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Caring for the Critically Ill Patient with COVID-19

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KEYWORDS

• Critical care • COVID-19 • SARS-CoV-2 • Pandemic • Healthcare disparities • Resource allocation

KEY POINTS

- One in 4 patients hospitalized with COVID-19 become critically ill, with up to 80% of those requiring mechanical ventilation.
- In-hospital mortality varies but with appropriate resources and capacity, it can be as low as 12% in some cohorts.
- Long-term outcomes after COVID-19 remain poor, with 50% to 70% reporting persistent symptoms such as shortness of breath or fatigue.
- Acute respiratory failure from COVID-19 represents a similar spectrum of disease to other historical cohorts of viral acute respiratory distress syndrome (ARDS).
- Corticosteroids remain the mainstay of treatment of COVID-19, though optimal dosing and duration remain unknown.

INTRODUCTION

Since its identification in late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leading to COVID-19 illness has become a global pandemic, with nearly 182,101,209 cases and 3,950,876 deaths worldwide as of July 2, 2021.[1] Best practices for critical care, including intensive care unit (ICU) bed capacity and staffing,[2,3] respiratory support,[4] and therapeutics,[5] evolved rapidly during the course of the pandemic as our understanding of transmission,[6] virus variants,[7] and outcomes matured. SARS-CoV-2 fueled debates about the most basic aspects of supportive critical care, including the methods and timing of endotracheal intubation,[8] personal protective equipment, timing of prone positioning,[9,10] and oxygen saturation goals.[11] Furthermore, the global spread of COVID-19 has highlighted disparities in care not only between ethnic and racial minorities[12] but also between countries.[13] Special populations, including patients with hematologic malignancy, have demonstrated unique host factors contributing to higher mortality[14] and delayed viral clearance,[15] leading to persistent infectivity and need for further study on isolation precautions. Considering together, critical illness related to COVID-19 has proven to be the biggest challenge of our generation, causing us to reimagine research design and methods, develop innovative ways to expand critical care capacity, and adapt our communication strategies with patients, families, and providers (Fig. 1).

EPIDEMIOLOGY, OUTCOMES, RESOURCE UTILIZATION, AND DISPARITIES

Asia

Early in the pandemic, case series and cohort studies from China described the early epidemiology and outcomes of COVID-19.[16–20] Of 1099 patients hospitalized in China with COVID-19 during December 2019 and January 2020, 55 (5.0%)

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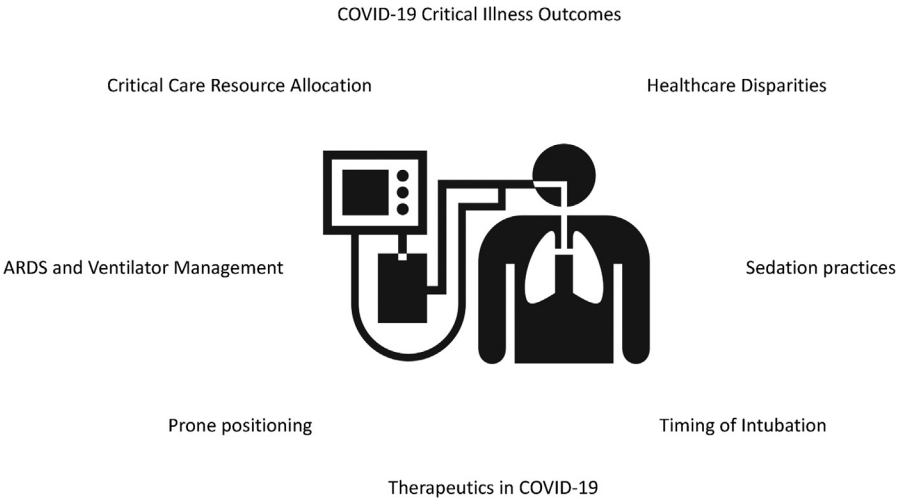

Fig. 1. Comprehensive care of the critically ill patient with COVID-19.

were admitted to the ICU, 25 (2.3%) underwent mechanical ventilation, and 2 (1.4%) died.[19] In a similar cohort of 191 adults hospitalized with COVID-19 in China, 53 (28%) required ICU admission, of whom 42 (78%) ultimately died of multiorgan failure.[16] Among 32 patients treated with mechanical ventilation, 10 (31%) developed ventilator-associated pneumonia and 31 (97%) died after a median 8 days of ICU care (interquartile ratio (IQR) 4.0–12.0 days)[16] (**Table 1**). Half of the decedents (27/54) experienced a secondary infection.[16] Although these studies provided important early data on COVID-19 outcomes, caution was needed when interpreting such early reports because 613 patients (76.2% of the entire cohort) were still hospitalized at the time of publication and excluded from the original analysis.[16] Therefore, true rates of mortality, mechanical ventilation, and other outcomes were uncertain.

