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Evidence-Based Management of the Critically Ill Adult With SARS-CoV-2 Infection

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Abstract
Human infection by the novel viral pathogen SARS-CoV-2 results in a clinical syndrome termed Coronavirus Disease 2019 (COVID-19). Although the majority of COVID-19 cases are self-limiting, a substantial minority of patients develop disease severe enough to require intensive care. Features of critical illness associated with COVID-19 include hypoxemic respiratory failure, acute respiratory distress syndrome (ARDS), shock, and multiple organ dysfunction syndrome (MODS). In most (but not all) respects critically ill patients with COVID-19 resemble critically ill patients with ARDS due to other causes and are optimally managed with standard, evidence-based critical care protocols. However, there is naturally an intense interest in developing specific therapies for severe COVID-19. Here we synthesize the rapidly expanding literature around the pathophysiology, clinical presentation, and management of COVID-19 with a focus on those points most relevant for intensivists tasked with caring for these patients. We specifically highlight evidence-based approaches that we believe should guide the identification, triage, respiratory support, and general ICU care of critically ill patients infected with SARS-CoV-2. In addition, in light of the pressing need and growing enthusiasm for targeted COVID-19 therapies, we review the biological basis, plausibility, and clinical evidence underlying these novel treatment approaches.

Keywords
coronavirus, SARS-CoV-2, COVID-19, pandemic, critical care, acute respiratory failure, acute respiratory distress syndrome (ARDS), hypoxemia

Since the first reports of a novel viral respiratory illness emerged in December 2019 in Hubei Province, China,1 the illness has spread to pandemic proportions—infecting tens of millions of individuals on all populated continents and responsible for over a million deaths.2 Both professional society guidelines3 and individual approaches4-7 for the care of patients with what became known as Coronavirus Disease 2019 (COVID-19) were rapidly promulgated. These early efforts naturally preceded the wealth of clinical and basic science data8 which have since become available regarding the pathophysiology and clinical management of COVID-19. In this review, we synthesize what is now known about COVID-19 critical illness into a consensus, evidence-based approach informed by the pre-existing critical care literature, emerging basic biology,9-11 multiple observational reports,12-18 and recently published randomized controlled trial data.19,20

Epidemiology, and Pathophysiology of SARS-CoV-2

Epidemiology and Transmission
Reports of a respiratory illness among individuals linked to an indoor seafood market in Wuhan first arose in late 2019.1 Bronchoalveolar lavage samples from 3 affected patients with pneumonia revealed the presence of a previously unidentified viral sequence, “2019-nCoV,” aligning to lineage B of the betacoronavirus (Beta-CoV) family and highly homologous to a bat coronavirus, CoV ZXC21.9 Existing Beta-CoV family members, namely SARS-CoV and MERS-CoV, had previously been linked to epidemic respiratory viral infections (SARS and MERS, respectively), strongly suggesting a causal role for this novel agent in disease pathophysiology. Further sequence
analysis established 2019-nCoV as most similar to SARS-CoV among previously identified coronaviruses; it was therefore renamed “SARS-CoV-2” and the disease that it causes in humans was termed Coronavirus Disease 2019, abbreviated COVID-19.

Early analyses of disease transmission estimated the SARS-CoV-2 basic reproductive number (R0) between 2.0 and 2.5, indicating that an average infected individual would infect ~2 others and thereby propagate disease. Given a modest case fatality rate under 5% (versus, for example, MERS’ of >25%) these data raised concern for the possibility of widespread dissemination within and outside of China. In the approximately 7 months following the initial report and characterization of COVID-19, the illness has indeed spread to pandemic proportions. Given the challenges in case identification these data are almost certainly substantial underestimates, highlighting the pressing need for physical distancing and other public health responses in curbing COVID-19 spread. Even if such efforts are successful, however, the burden of disease already present worldwide guarantees a surge in this infection and its sequelae.

**Virology and Pathophysiology**

An appreciation of SARS-CoV-2 life cycle and pathobiology is worthwhile for the practicing clinician, particularly in understanding the basis for therapies currently in development and trials. Like other betacoronaviruses, SARS-CoV-2 is an enveloped, positive-strand RNA virus and, as for SARS-CoV and MERS-CoV, is transmitted primarily through respiratory droplets harboring intact virions. Unlike SARS, however, multiple reports indicate the potential for viral transmission from currently asymptomatic individuals and even those in whom symptoms never develop. In addition to respiratory droplets, SARS-CoV-2 exhibits laboratory stability in aerosols (half-life ~1 hour) and on a wide variety of inorganic surfaces. Epidemiologic investigations to date indicate that droplet and contact transmission are the major routes of transmission of SARS-CoV-2, in line with the longstanding recognition that persistence in aerosols is but one parameter required for airborne transmission. Accordingly, true airborne transmission is rare, having been firmly established for only a very small number of pathogens. Nevertheless, it remains possible that special circumstances may allow droplet-transmitted pathogens such as SARS-CoV-2 to traverse larger times and distances as in airborne transmission. Some reports during the SARS outbreak indicated that such permissiv e airborne transmission may have occurred, while others suggested transmission was exclusively by the droplet route. As discussed in following sections, the precise contribution of droplets, direct contact, aerosols, and fomites in driving SARS-CoV-2 spread remains a topic of intense debate, with attendant implications for contact and respiratory precautions among healthcare providers: droplet-transmitted pathogens spread via close, relatively extended contact with an infected person whereas airborne-transmitted pathogens can remain in the environment for hours and are far more easily transmissible.

Although potent, specific therapies against SARS-CoV-2 remain elusive to date, a large number of candidate drug therapies targeting the viral life cycle are under investigation in pre-clinical and clinical studies and one agent (remdesivir) has been approved for clinical use. Here we briefly review key steps in viral pathophysiology (Figure 1) in order to place these therapies (addressed later) in context.

Whether encountered directly in respiratory secretions or via an intermediate fomite, SARS-CoV-2 enters cells of the host respiratory tract by way of a viral envelope protein (spike protein, “S”) that engages cell-surface receptors. The receptor-binding region of SARS-CoV-2 S protein is nearly identical to SARS-CoV, which has previously been established to engage at least 2 cell surface transmembrane proteins — angiotensin-converting enzyme 2 (ACE2) and CD209 L (L-SIGN). Recent work has definitively established that ACE2 can engage the SARS-CoV-2 S protein as well but whether this is the only relevant receptor in vivo remains unclear and the observed pattern of affected tissues is not entirely consistent with the known ACE2 expression domain. Following receptor binding, coronaviruses may enter host cells through either of 2 mechanisms: (1) direct fusion or (2) receptor-mediated endocytosis (Figure 1). In the former case, one or more host cell surface proteases cleave the S protein, driving fusion of the viral envelope with host cell membrane and delivering the naked virus to the cytoplasm. In the latter case, the entire virion is internalized into an “endosome” from which it must escape in a lysosome-dependent process.

Once in the cell, SARS-CoV-2 replicates its genome using a virally-encoded RNA-dependent RNA polymerase (RdRp) and hijacks host cell translation machinery to produce viral polyproteins required for virion assembly. These polyproteins are cleaved by a virally encoded protease (CoV Mpro), after which viral assembly can occur. Infected cells transport assembled virions to the cell surface, where they are released through exocytosis to infect other host cells. As for SARS-CoV before it, the specific mechanisms that account for the ability of SARS-CoV-2 to cause severe disease in humans remain poorly understood. Early lung pathology reports from biopsy and autopsy specimens indicate (as for SARS and MERS) diffuse alveolar damage (DAD) with alveolar desquamation, hyaline membranes, and variable degrees of viral cytopathic changes — overall consistent with viral-induced acute respiratory distress syndrome (ARDS). In patients who recover, a polyclonal humoral (antibody) and cellular immune response typically develops with evidence of neutralizing antibodies. The duration and quality of immunity provided by these antibodies against re-infection remains to be comprehensively characterized, though analogous responses in nonhuman primates confer protection against SARS-CoV-2 re-challenge.
escape, RdRp activity, and \( M^{\text{pro}} \) activity are in active development and testing, as are approaches aimed at vaccination and adoptive transfer of neutralizing antibodies from convalescent sera.

