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 SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <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", "therapeutics", and "complications". We included articles on the basis of the quality of the study and

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)

favored 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 2020[14]) 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-2[42] although expansion of in vitro studies, animal models, and covid-19 patient serum profiles has been

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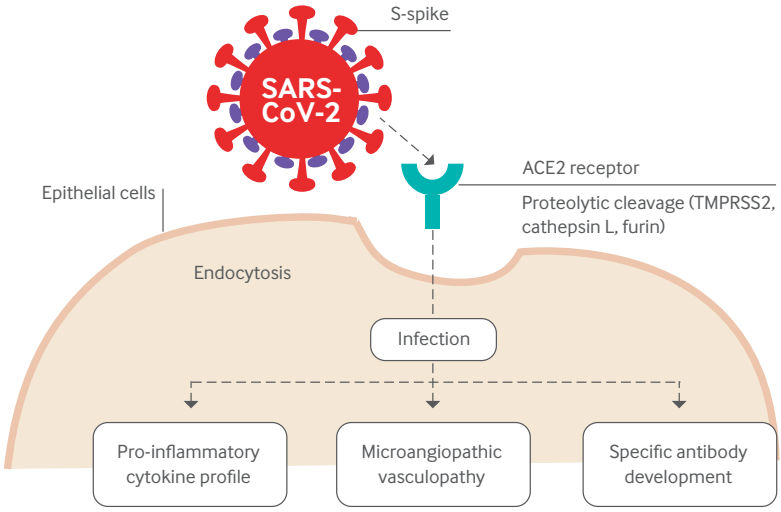

Fig 1 | SARS-CoV-2 S spike protein binds to the ACE2 receptor, which leads to proteolytic cleavage by TMPRSS2, cathepsin L, and furin in the epithelial cell of the respiratory tract. The virus undergoes endocytosis, viral maturation, replication, and release of more virus within the cytoplasm infecting 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-1β, 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 NIH[1] 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 hypoxemia[64] 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_iO_2 table[72] 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_aO_2/F_iO_2 <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

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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 measures[84] 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 alveoli[88] 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