Europe

Outside Asia, Italy was among the first countries to experience a surge of COVID-19. Among 17,713 laboratory-confirmed cases in Italy through March 18, 2020, 1593 (9%) were admitted to tier 3 ICUs (highest level of care) and included in an early case series.[21] This critically ill cohort was a majority male (82%), median age of 63 years (IQR 56–70), and most had at least one comorbidity (N = 709, 68%).[21] Among 1300 with available treatment data, 1150 (88%) received mechanical ventilation and 137 (11%) received noninvasive ventilation (NIV); median positive end expiratory pressure (PEEP) was 14 cm H_2O (IQR 12–16), and median P/F ratio was 160 (IQR 114–220).[21] In a subgroup of the first 1715 patients, as of May 30 2020,[22] 865 (50.4%) were discharged from the ICU, 836 (48.7%) died, and 14 (0.8%) were still in the ICU.[22] Risk factors for mortality included older age (HR 1.75 [95%CI: 1.60–1.92]) and male gender (HR 1.57 [95%CI: 1.31–1.88]), whereas higher P/F ratio on ICU admission (HR 0.8 per 100 units [95%CI: 0.74–0.87]) was protective.[22]

North America

By March 2020, COVID-19 was spreading rapidly within the United States. Small, early case series from Seattle, Washington highlighted the severity of illness,[23,24] with nearly 70% of patients receiving mechanical ventilation, and in-hospital mortality ranging from 50% to 67%.[23,24] Half of all patients received vasopressors, and median durations of ICU and mechanical ventilation were 14 and 10 days, respectively.[23] By late March 2020, New York city became the epicenter of COVID-19 in the United States, yielding larger cohort studies.[25–27] Of 1150 adults hospitalized with COVID-19 in New York city through April 1, 2020, 257 (22%) were critically ill.[27] Of these 257, 203 (79%) received mechanical ventilation for a median of 18 days (IQR 9–28), 170 (66%) received vasopressors, and 79 (31%) received renal replacement therapy.[27] In a larger cohort of 2741 patients hospitalized from March through April 2020 in New York city, 647 (23.6%) received mechanical ventilation but was lacking in data in terms of duration, vasopressor use, or renal replacement therapy.[26] In a subsequent cohort of 5700 adults hospitalized during March and April 2020, 373 (14.2%), who had either died or were discharged from the hospital, required intensive care.[25] Of the 373 critically ill patients, 320 (85.8%) received mechanical ventilation, and 81

Table 1
Epidemiologic studies of critically ill patients with COVID-19

Author(s)	Population	Mechanical Ventilation (N, %)	Duration of Mechanical Ventilation (Median, IQR)	Prone Positioning (N, %)	PEEP (Median, IQR)	P/F Ratio (Median, IQR)	Compliance (Median, IQR)	Outcomes
Guan et al,[19] 2020	1099 hospitalized patients with COVID-19 across China	25 (2.3%)	-	-	-	-	-	In-hospital mortality, 2 (1.4%)
Zhou et al,[16] 2020	191 patients hospitalized with COVID-19 who were either discharged or died by Jan 31, 2020	32 (16.8%)	-	-	-	-	-	31/32 (97%) of mechanically ventilated patients died
Grasselli et al,[21] 2020	1591 critically ill patients with COVID-19 in Italy	1150 (88%)	-	240 (27%)	14 (12–16)	160 (114–220)	-	405 (26%) died, 920 (58%) still admitted
Richardson et al,[25] 2020	373 critically ill patients with COVID-19 in United States	320 (85.8%)	-	-	-	-	-	282/320 (88.1%) mortality for mechanically ventilated patients
Petrilli et al,[26] 2020	990 critically ill patients with COVID-19 in United States	647 (65.4%)	-	-	-	-	-	57% mortality among all ICU or ventilated patients
Cummings et al,[27] 2020	257 critically ill patients with COVID-19 in United States	203 (79%)	18 d (9–28)	35 (17%)	15 (12–18)	129 (80–203)	27 (22–36)	41% mortality for mechanically ventilated patients
Ziehr et al,[62] 2020	66 mechanically ventilated patients with COVID-19	66 (100%)	16 d (10–21)	31 (47%)	10 (8–12)	182 (135–245)	35 (30–43)	16.7% mortality, 62% successfully extubated, 21% underwent tracheostomy

(21.7%) were received renal replacement therapy. As of April 4, 2020, 1151 (20.2%) patients requiring mechanical ventilation, 38 (3.3%) were discharged alive, 282 (24.5%) died while admitted, and 831 (72.2%) remained in the hospital.[25] Pulmonary dysfunction was a key driver of mortality, accounting for 56.1% of COVID-related hospital deaths compared with just 21.6% of deaths in recent cohorts of decedents with acute hypoxemia respiratory failure.[28]