Clinical Presentation, Diagnostic Testing, and Triage

Clinical Features

The initial presentation of COVID-19 is non-specific and may include fever, malaise, sore throat, cough, and myalgias—though no single symptom is present in a majority of cases. Fever is the most common presenting symptom but is present on presentation in less than half of cases. “Atypical” respiratory viral symptoms including anosmia and gastrointestinal complaints have also been reported, sometimes as the dominant or sole early symptoms. In published case series, the median incubation period is approximately 4 days and the median time to ICU transfer from symptom onset is approximately 10 days.

Data from Wuhan, China and Lombardy, Italy indicate that a minority (7% and ~16%, respectively) of patients progress to require ICU admission, almost universally for hypoxemic respiratory failure. While initial reports indicated that ICU mortality was quite high, subsequent cohorts have reported substantially lower mortality rates in line with pre-COVID-19 mortalities in moderate to severe ARDS.

Patient characteristics associated with need for critical care include age >60 years, male sex, active or historical smoking, and presence of comorbidities including cardiac disease, diabetes, and chronic pulmonary disease. Laboratory abnormalities significantly associated with risk of severe disease include lymphopenia, elevated troponin, elevated creatine phosphokinase (CPK), elevated creatinine, elevated lactate dehydrogenase (LDH), elevated d-dimer, prolonged international normalized ratio of prothrombin time (PT/INR), and increased C-reactive protein (CRP); procalcitonin and total leukocyte count are often normal. The vast majority of patients exhibit abnormalities on chest imaging—typically bilateral patchy opacities and/or consolidation. CT imaging does not reliably distinguish COVID-19 from other causes of infectious...
Table 1. Clinical Characteristics and Preliminary Outcomes of COVID-19 Respiratory Failure.a

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Location</th>
<th>Number of patients</th>
<th>Patient population</th>
<th>P:F ratio (median)</th>
<th>Respiratory system compliance (median)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schenck et al15</td>
<td>New York City, NY, USA</td>
<td>267</td>
<td>Mechanical Ventilation</td>
<td>101</td>
<td>28</td>
<td>18.3%</td>
</tr>
<tr>
<td>Ziehr et al12</td>
<td>Boston, MA, USA</td>
<td>66</td>
<td>Mechanical Ventilation</td>
<td>182</td>
<td>35</td>
<td>16.7%</td>
</tr>
<tr>
<td>Auld et al13</td>
<td>Atlanta, GA, USA</td>
<td>217</td>
<td>ICU</td>
<td>132</td>
<td>34</td>
<td>25.8%</td>
</tr>
<tr>
<td>Mitra et al14</td>
<td>Vancouver, BC, Canada</td>
<td>117</td>
<td>ICU</td>
<td>180</td>
<td>35</td>
<td>15.4%</td>
</tr>
<tr>
<td>Bhatraju et al16</td>
<td>Seattle, WA, USA</td>
<td>24</td>
<td>ICU</td>
<td>142</td>
<td>37</td>
<td>50%</td>
</tr>
<tr>
<td>Cummings et al17</td>
<td>New York City, NY, USA</td>
<td>257</td>
<td>ICU</td>
<td>129</td>
<td>27</td>
<td>39%</td>
</tr>
</tbody>
</table>

aThe table summarizes physiologic variables and outcomes of patients with severe (requiring ICU admission) COVID-19 in North America. Mortality figures include outcomes for all patients at the time of data censoring, including those still hospitalized, in the ICU or one mechanical ventilation. P: F refers to the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen. Reported values are medians. Respiratory system compliance values are also reported as medians.

pneumonitis, but SARS-CoV-2 has been associated with a preferentially peripheral distribution of opacities, absence of pleural effusions, and absence of lymphadenopathy. The most common severe manifestation of COVID-19 in the ICU is ARDS, defined clinically by acute onset of hypoxemia, bilateral opacities not clearly caused by heart failure, and hypoxemia that persists on at least 5 cm H₂O of positive end-expiratory pressure (PEEP).

Controversies Regarding Clinical Features of Severe COVID-19

Some controversy as to the nature of COVID-19 ARDS has arisen following early anecdotal reports suggesting that, as compared with patients suffering from comparable degrees of hypoxemia from alternate causes, COVID-19 patients exhibit lower driving pressures (plateau pressure—PEEP), lower “recruitability,” and higher respiratory system compliance. It was suggested from such reports that COVID-19 uniquely presents with a novel phenotype characterized by preserved compliance in the face of severely impaired oxygenation. Some went further to propose that COVID-19 respiratory failure represents a state analogous to high-altitude pulmonary edema (HAPE) and should be treated accordingly. It was not immediately clear from these reports why (or even how) organ-level mechanical consequences of biopsy-proven DAD might systematically differ by inciting pathogen, and such speculation has not been supported by subsequent investigations. Instead, multiple reports demonstrate that critically ill patients with COVID-19 have, on average, both low respiratory system compliance and arterial oxygenation (as measured by the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, P: F, Table 1). Indeed, reported data on gas exchange and pulmonary mechanics in COVID-19 are entirely in line with published series on ARDS in the pre-COVID-19 era and are inconsistent with HAPE. These findings have important implications for therapy and strongly support the application of evidence-based ARDS therapeutic strategies in this disease, as discussed below.

A second controversial topic surrounds the possibility of a pathologically hyperinflammatory state in severe COVID-19, colloquially described as “cytokine storm.” Similar pathophysiology has been proposed in SARS and influenza as well, though definitive evidence of a causative role for immune dysfunction in driving mortality remains lacking. The majority of data supporting a role for “cytokine storm” in SARS-CoV-2 infection have focused on interleukin-6 (IL-6) and ferritin, secreted factors previously associated with immunotherapy-related cytokine release syndrome (CRS) and hemophagocytic lymphohistiocytosis (HLH). For example, Ruan and colleagues reported ~2-fold higher IL-6, ferritin, and CRP levels in COVID-19 non-survivors than survivors while Zhu et al. identified IL-6 elevation as highly predictive of outcome. However, the mere presence of particular laboratory abnormalities in a heterogeneous disease (or in severe cases of the disease) does not imply an etiologic role for the analyte in question. Accordingly, hemophagocytosis and hypercytokinemia have long been recognized as relatively common findings in patients who die with ARDS or sepsis. There has, however, been a longstanding interest in defining subtypes or endotypes of ARDS which are characterized by hyperinflammation. Hyperinflammatory sub-types of ARDS have previously been linked with poor outcome and differential treatment responses but were associated with significantly higher levels of cytokines than have been reported in COVID-19. Indeed, IL-6 levels reported in severe COVID-19 would actually have been classified as hypo-inflammatory by previous subtyping schemes. In 2 large (>200 patient) independent cohorts of severe COVID-19, for example, median IL-6 levels of 25 pg/ml and 26 pg/ml were reported; by contrast, Calfee and colleagues have previously described hyper- and hypo-inflammatory subtypes of ARDS wherein the hypo-inflammatory subtype was characterized by mean IL-6 levels of 282 pg/ml and the hyper-inflammatory by mean levels of 1618 pg/ml. Another study examined levels of TNFα, IL-6, and IL-8 in COVID-19 ARDS patients and again found lower concentrations of these cytokines in critically-ill
COVID-19 patients than in matched cases of ARDS due to bacterial septic shock. Thus, while a fascinating hypothesis, it is far from clear whether immune activation in COVID-19 represents a causal event in disease progression (ie, “hyperinflammation”) or instead identifies critically ill patients with robust and possibly appropriate immune response. As discussed below, these data have important implications for the use of targeted immunomodulators in the treatment of COVID-19 patients admitted to the ICU.

Initial Diagnostic Testing, ICU Triage, and Care Delivery Considerations

A detailed technical discussion of various SARS-CoV-2 diagnostic assays is well beyond the scope of this critical care-focused article, but treating physicians should be familiar with the strengths and limitations of current tests. The most sensitive assay for lower respiratory tract infection is likely bronchoalveolar fluid (BAL) reverse transcription polymerase chain reaction (RT-PCR) but is rarely performed owing to invasiveness and aerosol exposure risk to healthcare providers. By far the most commonly used diagnostic test for SARS-CoV-2 infection is RT-PCR from nasal or nasopharyngeal swab samples, which recent data suggest perform comparably. Notably, and in contrast with SARS-CoV, SARS-CoV-2 RNA is detectable early in the course of (if not prior to) symptoms. It has been suggested, based in large part on a study indicating high sensitivity of imaging compared to RT-PCR, that computed tomography (CT) of the chest may be used to diagnose COVID-19. This study, however, has been criticized for the quality of the PCR assay used and the American College of Radiology recommends against the routine use of CT in the diagnosis of COVID-19, concluding that imaging findings are neither adequately sensitive nor specific for ruling in or ruling out the disease. As such, imaging does not significantly add to the diagnostic yield in an RT-PCR+ COVID-19 patient and should be reserved for situations where alternate diagnoses need to be evaluated (ex. pulmonary embolism, pleural effusion) or to identify high risk PCR-negative patients for further work-up. In at least a subset of such patients, a definitive diagnosis could change management, particularly as targeted SARS-CoV-2 therapies become more available. Some evidence does indicate that lower respiratory tract sampling is likely to enhance diagnostic sensitivity for SARS-CoV-2 and a recent ACCP/AABIP consensus statement suggests non-bronchoscopic endotracheal sampling as a reasonable next diagnostic step.

