortality in patients with coronavirus disease 2019. *Crit Care Explor* 2020;2:e0254. doi:10.1097/CCE.0000000000000254
 - 148 Hernandez-Romieu AC, Adelman MW, Hockstein MA, et al, Emory COVID-19 Quality and Clinical Research Collaborative. Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. *Crit Care Med* 2020;48:e1045-53. doi:10.1097/CCM.0000000000004600
 - 149 Wunsch H. Mechanical ventilation in covid-19: interpreting the current epidemiology. *Am J Respir Crit Care Med* 2020;202:1-4. doi:10.1164/rccm.202004-1385ED
 - 150 Martin-Villares C, Perez Molina-Ramirez C, Bartolome-Benito M, Bernal-Sprekelsen M, COVID ORL ESP Collaborative Group (*). Outcome of 1890 tracheostomies for critical COVID-19 patients: a national cohort study in Spain. *Eur Arch Otorhinolaryngol* 2020;4:1-8. doi:10.1007/s00405-020-06220-3
 - 151 Lu W, Liu X, Wang T, et al. Elevated MUC1 and MUC5AC mucin protein levels in airway mucus of critical ill covid-19 patients. *J Med Virol* 2020. doi:10.1002/jmv.26406
 - 152 Pinciroli R, Mietto C, Piriapatsom A, et al. Endotracheal tubes cleaned with a novel mechanism for secretion removal: a randomized controlled clinical study. *Respir Care* 2016;61:1431-9. doi:10.4187/respcare.04363
 - 153 Luo M, Mei Z, Wei L, Cao S, Su S, Wang Y. Precautions for weaning from invasive mechanical ventilation with critically ill COVID-19. *Heart Lung* 2020;49:869-71. doi:10.1016/j.hrtlng.2020.07.005
 - 154 D'Silva DF, McCulloch TJ, Lim JS, Smith SS, Carayannis D. Extubation of patients with COVID-19. *Br J Anaesth* 2020;125:e192-5. doi:10.1016/j.bja.2020.03.016

- 155 Tobin MJ, Amal J. *Weaning from mechanical ventilation. Principles and practice of mechanical ventilation*. McGraw-Hill Education, 2013.
- 156 Abe T, Madotto F, Pham T, et al, LUNG-SAFE Investigators and the ESICM Trials Group. Epidemiology and patterns of tracheostomy practice in patients with acute respiratory distress syndrome in ICUs across 50 countries. *Crit Care* 2018;22:195. doi:10.1186/s13054-018-2126-6
- 157 Chen W-Q, Ling W-H, Lu C-Y, et al. Which preventive measures might protect health care workers from SARS? *BMC Public Health* 2009;9:81. doi:10.1186/1471-2458-9-81
- 158 Botti C, Lusetti F, Peroni S, et al. The role of tracheotomy and timing of weaning and decannulation in patients affected by severe covid-19. *Ear Nose Throat J* 2020;9:145561320965196.
- 159 Avilés-Jurado FX, Prieto-Alhambra D, González-Sánchez N, et al. Timing, complications, and safety of tracheotomy in critically ill patients with covid-19. *JAMA Otolaryngol Head Neck Surg* 2020;147:41-8. doi:10.1001/jamaoto.2020.3641
- 160 Meister KD, Pandian V, Hillel AT, et al. Multidisciplinary safety recommendations after tracheostomy during covid-19 pandemic: state of the art review. *Otolaryngol Head Neck Surg* 2020;194:599820961990. doi:10.1177/0194599820961990
- 161 Rovira A, Dawson D, Walker A, et al. Tracheostomy care and decannulation during the covid-19 pandemic. A multidisciplinary clinical practice guideline. *Eur Arch Otorhinolaryngol* 2020;17:1-9. doi:10.1007/s00405-020-06126-0
- 162 Lundgren JD, Grund B, Barkauskas CE, et al, ACTIV-3/TICO LY-CoV555 Study Group. A Neutralizing monoclonal antibody for hospitalized patients with covid-19. *N Engl J Med* 2020. doi:10.1056/NEJMoa2033130
- 163 US Food and drug Administration. Emergency use authorization (EUA) of bamlanivimab. 2020. <https://www.fda.gov/media/143603/download>.