Hospital Mortality

Estimates of hospital mortality have varied markedly across studies and over time, likely reflecting differences in completeness of COVID case ascertainment, patient case-mix, hospital resource availability, prevalence of different SARS-CoV-2 strains, COVID treatments, and overall volume of patients. In a study of 8516 patients admitted to 88 US Veterans Affairs hospitals, Bravata and colleagues showed that in-hospital mortality varied by month (22.9% in March 2020, 25% in April, 15.5% in May, 13.6% in June, 12.5% in July, and 12.8% in August) and was strongly associated ICU demand.[29] In particular, when COVID-19 ICU demand was more than 75% to 100% of baseline ICU demand, risk of mortality increased markedly [HR 1.94 (95%CI: 1.46–2.59)].[29] A meta-analysis across the United States, Europe, and Asia included 10,150 patients admitted to the ICU with COVID-19, assessing outcomes for those who were discharged from the ICU or died.[30] Reported mortality across studies varied widely from 0% to 84%. In studies with complete ICU disposition data (ie, death or discharge), combined ICU mortality was 41.6% (95% CI: 34.0%–49.7%).[30] The meta-analysis did not account for patients still admitted to the ICU; therefore, interpretation and generalizability are limited. Other studies have similarly shown that mortality rates have waxed and waned in conjunction with hospital demand.

Resource Allocation and Availability

Critical care requires trained clinicians, supplies, and space. Early in the pandemic, there was widespread fear that a shortage of ventilators[31–33] would contribute to excess mortality. With roughly 62,000 working ventilators in the United States before the pandemic,[34] the feasibility of ventilator sharing was considered. In one New York hospital, 3 pairs of critically ill patients (N = 6) were placed on one mechanical ventilator, using volume control mode.[32] Deep sedation and continuous paralysis were used to avoid ventilator dyssynchrony. Although the authors concluded that ventilator sharing may be safe and feasible for short periods of time, multiple professional societies published a consensus statement advising against ventilator sharing due to the risk for causing more harm than good.[35] Ultimately, industry partners (eg, Ford, General Motors, Dyson) helped to manufacture ventilator equipment[34] and expand the US supply of ventilators to nearly 120,000 by August 2020, alleviating concerns of ventilator shortage.[34]

Despite the early focus on ventilator availability, it quickly became evident that having trained clinicians, adequate space, and basic supplies were more important than ventilators. In particular, the availability of nurses,[36] respiratory therapists,[37] acute care providers,[38] and well-ventilated space[29] proved to be the most important scare resources. Many hospitals had to rapidly expand ICU bed capacity with critical care trained and noncritical care trained staff.[3] Using a tiered system, the most experienced critical care provider can safely supervise midlevel or noncritically-care trained providers to care for up to 24 patients at some institutions with appropriate bed capacity and resources.[3] Alternatively, telemedicine services where an off-site hospital provides critical care expertise serves as another method for expanding capacity in resource-constrained areas.[39] To expand physical ICU space, some hospital repurposed floor rooms to serve as ICU beds with negative pressure capabilities, whereas other countries such as China rapidly built new ICUs.[40] Personal protective equipment was sanitized and reused to maintain supply. Incentive programs were developed to hire traveling nurses in areas of shortage, or to have a back-up supply of staff in the event of health-care workers contracting COVID-19. Nevertheless, shortages of key resources required organizations to develop triage committees, if critical care demand would far exceed available resources.[41]

Long-Term Outcomes

Data on longer-term outcomes from COVID-19 continue to accrue but existing evidence indicates not only high in-hospital mortality but also a high burden of subsequent morbidity among hospital survivors.[42,43] Among 1648 patients hospitalized with COVID-19 at 38 Michigan hospitals, 398 (24.2%) died in-hospital, and an additional 84 (5.1% of the cohort, 6.7% of hospital survivors) died within 60 days of discharge. Total mortality by 60 days postdischarge was 29.2% (482/1648) but was much higher among ICU-treated patients (257/405, 63.5%).[42] Among 488 who completed 60-day postdischarge telephone follow-up, 159 (32.6%) reported at least one new or worsened

cardiopulmonary symptom, 188 (39%) were not yet back to their normal activities, 78 (40% of previously employed) were not yet back to work, 124 (25%) were at least moderately emotionally impacted, and 124 (25%) were at least moderately financially impacted as a result of COVID.[42]

Subsequent studies have examined outcomes at 4 to 6 months posthospitalization and similarly shown persistent morbidity in a large subset of patients. Among 478 adult survivors of COVID-19 in France who completed 4-month telephone follow-up after being hospitalized between March 1, 2020 and May 20, 2020, 244 (51%) reported at least 1 new symptom including fatigue (31%), cognitive symptoms (21%), and new onset dyspnea (16%).[43] Among 2469 patients hospitalized with COVID-19 in China and discharged between Jan 7, 2020 and May 20, 2020, 1733 were followed to 6 months.[44] Among patients seen at 6-month follow-up, 63% (1038 of 1655) endorsed fatigue or muscle weakness, 26% (437 of 1655) endorsed sleeping difficulties, and 23% (367 of 1617) endorsed anxiety or depression.[44] Among 116 who were critically ill at the time of hospitalization, 29% (34 of 116) had a 6-minute walk test result below the lower limit of normal, 56% (48 of 86) had reduced diffusion on pulmonary function testing, and 45% (41 of 92) had persistent ground glass opacities seen on chest CT imaging.[44] Furthermore, a recent systematic review of 9751 COVID-19 survivors found that 72.5% (IQR 55%–80%) reported at least 1 persistent symptom, including dyspnea in 36% (IQR 27.6%–50.0%), fatigue in 40% (IQR 31%–57%), and sleep difficulties in 29.4% (IQR 24.4%–33.0%), although there was significant heterogeneity of symptom onset, follow-up, and patient care settings among studies included.[45]