While no direct clinical data can yet support this practice as changing outcomes, endotracheal sampling would likely be performed regardless to evaluate for other infectious causes of respiratory failure in an intubated patient and is therefore a reasonable strategy. Importantly, any sampling associated with opening the ventilator circuit to room air should be considered an aerosol-generating procedure (implications discussed further below).

The vast majority of patients in whom a critical care consultation is sought will have already undergone targeted SARS-CoV-2 testing but may not have had the full complement of ancillary laboratory evaluation useful for risk stratification and triage. As lymphopenia and elevations in CPK, d-dimer and LDH have been associated with poor prognosis in COVID-19, we suggest obtaining CBC with differential, complete metabolic panel, CPK, d-dimer, and LDH. ARDS is associated with an increase in the risk of renal failure and elevated indices of liver function have been associated with poor outcome. For these reasons we recommend a comprehensive metabolic panel including liver function tests. Routine echocardiography is discouraged by the American Society for Echocardiography but may be of use for patients in whom initial cardiac biomarkers are markedly elevated or if there exists suspicion for a component of cardiogenic shock. The greatest utility of these data may be in adding to clinical parameters for risk stratification and ICU triage decisions which should, as always, be guided by clinical assessment, trajectory, laboratory evaluation, and resource availability. There are few evidence-based criteria for triggering ICU transfer in critical illness generally, and certainly not in COVID-19 specifically, so the decision to escalate care setting remains a function of physician and nursing assessment, institutional resources, and clinical trajectory.

In addition to level of care, it is important to conduct triage in such a way as to minimize risk to staff and the possibility of nosocomial transmission. Considerable debate continues to exist regarding the most appropriate forms of personal protective equipment (PPE) for healthcare workers. The U.S. Centers for Disease Control suggests a number of measures including strict contact and droplet precautions and, where possible, cohorting COVID-19 patients to dedicated units with staff trained in donning and doffing PPE. Current CDC guidelines recommend routine use of N95 respirators for healthcare workers caring for COVID-19 patients (when possible), based largely upon the theoretical possibility of airborne transmission as discussed above. World Health Organization (WHO) guidelines instead specify standard surgical masks outside of specifically aerosol-generating procedures (AGPs), in line with multiple studies which have found such standard droplet precautions effective in protecting hospital staff. Furthermore, a meta-analysis examining RCTs which compared the efficacy of standard masks to N95 respirators in preventing transmission of viral pathogens (including coronaviruses) likewise found no clear benefit associated with N95 use during standard care. Our conclusion from the available evidence is that N95 respirators may be safely reserved for situations with high risk of aerosol exposure, but in resource-rich environments may theoretically provide some small additional margin of protection in routine use. For patients undergoing aerosol-generating procedures, staff use of N95 or more stringent particle-restricting respirators should be compulsory. Recent evidence also suggests that masks worn by patients may further reduce the risk of droplet and aerosol-mediated infection of others.

Beyond personal protective equipment for care providers, efforts should be made to minimize the number of staff in and
out of all patient rooms, and examinations limited to the minimum necessary for care provision. In the intensive care unit, one practical change in physician practice to facilitate this is the “bundling” of procedures such as central venous catheter placement, arterial line placement, and orogastric tube placement to limit staff exposure and PPE use. Nursing interventions such as patient assessment, medication administration, lab draws, and turns may likewise be combined to reduce donning/doffing and exposure. Finally, technological and practice changes may allow adequately equipped ICUs to place infusion pumps and ventilator control panels outside of patient rooms, thereby allowing titration of continuous infusions and respiratory support without direct contact.

A further challenge in caring for critically ill COVID-19 patients surrounds the difficulties in adequately communicating with patients and families while maintaining the aforementioned infection controls. As has been documented in prior epidemiologic infectious disease outbreaks requiring limitation of physical visitation, such communication challenges can, in turn, erode the therapeutic alliance as well as staff morale if underaddressed. Few data can inform a specific set of best practices to facilitate communication, but many ICUs have taken advantage of the near universal access to smartphones capable of video calling to supplement or supplant traditional visitation and communication. No matter an institution’s individual technical and logistical chosen solutions, we would stress the importance of retaining principles of family-centered care in the ICU.

Management of Respiratory Failure in SARS-CoV-2 Infection

As discussed above, hypoxemic respiratory failure caused by SARS-CoV-2 represents a form of ARDS and should therefore be managed as such, drawing upon the decades of available basic, translational, and clinical evidence in this area. Anecdotal reports from early in the COVID-19 pandemic suggesting an atypical or unique combination of high compliance and severely impaired gas exchange which might merit non-standard treatment have been conclusively refuted by more comprehensive subsequent analyses. Since evidence to date supporting significant deviation from guideline-based care of ARDS in this illness is lacking, treatment algorithms should codify the primacy of established, evidence-based principles (Figure 2). That said, there are some specific ways in which care of COVID-19 does differ from usual care. These differences stem from (1) infection control issues associated with SARS-CoV-2, (2) the expectation that ICU resources may be limited in the course of a pandemic, and (3) the use of therapies specific to SARS-CoV-2.

Use of Non-Invasive Support Strategies: HFNC and NIPPV

Oxygen delivery by humidified high-flow nasal cannula (HFNC) circuits has become increasingly utilized in hypoxemic inpatients. Meta-analyses suggest HFNC may reduce the need for endotracheal intubation, though without altering mortality risk. In a setting where ICU and ventilator resources may be limited, this finding provides a potentially compelling rationale for HFNC use. Potential benefits to HFNC must, however, be weighed against potential harms both to the patient and to caregivers. To the extent that hypoxemia in COVID-19 represents ARDS, HFNC presents a theoretical (but yet unproven) risk of propagating lung injury by allowing uncontrolled tidal volumes and large pleural pressure swings. While the importance of such patient self-induced lung injury remains highly controversial and supported primarily by animal data and limited clinical studies is also true that there is currently no direct trial evidence demonstrating the superiority of HFNC to invasive ventilation with regard to patient centered outcomes such as mortality. Furthermore, HFNC is unlikely to provide any meaningful alveolar recruitment and attendant mitigation of shunt fraction. For caregivers, HFNC has been suggested to increase the risk of aerosol generation. While plausible, the risk of increased droplet dispersion or aerosol generation with HFNC has been called into question by extensive experimental data indicating the risk is similar to other forms of oxygen support. Modeling studies, in addition, suggest that whatever droplet dispersion exists can be substantially mitigated by placing a surgical mask on the patient while employing HFNC. Non-invasive positive pressure ventilation suffers from many of the same disadvantages as HFNC (potential for lung injury and potential for aerosol generation) and has, in previously published studies, underperformed HFNC. Furthermore, it is less comfortable for most patients and does not represent a practical strategy for extended periods of support as is typically required in ARDS. “Helmet” based NIPPV has recently been associated with reduction in need for intubation and reduced mortality in hypoxemic respiratory failure, but this modality has yet to be established in large ARDS cohorts. Published guidelines on the care of COVID-19 patients generally recommend a trial of HFNC (over NIPPV) prior to intubation but the level of evidence for these recommendations is graded as low. NIPPV, with appropriate aerosol safeguards, should still be offered to patients with primarily hypercarbic respiratory failure (ex. known COPD), an indication for which there exist high quality data for benefit. The available evidence does suggest that a trial of HFNC may reduce intubations in COVID-19 associated hypoxemic respiratory failure, but is unlikely to affect mortality.