- 164 Sterne JAC, Murthy S, Diaz JV, et al, WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with covid-19: a meta-analysis. *JAMA* 2020;324:1330-41. doi:10.1001/jama.2020.17023
- 165 Horby P, Lim WS, Emberson JR, et al, RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19—preliminary report. *N Engl J Med* 2020. doi:10.1056/NEJMoa2021436
- 166 Eastman RT, Roth JS, Brimacombe KR, et al. Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of covid-19. *ACS Cent Sci* 2020;6:672-83. doi:10.1021/acscentsci.0c00489
- 167 Beigel JH, Tomashek KM, Dodd LE, et al, ACTT-1 Study Group Members. Remdesivir for the treatment of covid-19—final report. *N Engl J Med* 2020;383:1813-26. doi:10.1056/NEJMoa2007764
- 168 Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for covid-19 –interim WHO SOLIDARITY trial results. *medRxiv* [Preprint] 2020:2020. doi:10.15.20209817
- 169 Spinner CD, Gottlieb RL, Criner GJ, et al, GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate covid-19: a randomized clinical trial. *JAMA* 2020;324:1048-57. doi:10.1001/jama.2020.16349
- 170 Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;395:1569-78. doi:10.1016/S0140-6736(20)31022-9
- 171 Goldman JD, Lye DCB, Hui DS, et al, GS-US-540-5773 Investigators. Remdesivir for 5 or 10 days in patients with severe covid-19. *N Engl J Med* 2020;383:1827-37. doi:10.1056/NEJMoa2015301
- 172 Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol* 2020;2:e474-84. doi:10.1016/S2665-9913(20)30173-9
- 173 Klopfenstein T, Zayet S, Lohse A, et al, HNF Hospital Tocilizumab multidisciplinary team. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Med Mal Infect* 2020;50:397-400. doi:10.1016/j.medmal.2020.05.001
- 174 Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol* 2020;92:814-8. doi:10.1002/jmv.25801
- 175 Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, CORIMUNO-19 Collaborative Group. Effect of tocilizumab vs usual care in adults hospitalized with covid-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021;181:32-40. doi:10.1001/jamainternmed.2020.6820
- 176 Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with covid-19 pneumonia. *medRxiv* [Preprint] 2020:2020.08.27.20183442. doi:10.1101/2020.08.27.20183442
- 177 Salvarani C, Dolci G, Massari M, et al, RCT-TCZ-COVID-19 Study Group. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with covid-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021;181:24-31. doi:10.1001/jamainternmed.2020.6615
- 178 Stone JH, Frigault MJ, Serling-Boyd NJ, et al, BACC Bay Tocilizumab Trial Investigators. Efficacy of tocilizumab in patients hospitalized with covid-19. *N Engl J Med* 2020;383:2333-44. doi:10.1056/NEJMoa2028836
- 179 Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with covid-19 pneumonia. *N Engl J Med* 2021;384:20-30. doi:10.1056/NEJMoa2030340
- 180 REMAP-CAP Investigators, Gordon AC. Interleukin-6 receptor antagonists in critically ill patients with covid-19—preliminary report. *medRxiv* [Preprint] 2021. <https://www.medrxiv.org/content/10.1101/2021.01.07.21249390v1>.
- 181 Veiga VC, Pratts JAGG, Farias DLC, et al. Coalition covid-19 Brazil VI Investigators. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ* 2021;372.
- 182 Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv* [Preprint] 2021. <https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1>
- 183 Casadevall A, Dadachova E, Pirofski LA. Passive antibody therapy for infectious diseases. *Nat Rev Microbiol* 2004;2:695-703. doi:10.1038/nrmicro974
- 184 Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with covid-19: Initial three-month experience. *medRxiv* [Preprint] 2020:2020.08.12.20169359. doi:10.1101/2020.08.12.20169359
- 185 Klassen SA, Senefeld JW, Johnson PW, et al. Evidence favoring the efficacy of convalescent plasma for covid-19 therapy. *medRxiv* [Preprint] 2020:2020.07.29.20162917. doi:10.1101/2020.07.29.20162917
- 186 Libster R, Perez Marc G, Wappner D, et al. Prevention of severe COVID-19 in the elderly by early high-titer plasma. *medRxiv* [Preprint] 2021. <https://www.medrxiv.org/content/10.1101/2020.11.20.20234013v1>
- 187 Berger JS, Kunichoff D, Adhikari S, et al. Prevalence and outcomes of D-Dimer elevation in hospitalized patients with covid-19. *Arterioscler Thromb Vasc Biol* 2020;40:2539-47. doi:10.1161/ATVBAHA.120.314872
- 188 National Institutes of Health. NIH ACTIV trial of blood thinners pauses enrollment of critically ill covid-19 patients. 2020. <https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients>