In a cohort study of 2354 patients hospitalized with critical COVID-19 in Sweden during March through June 2020, 90-day mortality was 26.9%. In multivariable models, male sex [HR 1.28 (95% CI: 1.06–1.55)], malignancy [HR 1.81 (95%CI: 1.19–2.74)], and morbid obesity [HR 1.46 (95% CI: 1.05–1.99)] were identified as risk factors for 90-day mortality.

Disparities

Disparities in health outcomes by race and ethnicity have been on stark display during the COVID-19 pandemic.[46] COVID incidence and outcomes have differed by race and ethnicity, driven by inequalities in risk of SARS-CoV-2 exposure and chronic health status that are perpetuated by structures and policy that perpetuate inequality.[47] People of color are more likely to live in densely populated or polluted areas, be unable to do their job remotely (or in a physically distanced manner), and experience a disproportionate burden of comorbid illnesses,[46] all of which increase the risk of exposure to SARS-CoV2 and worse outcomes from COVID-19.[48] Poverty alone prevents access to critical care resources, with 49% of low-income areas having no ICU beds compared with just 3% of high-income communities.[49]

Of 94,683 patients with COVID-19 who presented to emergency departments at 87 US Health Systems between December 1, 2019 and September 30, 2020, Black people accounted for 26.7% and Hispanic 33.6%,[50] far more than their corresponding US population percentages of 13.4% and 18.5%, respectively.[51] Of the 29,687 patients who were admitted with COVID-19 through the emergency department, admission rates were similar across racial and ethnic groups, although in-hospital mortality was greater in Black (RR 1.18, 95%CI: 1.06–1.31) and Hispanic patients (RR 1.28, 95%CI: 1.13–1.44) compared with White patients.[50]

Similarly, of 1551 patients who tested positive for COVID-19 in Houston, Texas, between March 5, 2020 and May 31, 2020, 22% (N = 341) were Black and 18% (N = 279) were Hispanic.[52] The authors postulated that population density contributed to the disparities in infection rates, with non-Hispanic-Black (OR 2.23, 95% CI: 1.90–2.60) and Hispanic (OR 1.95, 95%CI: 1.72–2.20) residents having a higher likelihood of infection compared with White residents of Houston.

MANAGEMENT

Because of infection precautions and high patient volume, many ICU practices changed during the COVID-19 pandemic, including delirium assessment, sedation practices, family involvement, and end-of-life care. Meanwhile, clinicians debated the optimal approach to respiratory support, including the threshold for initiation and approach to mechanical ventilation. Finally, therapeutics were controversial and evolved rapidly as clinical trial data emerged.

Supportive Care: ABCDEF Bundle

The ABCDEF bundle[53] is a collection of 6 evidence-based practices (pain assessment and treatment, spontaneous awakening and breathing trials, choice of sedation, delirium assessment, early mobility, and family engagement) that serve as the cornerstone for supportive care in the ICU. In a 2-day point prevalence study of ABCDEF bundle implementation in 212 ICUs in 38 countries on June 3, 2020 and July 1, 2020, there was low

implementation of all elements, including pain assessment (45%), spontaneous breathing trials (28%), sedation assessment (52%), delirium assessment (35%), early mobility (47%), and family engagement (16%).[54] The study did not assess reasons for low compliance but hypothesized reasons include high patient census, scarcity of personnel, drug shortages, and time needed to don/doff PPE.

Sedation practices have differed during the pandemic as well. In a multinational study of 2088 critically ill patients, across 69 ICUs (January 20, 2020 through April 28, 2020), 1337 (64%) were sedated with benzodiazepine infusions for a median of 7 days (IQR 4-12 days).[55] As would be expected, benzodiazepine infusion (OR 1.59 [95% CI: 1.33–1.91]) was associated risk of acute brain dysfunction.[55] Despite guidelines[56] recommending against benzodiazepine infusions, their use have increased during the pandemic due to drug shortages, need for multiple sedating medications to prevent self-extubation, and high patient-to-nurse ratios limiting the ability to reorient and calm patients.