Decision to Intubate

Specific triggers for intubation in hypoxemic respiratory failure remain controversial and largely in the realm of clinician judgment; indications include increased work of breathing (accessory muscle use, tachypnea), persistent hypoxemia despite supplemental oxygen, agitation/ altered mental status precluding care, and trajectory of worsening hypoxemia. In the presence of bilateral pneumonia (and thus heterogeneous inflation), mechanical ventilation with low
tidal volumes may theoretically be less injurious than continued vigorous spontaneous breathing with or without non-invasive support but this theoretical benefit is balanced by the risks of sedation and invasive procedures associated with mechanical ventilation, particularly as sedation has been independently associated with increased mortality in ICU patients. In the particular case of COVID-19, mechanical ventilation results in the patient breathing in a closed, filtered circuit that may also reduce the risk of viral transmission. Reports on the use of non-invasive ventilation in prior outbreaks of MERS have indicated a high rate of failure and progression to mechanical ventilation and initial reports of outcomes in COVID-19 from centers employing an “early intubation” (ie. minimal use of HFNC/NIPPV) strategy suggests favorable outcomes. Prior analyses of intubation complications (particularly cardiac arrest) have also identified pre-intubation hypoxemia and lack of pre-oxygenation as major risk factors, arguing against delaying intubation to the point of truly refractory hypoxemia. However, as for other forms of respiratory failure, no specific objective cutoffs to guide this decision are likely forthcoming and the decision to intubate must be made based on individual provider clinical judgment. In practice, one argument for erring on the side of “early” intubation in COVID-19 may be logistical:

Figure 2. Evaluation and management of critically ill adults with SARS-CoV-2. This single-page guideline outlines consensus recommendations for the evaluation and the management of critically ill patients with COVID-19. The left panels describe clinical and laboratory diagnostics, the middle panel provides a stepwise algorithm for respiratory failure management, and the right panel highlights COVID-19 specific aspects of general critical care. URI, upper respiratory infection; HTN, hypertension; CBC, complete blood count; CMP, comprehensive metabolic panel; PT, prothrombin time; PTT, partial thromboplastin time; EKG, electrocardiogram; LFTs, liver function tests; CPK, creatine phosphokinase; CRP, C-reactive protein; FiO2, fraction of inspired oxygen; SaO2, arterial hemoglobin oxygen saturation; Vt, tidal volume; PEEP, positive end-expiratory pressure; POCUS, point-of-care ultrasound; MDI, metered dose inhaler; CVO2, central venous hemoglobin oxygen saturation; SAT, spontaneous awakening trial; SBT, spontaneous breathing trial; ABCDEF bundle, SCCM ICU liberation bundle; VTE, venous thromboembolism, NMB, Neuromuscular blockade.
non-emergent intubation allows staff adequate time to don appropriate PPE and prepare for the procedure.

**Initial Ventilator Settings**

Management of ARDS in the setting of COVID-19 does not meaningfully differ from standard ARDS management. Based on extensive clinical trial data demonstrating mortality benefits of a low-tidal volume strategy, patients should be initially placed on assist/control ventilation with tidal volume of approximately 4-8cc/kg predicted body weight (PBW, calculated from height) and a set rate less than or equal to 35 breaths per minute. A number of published approaches to setting positive end-expiratory pressure (PEEP) level are available and are discussed below. Median PEEP levels in most available series of COVID-19 patients are in the range of 8-12 cm H2O and moderate (8-10 cm H2O) initial PEEP is therefore suggested. Strategies employing higher or individualized PEEP, despite strong physiologic rationale and promising results in retrospectively identified subsets of patients, have not been shown to be beneficial in prospective randomized, controlled trials. Plateau airway pressure (Pplat) measured during an end-inspiratory pause should be maintained below 30 cmH2O, though more recent evidence indicates that driving pressure (Pplat—PEEP) <15cmH2O better predicts mortality than either set tidal volume or plateau pressure. Hypercarbia is acceptable if there is no evidence of increased intracranial pressure and arterial pH remains greater than 7.25. Initial tidal volume and PEEP should be adjusted (see below) to maintain targeted driving pressures, oxygen saturation, and plateau pressure. A discussion of alternative modes of ventilation is beyond the scope of this article, but pressure-cycled modes such as pressure-assist control (PC), volume support ventilation, and airway pressure-release ventilation (APRV) should be avoided insofar as these modes are inconsistent with the maintenance of low tidal volumes. May respond inappropriately to increases in patients respiratory demand, and have not conclusively been shown to improve outcomes. In this context it is worth reiterating that the benefit of low tidal volume ventilation is among the most robust results in the critical literature. In a recent re-analysis of trials reporting an effect on mortality in critical care, low tidal volume ventilation and prone ventilation represented 2 of only 4 (out of 862 studied) interventions with robust fragility index and positive effect on mortality.

**Adjustment of Ventilator Settings in COVID-19 ARDS**

Patients with ARDS may fail to respond to initial ventilator settings, either through persistent high airway pressures (Pplat > 30cm H2O and/or driving pressure > 15cmH2O) or persistent hypoxemia (ScO2 <90% and/or persistently low PaO2 to FiO2 ratio. Although ideally oxygen saturation should be maintained between 90 and 96%, trial data suggest optimization of airway pressures is to be prioritized over correcting moderate hypoxemia without evidence of end organ hypoxia. While no single algorithmic approach to optimizing ventilator settings can be succinctly summarized, below we outline a reasonable approach which incorporates physiological and clinical trial evidence:

If Pplat exceeds 30 cm H2O and/or driving pressure exceeds 15 cm H2O, patients may be at risk of barotrauma despite low tidal volume ventilation. One common situation in which high plateau pressures do not necessarily indicate high transpulmonary pressures (and thus risk for barotrauma) is in the obese, in whom elevated plateau pressure may nevertheless be associated with low transpulmonary pressures (Ppl) due to elevated pleural pressure (Ppi; Ppi = Pairway opening—Ppl). In circumstances where persistent high plateau pressures and concern for barotrauma persist, it may be beneficial to further reduce tidal volume below 6cc/kg to as low as 4cc/kg PBW. The lower limit on the ability to decrease tidal volume is determined by the associated decrease in minute ventilation and resultant hypercarbia. Respiratory rate can be increased as needed to compensate minute ventilation, as long this does not result in significant auto-PEEP—a phenomenon in which expiratory time is insufficient for complete exhilation. Patients with pre-existing obstructive lung disease (COPD, asthma, or bronchiectasis) and subsequent flow limitation are at highest risk of auto-PEEP. Auto-PEEP can be recognized by an expiratory flow curve that does not return to zero prior to the initiation of the next inspiration. Auto-PEEP can be mitigated or eliminated most effectively by decreasing respiratory rate but also, potentially, by increasing inspiratory flow rate (thereby decreasing I:E ratio) and by treating reversible airflow obstruction with bronchodilators.

In the presence of persistent hypoxemia (ScO2 <90%) requiring high FiO2, attempts should be made to formally optimize the PEEP. The physiological consequences of varying PEEP are well-reviewed elsewhere but increased PEEP can maintain in the open state alveoli at risk for collapse. This results in decreased intrapulmonary shunt and augmented oxygenation. However, higher PEEP may also impair respiratory system mechanics, paradoxically increase intrapulmonary shunt, and precipitate hemodynamic instability (particularly in the setting of hypovolemia or limited right ventricular reserve). A physiological approach to PEEP titration attempts to identify the end-expiratory pressure that maximizes the benefits of PEEP and minimizes its potential harms. Despite numerous clinical trials, however, no method of PEEP optimization in ARDS has been demonstrated as clearly superior to any other and some titration protocols can cause harm.

In addition, physiological PEEP titration may be laborious and require substantial time investments on the part of intensivists and respiratory therapists—both likely in short supply in the setting of a pandemic. Thus, it is our opinion that a reasonable initial approach to persistent hypoxemia is to implement the ARDSnet “low PEEP” algorithm in most circumstances.