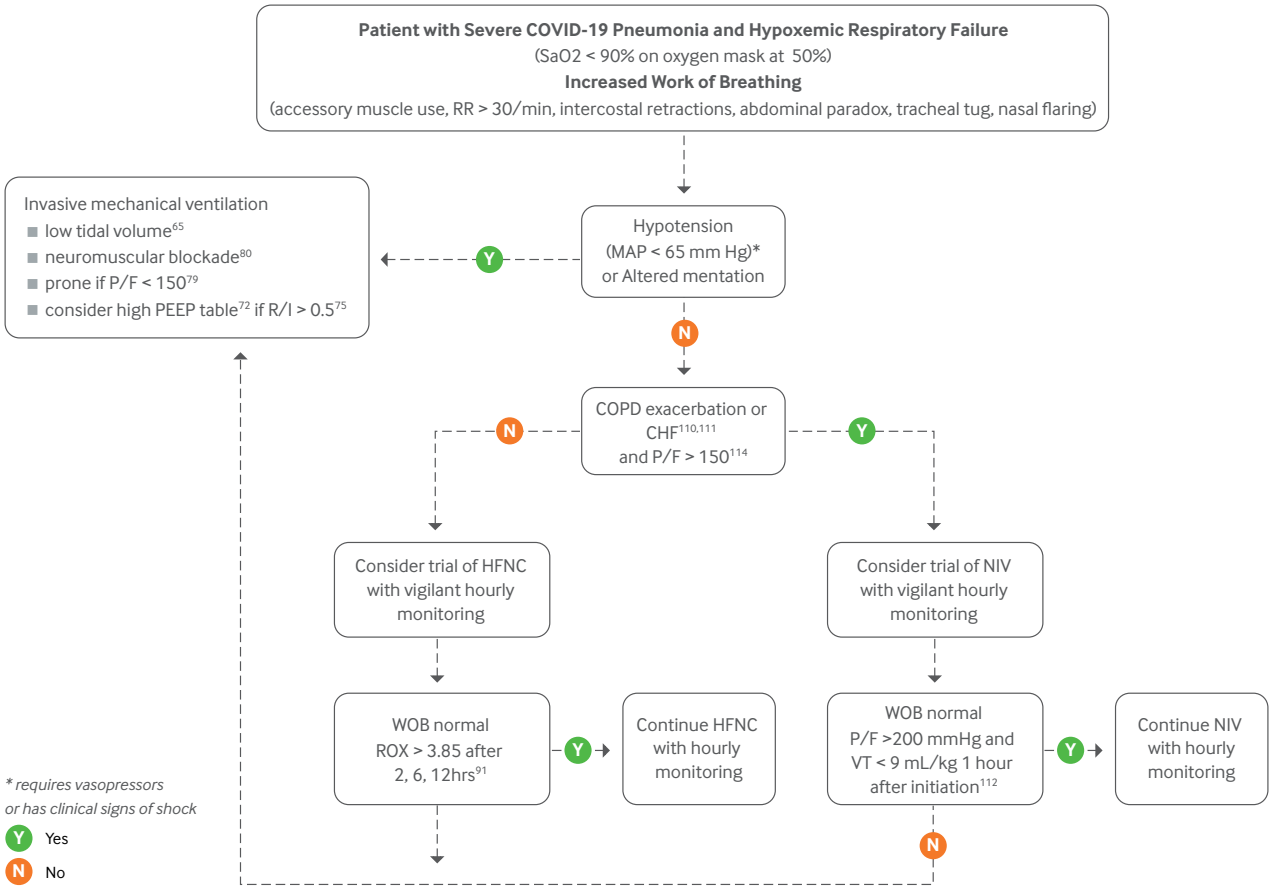

Fig 2 | Algorithm for the respiratory management of a patient with covid-19 pneumonia. RR=respiratory rate, PEEP=positive end expiratory pressure, R/I=recruitment/inflation ratio, COPD=chronic obstructive pulmonary disease, CHF=congestive heart failure, HFNC=high flow nasal cannula, WOB=work of breathing, 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 proned 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 infection[107] 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 stay[109] 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 ≤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 ≤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 epidemics[103] 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 study[125] 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

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(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 safe[133] and potentially superior to early intubation[134-136] 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 H_2O, delivered PEEP was 8.4 (8.3-8.6) cm H_2O, 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 study[144] 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 patients[143] 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 H_2O) 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 intubation[147] 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 ventilation[149]: 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 devices[152] 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/Fi_02	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_iO_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 ≥5.37, 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 ±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_pO_2/F_iO_2 113.4 ±6.6 (success) 93.7 ±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_aO_2/F_iO_2 ≤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 SD14	48%	196 ±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_aO_2/F_iO_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 ±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 ±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

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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/Fi_02	Duration of use	Outcome	Comment
Oranger et al	38 (All CPAP) 14 controls (no CPAP)	63 (55-70)	32	P_aO_2 71 (63.5-88.5) On 5 (3-6) L/min O2	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_2O) 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_aO_2/F_iO_2 160 (114-220) mm Hg No lung mechanics PEEP 14 (12-16) cm H_2O FiO2 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_aO_2/F_iO_2 120 (83-177) mm Hg Static compliance: 35 (27-45) ml/cm H_2O Plateau pressure 25 (22-29) cm H_2O Driving pressure 12 cm H_2O (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_aO_2/F_iO_2 103 (82-134) mm Hg Static compliance 28 (23-38) ml/cm H_2O Plateau pressure 25 (21-29) cm H_2O Driving pressure 14 (11-17.2) cm H_2O	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_2O
Cummings et al 2 NY Presbyterian hospitals (Columbia Univ.)	203 (Full cohort 257)	62 (51-72)	33	P_aO_2/F_iO_2 129 (80-203) mm Hg Driving pressure 15 (11-18) cm H_2O PEEP 15 (12-18) cm H_2O FiO2 1 (0.8-1) Plateau pressure 27 (23-31) cm H_2O	18 (9-28) days	In-hospital mortality 39% 23% discharged alive 2% transfer to another hospital 37% remained hospitalized	25% received NMB 17% proned ECMO 3%
Auld et al Emory Healthcare acute care hospitals	165 (Full cohort 217)	64 (54-73)	45.2	P_aO_2/F_iO_2 132 (100-178) mm Hg Static lung compliance 34 (28-46) mL/cm H_2O	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_aO_2/F_iO_2 182 (135-245) mm Hg Static compliance 35 (30-43) mL/cm H_2O Driving pressure 11 (9-12) cm H_2O	16 (10-21) days	Mortality 16.7% 62% extubated 21.2% received tracheostomy Length of stay 17.5 (13-25)	42% received NMB 47% proned 95% on vasopressors 5% received ECMO
Bhatraju et al 9 Seattle hospitals	18 24 patients in cohort	64 SD 8	37	P_aO_2/F_iO_2 142 (94-177) mm Hg Compliance 29 (25-36) mL/cm H_2O Driving pressure 13 (11-17) cm H_2O Plateau pressure 25 (20-28) cm H_2O FiO2 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 since 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 patients[164] 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-2[160] was an RCT specifically designed to evaluate remdesivir in hospitalized patients with moderate covid-19 (not needing supplemental oxygen), although ACCT-1[167] and SOLIDARITY[168] 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

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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)	• 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)	• 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)	• 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 subanalysis 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 CAR-T 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 (COVATA[176], REMAP-CAP[180] 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	• 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 stay[194] • 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	• 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 cases[196-198] • 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 itself[199] • 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	• Persistent pulmonary symptoms are common after covid-19[195] • 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 discharge[201] • An observational study from China of 51 covid-19 patients showed that 45% had abnormal computed tomography scans four weeks after discharge[202]
Cardiac impairment	• 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	• While the occurrence of stroke due to covid-19 is relatively rare, other conditions including impairment of consciousness, encephalitis, seizure, encephalopathy, and ì brain fog have been reported 2-3 months after initial illness onset[205-207] • 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 thinking[208]

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 (saO_2<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 trials[175-179] 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 O_2 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 severity[187] 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 risk[196] 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 "ABCDEF" 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 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,[232 233] 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 tracheostomy[160 161] and respiratory failure[120] 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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