Family visitation, goals of care discussions, and end-of-life care were substantially impacted during COVID-19, changing a key element of critical care and the ABCDEF bundle. Of 89 hospitals across the state of Michigan, 49 (55%) responded to surveys conducted between April 6, 2020 and May 8, 2020.[57] One hospital (2%) indicated that visitation was still allowed, whereas all others (98%) had a "no visitation" policy during early months in the pandemic, with 29 (59%) making exceptions in certain situations such as end-of-life.[57] Of the 49 hospitals surveyed, 40 (82%) endorsed changes in communication strategies either through video conferencing or telephone. Patient and family communication was similarly altered, with 34 hospitals (69%) encouraging video communication through tablets or smart phones. Similarly, a single center case series found that family or friends were present in only one-third of deaths.[28]

Respiratory Support: Phenotypes, Intubation, Self-Proning, Ventilator Management, Fluid Resuscitation

From the early days of the pandemic, there has been ongoing debate over the extent to which the pathophysiology of COVID-19-related respiratory failure is similar (or not) to other causes of acute hypoxic respiratory failure, and, following along this line, whether we should treat patients with COVID-19-related respiratory failure as we would treat patients with non-COVID-related acute respiratory distress syndrome.

There was much debate about the pathophysiology of acute hypoxic respiratory failure due to COVID-19. Some believed the primary cause was due to endothelial dysfunction and hypoxic vasoconstriction with increased compliance relative to historical cohorts.[58–60] This led to the theoretic subphenotypes of COVID-19 respiratory failure: (1) "L" phenotype with low elastance, normal compliance and (2) "H" phenotype with high elastance and low compliance.[61] Investigators further postulated a need for differing ventilation strategies in each group, with the "L" phenotype requiring liberalized tidal volume with lower PEEP and the "H" phenotype requiring typical ventilation strategies including higher PEEP and low tidal volume ventilation.[58] As further evidence emerged, significant heterogeneity of disease was observed, with varying compliance consistent with prior cohorts of patients with ARDS.[62,63] This resulted in a call to study the disease further before changing decades of critical care practice and continuing to advocate for lung protective low tidal volume ventilation.[64] In a study comparing 130 critically ill mechanically ventilated patients with COVID-19 ARDS to 382 non-COVID ARDS mechanically ventilated patients, there was no difference in time-to-breathing unassisted at 28 days or 28-day mortality.[65] Other studies have similarly found similar outcomes when comparing COVID-19 ARDS to other viral ARDS cohorts.[66] Further investigation using semiquantitative methods found the "L" and "H" phenotypes were not mutually exclusive and likely represent a spectrum of disease.[67] Furthermore, historical investigation of personalized mechanical ventilation techniques have not improved outcomes in ARDS patients when compared with typical lung-protective ventilation techniques.[68] In summary, there is not enough evidence to suggest acute hypoxic respiratory failure from COVID-19 is different from historical ARDS cohorts, or that mechanical ventilation strategies should deviate from current best practice guidelines.

When Should the Hypoxic Patient with COVID-19 Be Intubated?

Early in the pandemic, there was widespread concern that heated high-flow nasal cannula (HHFNC) and NIV may increase the risk for aerosolization of SARS-CoV-2, and thereby drive the transmission of COVID-19 to health-care workers. This concern led many clinicians to electively intubate patients and initiate mechanical ventilation once oxygenation saturation could not be maintained with low levels of nasal cannula oxygen. However, subsequent studies have not borne out

this early concern. Humans are highly effective at generating aerosols via coughing but HHFNC and NIV do not cause meaningful increases in the aerosol generation over and beyond what is produced by patients on room air.[69]

Even after HHFNC and NIV were shown safe from the aerosol-generation standpoint, there remained equipoise regarding the optimal threshold for the initiation of invasive mechanical ventilation.[70] Some clinicians opt for earlier intubation, recognizing the added time associated with intubation under airborne precautions. Other clinicians delay intubation as long as possible, recognizing that some patients may be able to avoid invasive mechanical ventilation altogether.

Several observational studies have examined outcomes by timing of intubation. In a study of 47 patients with hypoxic respiratory failure in Korea (February 17, 2020 through April 23, 2020), 23 (48.9%) were intubated on the first day meeting ARDS criteria (P/F $\leq$ 300 with bilateral infiltrates not fully explained by heart failure), whereas 24 (51.1%) were intubated on a subsequent day, more than 24 hours after suspected ARDS diagnosis.[71] In-hospital mortality was numerically higher (56.5% vs 43.8%, $P = .43$), whereas ventilator free days were lower in the early intubation group (median 9 days vs 28 days, $P = .008$).[71]

In a study of 231 patients with hypoxic respiratory failure in Georgia (March 6, 2020 through May 7, 2020),[63] 109 (47.2%) were treated with high-flow nasal cannula, whereas 97 (42.0%) were intubated directly without preceding high-flow nasal cannula. Ultimately, 78 (71.6%) in the high-flow group required intubation.[63] In-hospital mortality was similar across subgroups defined by timing of intubation: 8 hours or less (38.2%), between 8 and 24 hours (31.6%), and $\geq$24 hours (38.1%), $P = .7$.