In unusual circumstances (refractory hypoxemia, extreme body habitus, unacceptable hemodynamic or respiratory mechanical parameters) and if time and staffing allow, PEEP...
may alternatively be set by best tidal compliance using a decremental “best PEEP” trial. In a decremental best PEEP trial, the optimal PEEP is the one that maximizes the compliance (Crs = V̇̇/driving pressure). When setting PEEP by best tidal compliance, a sustained application of high airway pressure (“recruitment maneuver”) is often performed first. However, the protocol of a recruitment maneuver followed by decremental PEEP was specifically associated with harm in the recent Alveolar Recruitment Trial (ART). This trial has been criticized for applying recruitment maneuvers in an unselected population and, in that context, it is notable that few of the patients in ART demonstrated evidence of recruitment. This leaves open the possibility that it may yet be possible to identify a subgroup of patients, such as those described above, in whom recruitment is beneficial but it remains unknown whether COVID-19 ARDS might be enriched or depleted for such patients. Therefore, while there may be a role for such maneuvers as a rescue for refractory hypoxemia, our opinion based on the available data is that they are best used rarely. A gentler approach, which attempts to reconcile the findings of ART and other PEEP titration trials with physiologic reasoning, may be to simply increment PEEP in a stepwise fashion, starting from current PEEP, with careful attention to driving pressure to ensure it is not increasing at each step. This maneuver can be followed by a decremental trial from some more modestly increased PEEP than the 25-30 cmH₂O traditionally used in recruitment maneuvers. The best PEEP is again chosen by best compliance as long as this coincides with hemodynamic stability and acceptable oxygenation (arterial oxygen saturation 90-96%).

**Prone Ventilation**

Prone ventilation for ARDS is strongly recommended in current clinical practice guidelines and should be implemented in intubated COVID-19 patients with persistent moderate to severe ARDS. Physiological benefits associated with prone positioning include improved recruitment, decreased inhomogeneity of ventilatory units, improved V/Q matching, and decreased pulmonary vascular resistance. Evidence-based indications for prone ventilation include a P:F ratio <100-150 and FiO₂ >0.6 following initial stabilization. However, since prone ventilation results in a host of improvements to lung mechanics and is associated with low risk and low cost, we feel it is reasonable to employ a relatively low threshold (P:F ~ 150) for considering prone positioning. Furthermore, as many of the physiological benefits associated with prone positioning do not depend on positive pressure ventilation, it is not unreasonable to consider employing this strategy even in spontaneously breathing COVID-19 patients ("self-pronning"). Mindful of the potential need to conserve ventilators, many centers have employed such a strategy in the current outbreak with evident benefit.

Prone ventilation can be carried out in the patient’s existing bed and requires minimal additional equipment, though it does require additional staff for physically positioning the patient. Anecdotally, several centers have established hospital-wide “proning teams” to ease these resource needs and ensure experienced operators are available for positioning critically ill patients. Contraindications to prone ventilation include an inability to turn the neck (e.g. fixed or unstable c-spine) and unstable sternum. Vascular access lines, thoracostomy tubes, and hemodialysis lines are not absolute contraindications to prone ventilation. The patient should be maintained in the prone position for at least 12 hours, and potentially longer (24+ hours) as patient care needs allow. One approach which may also mitigate the additional needs for caregiver PPE and exposure in COVID-19 patients is to supinate patients for daily care needs in the morning, allowing an extended period for prone positioning thereafter. The decision to discontinue prone ventilation is driven by physiological parameters: if P:F remains >150-200 and driving pressure <15 cmH₂O at the end of a 2 hour period of supine ventilation on PEEP <10 cmH₂O, we discontinue prone ventilation.

**Management of Ventilator Asynchrony**

Patients with ARDS may have a high respiratory drive, so attempts to reduce tidal volumes and airway pressures can result in dyspnea and ventilator asynchrony. Asynchrony commonly manifests as “double triggering,” during which ongoing inspiratory effort triggers a second ventilator-delivered breath prior to expiration. Double triggering results in high tidal volumes and airway pressures that can be injurious. Increasing inspiratory flow may decrease dyspnea, but if asynchrony is persistent then consider augmenting sedation and/or neuromuscular blockade (NMB). Effective sedation is a prerequisite for neuromuscular blockade and may obviate its need altogether; narcotics are particularly effective suppressors of respiratory drive. The initiation of neuromuscular blockade should be only undertaken in response to asynchrony or persistent high airway pressures as recent high-quality RCTs do not indicate a benefit to routine NMB in ARDS. Double triggering which increases with deep sedation may indicate “reverse triggering” or entrainment, a reflex breathing pattern which may abate with reducing sedation.

**Pulmonary Vasodilators**

In case of persistent hypoxemia despite optimization of ventilator settings, patients may be treated with inhaled pulmonary vasodilators as temporizing or salvage therapy. These agents work to match ventilation and perfusion by specifically redirecting pulmonary arterial blood flow to those regions that are best ventilated. The net effect is to decrease V/Q mismatch and thereby augment oxygenation. Importantly, while inhaled pulmonary vasodilators typically improve P:F ratios for approximately 24 hours in ARDS, their use has never been linked to reduced mortality or even liberation from mechanical ventilation—underscoring the pathophysiology of ARDS as a multi-organ system disorder of more than hypoxemia. While physiologically equivalent, the use of inhaled nitric oxide...
(iNO) over inhaled prostacyclin analogs in COVID-19 may be preferred in practice, if available, as inhaled prostacyclin requires the use of a filter in the ventilator circuit which has to be changed periodically, thus creating an additional exposure for staff. In addition, NO exerts anti-viral effects in vitro, theoretically a useful if clinically unproven adjunctive property in viral respiratory illness.\textsuperscript{178,179} A successful trial of iNO may be defined by a 20% increase in PaO\textsubscript{2} with administration of 40 ppm iNO; if a patient responds to iNO, its use should be maintained and ventilator settings re-titrated to maximize lung protection. There is, however, likely little benefit to prolonged use of iNO.

**Extracorporeal Membrane Oxygenation (ECMO)**

Patients with persistent hypoxemia or unacceptable airway pressures despite the optimization of ventilator settings, neuromuscular blockade, prone positioning, and inhaled pulmonary vasodilators are deemed to have “refractory” ARDS. In such cases, consideration should be given to initiation of venovenous extracorporeal membrane oxygenation (VV-ECMO) or transfer to a center where this therapy is available.\textsuperscript{180,181} Trial data are mixed and complex on the question of timing of ECMO initiation, but point to improved outcomes in refractory ARDS.\textsuperscript{180-182} Society guidelines generally recommend initiation of ECMO in COVID-19 patients only after the failure of less invasive therapies including mechanical ventilation and prone positioning.\textsuperscript{183} As ECMO therapy is associated with very high resource utilization\textsuperscript{184} and resources may be limited in the setting of a SARS-CoV-2 surge, the criteria for initiation of ECMO in the setting of COVID-19 may differ from criteria for non-COVID-19 ARDS. The Extracorporeal Life Support Organization (ELSO) has published guidelines\textsuperscript{185} which stress the dynamic nature of ECMO triage and emphasize the guiding principle that resource intensive therapies should be directed towards patients who are most likely to benefit. For that reason, guidelines suggest usual criteria for the initiation of ECMO while hospitals are functioning within normal capacity and more stringent criteria (prioritizing younger patients, those in single organ failure and those with non-COVID-19 indications which have been proven to benefit from ECMO) when capacity is stretched. Absolute contraindications to ECMO in COVID-19, according to ELSO guidelines, include limited life expectancy, clinical frailty, mechanical ventilation >10 days, inability to tolerate anticoagulation, severe neurologic injury, or severe multi-organ failure.\textsuperscript{186} Relative contraindications include body mass index (BMI) >40, immunocompromise, and multipressor shock not being considered for veno-arterial support.\textsuperscript{185} The decision to offer ECMO support should be multidisciplinary and take into consideration patient prognosis, resource availability, and comorbidities.\textsuperscript{186} Patients with co-existing cardiogenic shock may be candidates for veno-arterial ECMO (VA-ECMO), though the precise etiology and potential reversibility of myocardial dysfunction in COVID-19 remains poorly defined (discussed further below). Little outcome data is available for ECMO specifically in COVID-19 but some early reports\textsuperscript{183} indicate survival in line with pre-COVID-19 ECMO data.

**General Care of the Critically Ill COVID-19 Patient**

In addition to lung protective ventilation, ICU management of severe COVID-19 should focus on support of organ function while minimizing risk of transmission with effective isolation practices and avoidance of low-value diagnostics.\textsuperscript{3} Evidence-based management of common problems in the ICU should be employed as per usual care of ARDS and sepsis;\textsuperscript{187} and a comprehensive review of topics such as transfusion thresholds, indications for renal replacement therapy, glucose control, stress ulcer prophylaxis, nutrition, etc. are well beyond the scope of this work. Instead, below we discuss some of the ways in which care for critically ill COVID-19 patients may differ from standard practice, but stress again that these methods are more similar than not to those provided to patients with ARDS and/or sepsis generally (Figure 2).