- 189 National Institutes of Health. Full-dose blood thinners decreased need for life support and improved outcome in hospitalized covid-19 patients. 2021. <https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients>
- 190 Herridge MS, Moss M, Hough CL, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. *Intensive Care Med* 2016;42:725-38. doi:10.1007/s00134-016-4321-8
- 191 Herridge MS, Cheung AM, Tansey CM, et al, Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683-93. doi:10.1056/NEJMoa022450
- 192 Bakhr RN, Davidson JF, Bookstaver RE, et al. Physical function impairment in survivors of critical illness in an ICU Recovery Clinic. *J Crit Care* 2018;45:163-9. doi:10.1016/j.jccr.2018.02.001
- 193 Fan E, Dowdy DW, Colantuoni E, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med* 2014;42:849-59. doi:10.1097/CCM.0000000000000040
- 194 Needham DM, Wozniak AW, Hough CL, et al, National Institutes of Health NHLBI ARDS Network. Risk factors for physical impairment after acute lung injury in a national, multicenter study. *Am J Respir Crit Care Med* 2014;189:1214-24. doi:10.1164/rccm.201401-01580C
- 195 Carfi A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Group ftGAC-P-ACS. Persistent symptoms in patients after acute covid-19. *JAMA* 2020;324:603-5. doi:10.1001/jama.2020.12603
- 196 Desai SV, Law TJ, Needham DM. Long-term complications of critical care. *Crit Care Med* 2011;39:371-9. doi:10.1097/CCM.0b013e3181fd66e5
- 197 Bienvenu OJ, Friedman LA, Colantuoni E, et al. Psychiatric symptoms after acute respiratory distress syndrome: a 5-year longitudinal study. *Intensive Care Med* 2018;44:38-47. doi:10.1007/s00134-017-5009-4
- 198 Harvey MA, Davidson JE. Postintensive care syndrome: right care, right now...and later. *Crit Care Med* 2016;44:381-5. doi:10.1097/CCM.0000000000001531

- 199 Galea S, Merchant RM, Lurie N. The mental health consequences of covid-19 and physical distancing: the need for prevention and early intervention. *JAMA Intern Med* 2020;180:817-8. doi:10.1001/jamainternmed.2020.1562
- 200 Mazza MG, De Lorenzo R, Conte C, et al. COVID-19 BioB Outpatient Clinic Study group. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain Behav Immun* 2020;89:594-600. doi:10.1016/j.bbi.2020.07.037
- 201 Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EclinicalMedicine* 2020;25:100463. doi:10.1016/j.eclinm.2020.100463
- 202 Liu C, Ye L, Xia R, et al. Chest computed tomography and clinical follow-up of discharged patients with covid-19 in Wenzhou City, Zhejiang, China. *Ann Am Thorac Soc* 2020;17:1231-7. doi:10.1513/AnnalsATS.202004-324OC
- 203 Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (covid-19). *JAMA Cardiol* 2020;5:1265-73. doi:10.1001/jamacardio.2020.3557
- 204 Rajpal S, Tong MS, Borchers J, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from covid-19 infection. *JAMA Cardiol* 2021;6:116-8.
- 205 Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol* 2020;77:1018-27. doi:10.1001/jamaneurol.2020.2065
- 206 Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020;19:767-83. doi:10.1016/S1474-4422(20)30221-0
- 207 Lambert NJ, Corps S. Covid-19 "long hauler" symptoms survey report. Indiana University School of Medicine. 2020. <https://dig.abcclocal.go.com/wls/documents/2020/072720-wls-covid-symptom-study-doc.pdf>
- 208 Pandharipande PP, Girard TD, Jackson JC, et al. BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306-16. doi:10.1056/NEJMoa1301372
- 209 Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020;370:m3026. doi:10.1136/bmj.m3026
- 210 Tenforde MW, Kim SS, Lindsell CJ, et al. IVY Network Investigators, CDC COVID-19 Response Team, IVY Network Investigators. Symptom duration and risk factors for delayed return to usual health among outpatients with covid-19 in a multistate health care systems network—United States, March-June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:993-8. doi:10.15585/mmwr.mm6930e1
- 211 Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;93:1013-22. doi:10.1002/jmv.26368
- 212 Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012;40:502-9. doi:10.1097/CCM.0b013e318232da75
- 213 Griffiths J, Hatch RA, Bishop J, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. *Crit Care* 2013;17:R100. doi:10.1186/cc12745
- 214 Sese D, Biehle M. *Post intensive care syndrome (PICS) in the time of covid-19—implications post pandemic*. CCJM Curbside Consults, 2020, doi:10.3949/ccjm.87a.ccc055