In a study of 245 patients with hypoxic respiratory failure in 11 ICUs in France (February 15, 2020 through May 1, 2020), 117 (47.8%) received early mechanical ventilation, 85 (34.6%) high-flow nasal cannula, 18 (7.4%) CPAP, 16 (6.6%) nasal cannula, and 9 noninvasive positive pressure ventilation (3.6%).[72] The 60-day mortality was higher among patients treated with early mechanical ventilation versus noninvasive oxygen therapy (42.7% vs 21.9%, $P<.01$), and similar among patients who were intubated earlier (within 2 days) versus later (42.2% vs 42.7%).

In a study of 75 mechanically ventilated patients with COVID-19 at Temple University (February 2020 through May 2020), respiratory mechanics were compared by timing of intubation (before or after the median time of intubation, 1.27 days).[73] Patients in the late intubation group (>1.27 days) had higher P/F ratios (160 vs 205, $P = .46$), higher PEEP (11 vs 9, $P = .27$), and higher plateau pressure (26 vs 22, $P = .02$), with similar compliance (35 vs 41, $P = .13$) at the time of intubation.[73] The late intubation group had longer ICU length of stay (median 12.3 vs 7.4 days, $P = .001$) and duration of mechanical ventilation. This observational design, however, does not account for patients receiving alternative respiratory support such as HHFNC and never require intubation.

A recent meta-analysis included 8944 critically ill patients with COVID-19 across 12 studies, assessing the impact of early intubation, within 24 hours of ICU admission, versus later.[74] Interestingly, early versus late intubation did not affect all-cause mortality (45.4% vs 39.1%; RR 1.07, 95% CI: 0.99–1.15) or duration of mechanical ventilation (mean difference −0.58 days, 95% CI: −3.06–1.89). Secondary outcomes including ICU length of stay and need for renal replacement therapy were similar between groups.[74] One significant limitation, however, is that observational data may have residual confounding by indication. Patients with higher illness severity may be intubated sooner while also having higher risk of mortality, thereby introducing bias, and limiting our overall interpretation of these studies.

Considering together, observational data suggests later intubation is associated with worse respiratory mechanics,[73] although mortality among invasive mechanically ventilated patients may be the same regardless of timing of intubation.[63,72,74] Noninvasive support modalities (HHFNC, NIV) seem safe, although it is unclear whether they reduce mortality and may prolong the length of stay.[63,72] Bias associated with observational data limits interpretation of whether patients should be intubated early or late in their course, and randomized trials are not available presently.

Is Proning the Nonintubated Patient with COVID-19 Safe and Does It Prevent Intubation?

Given the benefits seen in historical groups of ARDS patients placed in the prone position,[75] providers began proning the awake nonintubated patient with respiratory failure from COVID-19 (self-proning), hoping to prevent intubation and utilization of scarce resources. New York city emergency medicine providers enrolled 50 consecutive patients with respiratory failure from COVID-19 between March 1, 2020 and April 1, 2020, excluding those with limited code status, those requiring NIV, and including those who remained hypoxic (saturation <94% with supplemental oxygen).[76] Of the 50 patients who self-proned, 13 (24%) were intubated

within 24 hours of arrival to the emergency room.[76] Of the remaining 37 patients admitted to the hospital, 5 (13.5%) were intubated during their hospital stay and 36% in total requiring intubation. Notably, 7 (14%) patients required intubation within 1 hour of proning.[76] Lack of a control group limits interpretation.

A separate case series of 24 awake nonintubated spontaneously breathing French patients with respiratory failure due to COVID-19 between March 27, 2020 and April 8, 2020 examined tolerance of prone positioning and outcomes.[10] Of the 24 patients enrolled, 4 (17%) did not tolerate prone positioning for more than 1 hour, 5 (21%) tolerated it for 1 to 3 hours, and 15 (63%) tolerated it for more than 3 hours. Of the 24 patients, 6 (25%) were considered responders defined as a PaO_2 increase 20% or greater during proning, with half of those nonsustained after resupination.[10] Lack of control group and lack of outcomes data are limiting factors.

An Italian series of 15 non-ICU patients with respiratory failure due to COVID-19 demonstrated that continuous positive airway pressure (CPAP) administration outside the ICU (10 cm H_2O and FiO_2 0.6), whereas prone was feasible.[77] Of the 15 patients who were proned for 3 hours with CPAP, all patients had reduction in respiratory rate, and improved p/f ratio while proned ($P<.001$). At 14-day follow-up, 9 (60%) were discharged home, 1 (6%) improved and stopped proning but remained hospitalized, 3 (20%) continued proning, 1 (6%) patient was intubated, and 1 (6%) patient died.[77] Of 29 patients enrolled in a New York city hospital with respiratory failure from COVID-19 between April 6, 2020 and April 14, 2020, 25 completed at least 1 hour of self-proning.[78] All patients had improvement in oxyhemoglobin saturation with a median improvement of 7% (range 1%–34%). Of the 25 patients, 12 (48%) required intubation and 5 (20%) after the initial hour of proning.[78]

Although self-proning seems feasible with improvement in oxygenation for some patients, it is difficult to draw conclusions with the lack of comparison groups, randomization, and long-term outcomes.[4] The time of prone positioning was relatively brief in most case series and difficult to tell if patients had sustained improvements, or whether intubations were simply delayed. Randomized trials are needed to answer this question with confidence.