**Antimicrobial Therapy**

Bacterial superinfection has been reported in ICU patients with COVID-19 but is not a frequent finding on initial presentation.\textsuperscript{16} If initial clinical or laboratory features raise concern for coincident bacterial infection (neutrophilia, elevated serum procalcitonin, lobar consolidation, purulent sputum, etc.), consideration should be given to the early initiation of empiric antibiotics with rapid de-escalation, as outlined in the ATS/IDSA guidelines.\textsuperscript{188} Intubated and critically ill patients should receive ventilator-associated pneumonia (VAP) therapy guided by cultures or, if an organism is not identified, empirically per usual hospital protocol. Invasive diagnostic techniques such as bronchoscopy and mini-BAL offer little benefit over endotracheal aspiration (using an in-line catheter and semiquantitative culture),\textsuperscript{188,189} increase transmission risk to staff, and should therefore generally be avoided. COVID-19 may alter the ease of providing evidence-based bundled care to reduce VAP risk.\textsuperscript{190} Some interventions, such as head of bed elevation and avoidance of protocolized ventilator circuit changes, should be largely unaffected. Others, including subglottic suctioning and targeted sedation may be impractical or unsafe given aerosol risks and inability for staff to rapidly enter rooms.

**Imaging**

Radiographic findings consistent with a diagnosis of COVID-19 are discussed above (See Clinical Features). Routine daily chest radiographs do not alter ICU outcomes\textsuperscript{191} and should certainly be avoided in the care of COVID-19 patients in light of staff exposure risks. Possible indications for chest radiography subsequent to ICU admission include hemoptysis, suspected lung volume loss consistent with mucus plugging, rapidly progressive hypoxemia and/or hypotension suggestive of pneumothorax, or concern for VAP. Various patterns
It was has been postulated\textsuperscript{195} that procedures such as broncho-Aerosol Generating Procedures (AGPs) in CRP, CPK, LDH, and D-dimer\textsuperscript{193} have been associated with (in order to surveil for renal and hepatic injury). Elevations of total lymphocyte count and surveil for activity. Recommended laboratory testing includes CBC with differential (in order to trend total lymphocyte count and surveil for superimposed infection) and complete metabolic panel (in order to surveil for renal and hepatic injury). Elevations in CRP, CPK, LDH, and D-dimer\textsuperscript{193} have been associated with poor outcome and are indicated for prognosis and triage; their role beyond initial risk-stratification remains ill-defined. Bacterial and fungal superinfection have been reported in a minority of cases, so routine sputum and blood cultures on ICU admission are reasonable. As discussed previously, the role of measuring inflammatory markers such as ferritin, IL-6, soluble IL-2 receptor, and CRP remains unclear outside of clinical trial settings in which immunomodulatory therapy may be considered, but may be reasonable to consider in patients with refractory shock, sustained fever, MODS, or other signs suggestive of “cytokine storm.” The role for biomarkers such as procalcitonin remains unvalidated, though low procalcitonin levels have previously predicted absence of bacterial infection in critically ill patients with influenza.\textsuperscript{194}

**Laboratory Investigation**

Recommended laboratory testing includes CBC with differential (in order to trend total lymphocyte count and surveil for superimposed infection) and complete metabolic panel (in order to surveil for renal and hepatic injury). Elevations in CRP, CPK, LDH, and D-dimer\textsuperscript{193} have been associated with poor outcome and are indicated for prognosis and triage; their role beyond initial risk-stratification remains ill-defined. Bacterial and fungal superinfection have been reported in a minority of cases, so routine sputum and blood cultures on ICU admission are reasonable. As discussed previously, the role of measuring inflammatory markers such as ferritin, IL-6, soluble IL-2 receptor, and CRP remains unclear outside of clinical trial settings in which immunomodulatory therapy may be considered, but may be reasonable to consider in patients with refractory shock, sustained fever, MODS, or other signs suggestive of “cytokine storm.” The role for biomarkers such as procalcitonin remains unvalidated, though low procalcitonin levels have previously predicted absence of bacterial infection in critically ill patients with influenza.\textsuperscript{194}

**Aerosol Generating Procedures**

It was has been postulated\textsuperscript{195} that procedures such as bronchoscopy, endotracheal intubation, extubation, nebulizer administration, and tracheostomy placement/manipulation may generate smaller, more persistent particles and thereby facilitate airborne transmission of agents more typically spread by respiratory droplets. That said, there is no experimentally validated reference list of such procedures\textsuperscript{101} and it is likely such activities represent a spectrum of risk rather than a binary distinction. While the risk of most such aerosol generating procedures (AGPs) remains somewhat controversial, both the CDC\textsuperscript{101} and WHO\textsuperscript{196} recommend conducting potentially aerosol generating procedures with all staff wearing N95 respirators and other appropriate PPE. The CDC further recommends such procedures ideally be performed in airborne infection isolation rooms (AIIRs). Intubation, in particular, seems to be high risk for aerosol generation\textsuperscript{197} and the decision to intubate should therefore be made early in the course of anticipated clinical deterioration to reduce the need for urgent or uncontrolled procedures which may carry higher risks of transmission. As outlined above, bronchoscopy is not indicated unless less invasive tests have not yielded sufficient diagnostic information both due to aerosol risk and limited evidence for additional diagnostic yield. Respiratory samples for diagnosis of bacterial superinfection may be obtained by close-loop endotracheal aspirate in intubated patients. Inhaled medications should be given by metered dose inhaler instead of nebulizer whenever possible to decrease the risk of viral transmission and ventilators should be set up with adaptors in the dry arm of the circuit to facilitate subsequent use of inhalers without opening the circuit.

**Hemodynamics and Fluid Management**

Case series from China and Italy\textsuperscript{18,67} indicated a predominance of isolated respiratory failure associated with COVID-19 with lower than expected rates of secondary organ failure, shock, and renal failure than unselected ARDS patients. Nevertheless, shock occurs in approximately a third of critically ill COVID-19 patients.\textsuperscript{16,18,67} Importantly, while distributive shock due to viral sepsis likely underlies the majority of such cases, it remains important for clinicians to entertain a broader differential diagnosis. Multiple case reports have described the occurrence of acute heart failure\textsuperscript{198} and cardiogenic shock\textsuperscript{199} associated with severe COVID-19. ACE2 is expressed in the heart and some reports have described the isolation of viral RNA in post-mortem samples of cardiac tissue.\textsuperscript{200} One small Chinese series reported an isolated cardiac cause of death in 7% of patients and an additional third of whom died of combined cardiac and respiratory failure.\textsuperscript{65} The extent to which these reports constitute evidence of a true viral myocarditis\textsuperscript{201} remains controversial, however, as endomyocardial biopsies in the setting of COVID-19 related heart failure showed no evidence of direct viral infection of cardiac myocytes.\textsuperscript{202} The diagnosis of a genuine myocarditis is also made challenging by the high prevalence of cardiac biomarker elevation in the critically ill, with COVID-19 patients being no exception.\textsuperscript{59} Thus, while the true incidence of viral myocarditis accompanying SARS-CoV-2 infection remains unclear, acute heart failure is well-appreciated in COVID-19 critical illness and requires exoneration in the decompensating patient. Beyond cardiogenic shock, multiple case reports have also suggested the presence of an elevated rate of acute mesenteric ischemia and accompanying shock in COVID-19. Kaafarani et al. reported acute mesenteric ischemia in 4/141 critically ill patients with COVID-19\textsuperscript{203} with similar findings independently reported elsewhere.\textsuperscript{204} Although ACE2 expression in the gut has been reported\textsuperscript{205} and SARS-CoV-2 can infect enterocytes in vitro,\textsuperscript{206} whether these observations are attributable to GI infection, microvascular thrombosis (see below), or some other pathophysiological process remains unclear. Computed tomography angiography (CTA) is the preferred imaging technique for the diagnosis of acute mesenteric ischemia.\textsuperscript{206} As abdominal CTA is not routinely performed in respiratory failure patients, the diagnosis of acute mesenteric ischemia requires a high index of suspicion in the face of evolving hemodynamic instability with urgent involvement of surgical consultants if identified.
In the majority of COVID-19 patients experiencing shock related to progressive viral sepsis, it is appropriate to treat per usual protocols for distributive shock with particular care taken to avoid fluid overload. Patients with hypoxemic respiratory failure should generally be managed with a conservative fluid strategy which includes (1) limiting fluid boluses to patients in shock who have indications of volume responsiveness, and (2) early initiation of diuresis in those with resolved shock. Positive fluid balance should be avoided in patients who are not volume responsive, a practice supported by high-quality randomized trial data. In addition, positive fluid balance over the course of ICU stay is associated with increased mortality. As for most critically ill patients, the use of balanced crystalloids (ex. lactated Ringer’s solution) is preferred over normal saline, albumin, or alternative colloid preparations. Current guidelines for treatment of distributive shock suggest titrating therapy to end-organ perfusion as indicated by renal function, mental status, serum lactate, and (if available) central venous oxygen saturation. Adjunctive therapies for septic shock such as glucocorticoids are the subject of conflicting trial data with evidence of minimal benefit or harm in prior respiratory viral illnesses. Nevertheless, steroids should be considered in refractory distributive shock associated with COVID-19, particularly in light of strong evidence for glucocorticoid benefit in COVID-19 ARDS (discussed below).