- 215 Montauk TR, Kuhl EA. COVID-related family separation and trauma in the intensive care unit. *Psychol Trauma* 2020;12(S1):S96-7. doi:10.1037/tra0000839
- 216 Marra A, Ely EW, Pandharipande PP, Patel MB. The ABCDEF bundle in critical care. *Crit Care Clin* 2017;33:225-43. doi:10.1016/j.ccc.2016.12.005
- 217 Devlin JW, O'Neal HR Jr, Thomas C, et al. Strategies to optimize ICU liberation (A to F) bundle performance in critically ill adults with coronavirus disease 2019. *Crit Care Explor* 2020;2:e0139. doi:10.1097/CCE.0000000000000139
- 218 Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018;46:e825-73. doi:10.1097/CCM.0000000000003299
- 219 Hodgson CL, Bailey M, Bellomo R, et al. Trial of Early Activity and Mobilization Study Investigators. A binational multicenter pilot feasibility randomized controlled trial of early goal-directed mobilization in the ICU. *Crit Care Med* 2016;44:1145-52. doi:10.1097/CCM.0000000000001643
- 220 McWilliams DJ, Atkinson D, Carter A, Foëx BA, Benington S, Conway DH. Feasibility and impact of a structured, exercise-based rehabilitation programme for intensive care survivors. *Physiother Theory Pract* 2009;25:566-71. doi:10.3109/09593980802668076
- 221 Elliott D, McKinley S, Alison JA, Aitken LM, King MT. Study protocol: home-based physical rehabilitation for survivors of a critical illness [ACTRN12605000166673][ACTRN12605000166673]. *Crit Care* 2006;10:R90. doi:10.1186/cc4949
- 222 Ullman AJ, Aitken LM, Rattray J, et al. Intensive care diaries to promote recovery for patients and families after critical illness: A Cochrane Systematic Review. *Int J Nurs Stud* 2015;52:1243-53. doi:10.1016/j.ijnurstu.2015.03.020
- 223 Jones C, Bäckman C, Capuzzo M, et al. RACHEL group. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. *Crit Care* 2010;14:R168. doi:10.1186/cc9260
- 224 Peris A, Bonizzoli M, Iozzelli D, et al. Early intra-intensive care unit psychological intervention promotes recovery from post traumatic stress disorders, anxiety and depression symptoms in critically ill patients. *Crit Care* 2011;15:R41. doi:10.1186/cc10003
- 225 Hosey MM, Jaskulski J, Wegener ST, Chlan LL, Needham DM. Animal-assisted intervention in the ICU: a tool for humanization. *Crit Care* 2018;22:22. doi:10.1186/s13054-018-1946-8
- 226 McPeake J, Hirshberg EL, Christie LM, et al. Models of peer support to remediate post-intensive care syndrome: a report developed by the Society of Critical Care Medicine Thrive International Peer Support Collaborative. *Crit Care Med* 2019;47:e21-7. doi:10.1097/CCM.0000000000003497
- 227 Haines KJ, Beesley SJ, Hopkins RO, et al. Peer support in critical care: a systematic review. *Crit Care Med* 2018;46:1522-31. doi:10.1097/CCM.0000000000003293
- 228 Mayer KP, Sturgill JL, Kalema AG, et al. Recovery from COVID-19 and acute respiratory distress syndrome: the potential role of an intensive care unit recovery clinic: a case report. *J Med Case Rep* 2020;14:161. doi:10.1186/s13256-020-02481-y
- 229 Sevin CM, Bloom SL, Jackson JC, Wang L, Ely EW, Stollings JL. Comprehensive care of ICU survivors: Development and implementation of an ICU recovery center. *J Crit Care* 2018;46:141-8. doi:10.1016/j.jcrc.2018.02.011
- 230 Haines KJ, Sevin CM, Hibbert E, et al. Key mechanisms by which post-ICU activities can improve in-ICU care: results of the international THRIVE collaboratives. *Intensive Care Med* 2019;45:939-47. doi:10.1007/s00134-019-05647-5
- 231 Del Rio C, Collins LF, Malani P. Long-term health consequences of covid-19. *JAMA* 2020;324:1723-4. doi:10.1001/jama.2020.19719
- 232 Bhimraj A, Morgan RL, Shumaker AH, et al. IDSA guidelines on the treatment and management of patients with covid-19. *Clin Infect Dis* 2021. <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>
- 233 Hanson KE, Caliendo A, Arias C, et al. IDSA guidelines on the diagnosis of covid-19: molecular diagnostic testing. *Clin Infect Dis* 2020. <https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/>
- 234 World Health Organization. Country & Technical Guidance—Coronavirus disease (COVID-19). 2021. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications>.
- 235 Society of Critical Care Medicine. Guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). 2021. <https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19>
- 236 National Institutes of Health. COVID-19 treatment guidelines. Clinical spectrum of SARS-CoV-2 infection. 2020. <https://www.covid19treatmentguidelinesnihgov/overview/clinical-spectrum>