Should Shock Be Treated Differently in Patients with COVID-19?

To date, there are no well-controlled trials randomizing patients to various hemodynamic treatment strategies. Extrapolation from septic shock studies has guided authors to recommend assessing for fluid responsiveness,[79] giving balanced crystalloids over colloids,[80] and using norepinephrine as a first-line vasopressor targeting a mean arterial pressure of 60 to 65 mm Hg.[79,80] Similarly, the use of stress dose steroids is a clinical decision and no different in patients with COVID-19 and distributive shock.[80] There are several opinions on how much volume should be given,[81] but there is a paucity of data presently to make conclusions. Similar to historical cohorts of septic shock, the resuscitation volume and type will likely be an ongoing debate. Once shock has resolved, there is a question of the utility of diuresis with loop diuretics, which has been shown to reduce duration of mechanical ventilation in non-COVID-19 ARDS trials.[82] Investigation regarding the utility of nebulized furosemide in respiratory failure from COVID-19 is ongoing.[83]

Pharmacologic Therapies

The COVID-19 pandemic brought about rapid investigation in therapeutics. Early reports of hydroxychloroquine, a medication used to treat autoimmune diseases, showed promise in small noncontrolled studies. However, large observational[84] and randomized[85,86] trials demonstrated no benefit with hydroxychloroquine. Since that time, numerous other agents have failed to show benefit, including Zinc and Vitamin C,[87] convalescent plasma,[88] sarilumab,[89] lopinavir,[86] interferon,[86] canakinumab,[90] and acalabrutinib.[91] However, others have shown promise for reducing duration of illness, as well as mortality.

Corticosteroids were the first agents shown to reduce mortality from COVID-19. Of 6425 patients hospitalized with COVID-19 in the United Kingdom, dexamethasone 6 mg daily versus usual care for up to 10 days reduced 28-day mortality among those receiving mechanical ventilation (29.3% vs 41.4%, rate ratio 0.64 95% CI: 0.51–0.81) and those receiving oxygen without mechanical ventilation (23.3% vs 26.2%, rate ratio 0.82 95% CI: 0.72–0.94)[92] (**Table 2**). Furthermore, a recent meta-analysis including 73 studies and 21, 350 patients hospitalized with COVID-19 found corticosteroids were used with increasing frequency in mechanically ventilated patients (35%), ICU patients (51.3%), and severely ill patients (40%), demonstrating an overall mortality benefit (OR 0.65; 95%CI: 0.51–0.83).[93] Notably, steroids were not found to prolong viral shedding but interpretations are somewhat limited due to heterogeneity of study methodologies and reporting. As a result, the World Health Organization (WHO)

Table 2
Therapeutics in critically ill patients with COVID-19

Author(s)	Population	Intervention	Outcome	Adverse Events
Horby et al.[92]	Hospitalized patients with COVID-19	Oral or intravenous dexamethasone 6 mg daily (N = 2104) vs usual care (N = 4321)	28-d mortality improved with dexamethasone in pts receiving oxygen without MV (23.3% vs 26.2%) and pts receiving MV (29.3% vs 41.4%)	4 in dexamethasone group (2 hyperglycemia, 1 GI hemorrhage, 1 psychosis)
Angus et al,[108] 2020	Critically ill patients with COVID-19, Bayesian randomized adaptive platform (REMAP)	50 mg or 100 mg hydrocortisone for 7-d (N = 143), shock dependent steroid course (N = 152), or no steroids (N = 108)	93% and 80% probability of superiority with regards to organ-failure free days	9 in steroid groups (neuropathy, fungemia, pneumonia, pulmonary embolism, elevated troponin, postop hemorrhage, intracranial hemorrhage)
Tomazini et al,[109] 2020	Hospitalized patients with COVID-19 ARDS	20 mg dexamethasone daily for 5 d, 10 mg daily for 5 d (N = 151) vs usual care (N = 148)	Increased number of ventilator-free days (6.6 vs 4.0, *P* = .04), no difference in 28-d mortality	No difference between groups for hyperglycemia or secondary infections
Beigel et al,[96] 2020	Hospitalized patients with COVID-19 and lower respiratory tract infection	200 mg remdesivir once, then 100 mg daily for 4 more doses (N = 541) vs placebo (N = 521)	No difference in survival. Improved median recovery time (10 vs 15 d, *P*<.001) for those requiring supplemental oxygen not requiring mechanical ventilation	No difference in adverse events between groups
Pan et al,[86] 2021	Hospitalized patients with COVID-19	Remdesivir (N = 2750) vs no trial drug (N = 4088)	No difference in overall mortality (10.9% vs 11.2%) or need for mechanical ventilation (10.8% vs 10.5%)	Not reported

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Table 2
(*continued*)