Coagulation Abnormalities and Thrombotic Risk

While microvascular and macrovascular pulmonary thrombosis are long-recognized features of ARDS, efforts at blunting coagulation in the setting of ARDS have largely failed to show benefit in clinical trials. Early observational reports from China indicated that COVID-19 was associated with abnormal indices of coagulation, a finding subsequently confirmed in larger independent cohorts which highlighted elevations in d-dimer and fibrinogen as consistent features of COVID-19. These findings have led multiple investigators to hypothesize that the tropism of SARS-CoV-2 for ACE2 and the expression of that receptor on endothelial cells might result in a systematic endotheliopathies and resultant widespread coagulation abnormalities. However these reports remain controversial, both because the extent of genuine endothelial cell involvement has come under scrutiny and because abnormalities in such parameters are common in the critically ill. Klok et al reported venous or arterial thrombosis in 31/184 (16.8%) critically ill patients with COVID-19, consistent with other case series from Italy, the United States, and France. By comparison, a large cohort of ICU patients with severe H1N1 influenza pneumonia was reported to have an incidence of venous thromboembolism of 10%. Complicating matters, however, the rates of bleeding complications in COVID-19 have not been fully characterized and there is some evidence that bleeding risk is elevated as well. Due to the uncertainties as to the magnitude thrombotic risk and possibly offsetting risks of bleeding, guidelines and published recommendations largely advise prophylactic anticoagulation for all COVID-19 patients and reserve therapeutic anticoagulation for those with confirmed thrombosis or pre-existing indications. Whether there is a role for augmented intensity VTE prophylaxis remains to be studied in controlled trials.

Role for Targeted Therapies and Immunomodulation

The pathophysiology of SARS-CoV-2 remains poorly defined and the precise mechanistic basis underlying severe, life-threatening COVID-19 is unknown. To date, 2 therapies have been shown in randomized controlled trials to improve outcomes in COVID-19: the antiviral nucleoside analog remdesivir and the steroid dexamethasone. However, dozens of additional trials are ongoing and can be broadly divided into 2 classes: (1) those that aim to directly target viral infectivity or replication and (2) those that aim to alter or modulate the host response to infection.

Experimental Therapies Targeting SARS-CoV-2 Life Cycle

As outlined in the “Virology and pathophysiology” section above, SARS-CoV-2 employs a well-characterized series of steps to enter host cells and replicate (Figure 1). A number of efforts aim to block viral engagement of the cell surface ACE2 receptor. One strategy centers on anti-spike protein neutralizing antibodies. Analogous blocking antibodies have been identified against SARS-CoV and there is intense interest in characterizing the structural basis for antibody recognition. One such antibody has been reported to efficiently block SARS-CoV-2 infection in vitro and it (among others) are moving toward clinical trials. However, it remains unclear whether such strategies will be effective in vivo or even whether they are necessarily safe, particularly in light of a recent report of anti-S protein immunoglobulin induced exacerbation of acute lung injury in SARS-CoV-infected non-human primates. The use of “decoy” ACE2 receptor to inhibit viral infection in human tissue organoids was also recently reported but whether such a strategy is viable in patients remains unclear.

On August 23, 2020 the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for convalescent plasma therapy in COVID-19. Convalescent plasma involves the transfusion of plasma from recovered patients in order to achieve a passive immunization. To date, there are no randomized clinical trials on the use of convalescent plasma. The administration of convalescent plasma resulted in decreased viral load and clinical improvement in 5 mechanically ventilated patients in an early report from China. The FDA based its decision, in part, on analysis of data from an expanded use program run by the Mayo Clinic. These data have, at the time of this writing, been released only as a non-peer reviewed pre-print and describe the transfusion of plasma in a total of 35,322 patients (52% requiring critical care). Mortality was 8.7% in patients who were transfused.
within 3 days of diagnosis and 11.9% in patients transfused after 4 days. A potential issue with convalescent plasma therapy is that the repertoire and titer of antibodies may vary by donor. Indeed, reported mortality was lower in patients transfused with high-titer plasma than those transfused with low-titer plasma. While the Mayo Clinic experience suggests that convalescent plasma therapy is likely to be safe, guidelines continue to recommend against consideration of convalescent plasma as standard of care until controlled trials are performed. It is thus too soon to know if convalescent plasma therapy is truly effective.

As outlined previously, following receptor engagement SARS-CoV-2 can enter cells by fusion or by endocytosis. The fusion-dependent pathway depends on host cell surface protein activity, a process recently found to be inhibited by the pancreatitis drug camostat mesylate.1 A placebo-controlled phase IIa trial of camostat is now underway (trial NCT04321096) following promising results in mouse models. As the endocytic pathway depends on endosome/lysosome escape, inhibitors of this process (particularly chloroquine derivatives) have also received intense interest in the scientific and lay communities. Chloroquine (CQ) belongs to a class of agents known as cationic amphiphilic drugs (CADs), which become trapped and highly concentrated in acidified subcellular compartments such as endosomes and lysosomes. By virtue of this trapping, CADs can increase pH and inhibit enzyme function within these organelles. CQ’s interference with endo-lysosomal processing of antigens likely accounts for its immunosuppressant activities, and a similar mechanism in virally infected cells provides an opportunity to block viral endosome escape and replication.243 Indeed, it has been appreciated for decades that various CADs can interfere with the replication of a diverse array of enveloped viruses including influenza, Ebola virus, HIV, dengue, Zika and hepatitis C in vitro. Building on these data, Wang and colleagues published 2 papers47,244 examining the effects of CQ and hydroxychloroquine (HCQ, more widely available and less toxic) on the novel SARS-CoV in vitro, uncovering that CQ dramatically inhibits SARS-CoV-2 replication at low micromolar concentrations, while HCQ inhibits replication at ~10 μM. However, previous experience with CQ/HCQ suggested skepticism was warranted; chloroquine failed to prevent influenza infection in a clinical trial,245 increased viral load in HIV-infected patients,246 and paradoxically increased viremia in non-human primates infected with Chikungunya virus.247 Indeed, more systematic investigations of the efficacy of CQ/HCQ in COVID-19 have largely disproved its suggested utility. Large observational series248 showed no evidence of benefit and large NIH- and WHO-sponsored trials of HCQ were stopped for futility249,250 (final data pending). Published clinical trials have also failed to demonstrate benefit251 and recently published data failed to identify any treatment effect to HCQ in non-human primates infected with SARS-CoV-2.252

Taken together, in line with the IDSA,253 FDA,254 and CDC101), we believe evidence for a therapeutic benefit for CQ/HCQ is lacking and that these drugs should therefore not be used for the treatment of SARS-CoV-2 infection.

As for HIV, HCV, and other clinically relevant viral pathogens, specific small molecule inhibitors of viral enzymes have proven more promising. Remdesivir (GS-5734), a nucleoside analog of adenosine, is an inhibitor of viral RNA-dependent RNA polymerases with broad antiviral activity.255 Notably, remdesivir exhibits potent inhibitory activity against SARS-CoV and MERS-CoV in vitro and in animal models256 and is not associated with development of fitness-maintaining resistance mutations. In non-human primates, remdesivir reduced lung injury after infection with SARS-CoV-2,257 though this model is notable for not inducing ARDS as observed in human patients. Remdesivir received an emergency use authorization from the FDA on the basis of the preliminary results from the Adaptive COVID-19 Treatment Trial-1 (ACTT-1). In ACTT-1, 1063 participants were randomized to receive up to 10 days of remdesivir versus placebo; patients in the remdesivir arm had a shorter time to recovery than those in the placebo group (11 versus 15 days).20 A subgroup analysis revealed this benefit was driven by the group requiring oxygen, rather than those requiring HFNC, NIPPV, mechanical ventilation, or ECMO. A subsequent trial258 showed comparable outcomes in oxygen-requiring non-critically ill patients treated with 5 and 10 days of remdesivir. Based on these data, current guidelines suggest remdesivir for hospitalized COVID-19 patients requiring oxygen, suggesting 5 (non-intubated patients) or 10 days (intubated patients) of therapy.253 Guidelines for the use of remdesivir are rapidly evolving, however, in part driven by drug shortages.259

Like RdRp, the viral Mprotease represents an attractive target for therapy as several existing antiviral agents may effectively inhibit its function. To date, attempts to repurpose HIV protease inhibitors have not borne fruit and more recent large clinical trials have been halted at interim analyses due to lack of evidence of benefit. Other trials remain ongoing but as of this writing off-label use of such agents outside of clinical trials is not supported by the evidence.

Experimental Immunomodulators

As introduced above, it has been suggested that some patients with SARS-CoV-2 infection may exhibit a hyperinflammatory phenotype or “cytokine storm”99,77,88 meriting therapy with immunomodulatory agents. Interest in such syndromes has burgeoned in recent years as targeted therapies have become available for the treatment of cytokine release syndrome (CRS) triggered by immune-activating oncologic therapies. However, it remains unclear whether such putative “hyperactivation” is necessarily a rational therapeutic target in COVID-19 given the challenges in distinguishing immune activation as a cause rather than a consequence of critical illness. Indeed, prior attempts at targeted immunomodulation260,261 in critical illness have largely proven ineffective. IL-6 antagonists such as tocilizumab have seen widespread recent use in the management of immunotherapy side effects, a context in which they mitigate
CRS and reduce need for steroids. It is less clear whether IL-6 is causally related to the pathogenesis of ARDS, though elevated cytokine levels have been associated retrospectively with improved response to steroids in septic shock.264 Numerous clinical trials are evaluating the use of IL-6 blockade (NCT04315480, NCT04320615, NCT04322773, NCT04330638, NCT04332913, NCT04335071), though at least one has already stopped for futility and potential harm.265 In line with IDSA guidelines,253 therefore, we suggest limiting cytokine-targeting therapy to the clinical trial setting.

Beyond such targeted therapies, a role for corticosteroids (which have a long and complex history of use in ARDS) is emerging in the management of severe COVID-19. The theoretical rationale for steroid therapy in ARDS generally (reviewed extensively elsewhere266,267) stems from the observation that this disease is characterized by exuberant lung inflammation and that glucocorticoids provide benefit in a variety of inflammatory human disease states via pleiotropic effects.268 That said, glucocorticoids exert myriad complex effects in the critically ill and the precise mechanistic basis for any steroid treatment effects in ARDS remains to be clarified. The history of steroid trials in ARDS spans some 3 decades269 and cannot be reviewed here comprehensively but, in brief, early data did not support the use of high-dose “pulse” therapy.270-273 Subsequent studies of lower-dose regimens indicated a benefit as evidenced by more rapid liberation from mechanical ventilation263,274 but without mortality benefit. A recent multicenter RCT275 reported a 60 day mortality benefit in moderate to severe ARDS patients treated with dexamethasone, but was hampered by low enrollment rates and open label design. These potential benefits of steroids in ARDS are tempered by signals for harm. Steinberg and colleagues identified an increase in mortality and rates of re-intubation associated with steroid therapy in late (>14d) ARDS.263 Furthermore, observational data from epidemics of influenza,276 SARS,279 and MERS220 suggested the immunosuppressive properties of glucocorticoids might actually exacerbate virally-induced acute lung injury. Accordingly, early expert opinion argued against the routine use of corticosteroids in COVID-19.280 This was the setting in which initial results from the RECOVERY trial were recently published.19 RECOVERY is a multi-arm, open-label platform trial testing a number of specific therapies for COVID-19 in hospitalized patients. Patients received dexamethasone (6 mg daily for up to 10 days, n = 2104) or usual care (n = 4321) with primary outcome of all-cause 28 day mortality. The trial revealed a 3% absolute risk reduction in favor of the steroid group, a benefit which varied by degree of respiratory support with greater benefit in the mechanically ventilated (absolute risk reduction 12%) and a trend towards harm in non-oxygen-requiring patients. With the caveats that long-term mortality data remain to be seen and that control arm mortality was at the upper end of reported ranges, these findings support a therapeutic effect for glucocorticoids in severe COVID-19. At the time of publication of RECOVERY a number of other trials of steroid therapy in COVID-19 were underway—using various steroid formulations and dosing strategies. A recent meta-analysis281 of data from 7 of these trials demonstrated lower mortality in steroid treated patients—increasing confidence in the RECOVERY results. Accordingly, steroid therapy should be considered standard of care in hospitalized COVID-19 patients requiring supplemental oxygen, mechanical ventilation, or ECMO support.

Statins, inhibitors of HMG CoA-reductase, mediate widespread effects on cellular metabolism beyond their roles in regulating serum LDL cholesterol levels. Arguments for the use of statins in severe COVID-19 infection arise from 2 independent rationales. The first is that patients with pre-existing cardiovascular disease appear to be at high risk for severe disease and death after SARS-CoV-2 infection; many of these patients are likely to meet existing guideline-based indications for statin therapy as primary or secondary prevention. A second, much more speculative, proposed indication for statin use is as modulators of the innate immune system. Because they inhibit signaling through the innate immune adaptor MYD88, statins have been posited to act as beneficial “anti-inflammatory” agents in viral respiratory infections,282 though it should be noted that such signaling is complex and exquisitely tightly controlled in vivo. Highlighting this point, genetic knockout of Myd88 has proven fatal in mouse models of SARS.256 As for ARDS more generally,283 there may exist a subgroup of hyperinflammatory COVID-19 patients in whom statins mediate protective effects, but there is no validated way to identify them prospectively at this time. In light of the risks of transaminitis and rhabdomyolysis with these agents, we therefore do not recommend their universal use in SARS-CoV-2 infection absent an evidence-based primary indication.

A final approach for immunomodulation in severe COVID-19 aims to augment, rather than inhibit, host response to SARS-CoV-2 in order to potentiate viral clearance. Granulocyte-monocyte colony stimulating factor (GM-CSF) is a growth factor with important functions in the lung—supporting the maturation of alveolar macrophages284 and promoting surfactant turnover and recycling. GM-CSF levels are elevated in the blood of COVID-19 patients,285 an observation that has triggered attempts both to augment and to inhibit signaling through this pathway—highlighting the urgent need for deeper pathophysiological understanding. Although it failed to show benefit in an RCT in ARDS,286 recombinant GM-CSF has shown preclinical promise in ameliorating influenza acute lung injury287 and is being studied in an active COVID-19 trial (trial NCT04326920). As for many of the experimental therapies discussed here, our conclusion is that there is an inadequate understanding of viral pathogenesis and host response to justify use of such agents outside of monitored clinical trial settings.

**Conclusion**

SARS-CoV-2 is a novel coronavirus of zoonotic origin that has infected millions of people worldwide and is placing severe demands on intensive care resource utilization across the globe.
The biology and natural history of COVID-19 is becoming increasingly well-understood and should inform the approach to diagnostic testing, healthcare worker precautions, and ICU triage. COVID-19 associated acute hypoxemic respiratory failure develops in a substantial fraction of affected patients and represents a form of ARDS, a finding consistent with what is now understood regarding the virology and pathophysiology of SARS-CoV-2. The keys to evidence-based management of COVID-19 therefore include lung-protective low-tidal volume ventilation, avoidance of barotrauma, a conservative fluid strategy, and prone ventilation, with utilization of inhaled pulmonary vasodilators, neuromuscular blockade, and ECMO when necessary. The lifecycle of SARS-CoV-2 and its effects on the host immune system suggest possible targets for therapy and, to date, 2 such drugs are indicated in hospitalized COVID-19 patients. In time, we anticipate the continued development and adoption of additional targeted therapies which will help bring the pandemic under control.

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