Author(s)	Population	Intervention	Outcome	Adverse Events
Rosas et al,[98] 2021	Hospitalized patients with COVID-19 pneumonia	Tocilizumab 8 mg/kg for 1 or 2 doses (N = 294) vs placebo (N = 144)	No difference in 28-d mortality (19.7% vs 19.4%) or clinical status improvement (between group difference −1.0, 95% CI: −2.5–0)	No difference in serious adverse events
Gordon et al,[99] 2021	Critically ill patients with COVID-19, Bayesian randomized adaptive platform (REMAP)	Tocilizumab (N = 353) vs control (N = 402)	99.9% posterior probability of improved survival, HR 1.61 (95%CI: 1.25–2.08)	No difference in serious adverse events (9 occurred including one secondary bacterial infection)

recommends dexamethasone 6 mg daily or 50 mg hydrocortisone every 8 hours for 7 to 10 days in severely or critically ill patients with COVID-19.[94] The optimal dose and duration of corticosteroids are not yet fully known.[95]

Remdesivir, an inhibitor of RNA-polymerase, was the next drug to show promise against the COVID-19 pandemic. Across 13 countries, 1062 patients hospitalized with COVID-19 from February 21, 2020 through April 19, 2020 were randomized to remdesivir versus placebo.[96] Although remdesivir did not confer survival benefit at 28 days (HR 0.73; 95% CI: 0.52–1.03), median recovery time (defined as time to neither being hospitalized nor hospitalized without supplemental oxygen requirement and no longer requiring medical care) was shorter with remdesivir (10 vs15 days; $P<.001$).[96] A larger randomized trial conducted by the WHO enrolled 2750 patients hospitalized with COVID-19, randomizing them to receive remdesivir and 4088 to no trial drug in 405 hospitals across 30 countries.[86] Authors concluded that remdesivir conferred no mortality benefit (RR 0.95; 95% CI: 0.81–1.11) or reducing need for mechanical ventilation, even when stratified by age and respiratory support at trial entry.[86] The Food and Drug Administration has approved remdesivir for use in patients hospitalized with respiratory failure from COVID-19, although not for those requiring mechanical ventilation.[97] Similarly, use beyond 10 days of symptoms is not recommended.

Tocilizumab, a monoclonal antibody targeting IL-6, was initially developed for the treatment of autoimmune diseases and cytokine release syndrome for chimeric antigen receptor therapy in patients with hematologic malignancy. Early investigations found no survival benefit with the use of tocilizumab in COVID-19.[98] Of 452 hospitalized patients with COVID-19 across 62 hospitals in 9 countries, treatment with tocilizumab versus placebo resulted in no difference in 28-day mortality (19.7% vs 19.4%, $P = .94$).[98] Similarly, tocilizumab treatment did not result in clinical status improvement, defined as being discharged home or hospitalized without supplemental oxygen need at 28-days from enrollment (ordinal clinical status score 1.0 vs 2.0, $P = .31$).[98] Later investigation using an adaptive platform randomized trial (randomizing to multiple domains allowing patients to be on multiple treatments) enrolled 353 patients treated with tocilizumab.[99] Interestingly, tocilizumab treatment resulted in more organ-failure-free days (10 versus 0 [OR 1.64; 95% CI: 1.25–2.14]) and improved 90-day survival (HR 1.61, 95% CI: 1.25–2.08) when compared with placebo.[99] Given the conflicting results, current recommendations are to consider adding tocilizumab to dexamethasone treatment when a patient has rapidly increasing oxygen requirements early in their illness with elevated C-reactive protein levels of 75 mg/L or greater (BIIa).[97]

Early observational data demonstrated a high incidence of venous thromboembolic disease in patients with COVID-19.[100] Further examination of autopsy investigations found up to 58% incidence of pulmonary emboli.[101] The American Society of Hematologists recommends using prophylactic dose anticoagulants over intermediate dose[102] based on randomized trial results.[103] The question of whether full dose anticoagulation should be used in the absence of clinically detected venous thromboembolism remains unknown. Early observations found improved in-hospital mortality with full-dose anticoagulation,[104] although increased rates of mechanical ventilation, raising questions of whether empiric full-dose should be used in all patients hospitalized with COVID-19. As a result, several ongoing trials are investigating full-dose anticoagulation effects on organ-failure free days and need for mechanical ventilation, although preliminary nonpeer-reviewed results suggests harm in the critically ill population but potential benefits in moderately ill patients with COVID-19 not requiring ICU level care or organ support (heated high flow, NIV, mechanical ventilation).[105]

The most effective treatment of COVID-19 is preventing infection from occurring. Among 43,548 participants aged 16 years and older across 152 sites around the world, 21,720 people received a 2-vaccine regimen 21-days apart, resulting in 95% efficacy in prevention of disease.[106] Preliminary nonpeer-reviewed work demonstrates a profound reduction in ICU admissions and deaths since vaccinations became available, by 65.6% (95%CI: 62.2%–68.6%) and 69.3% (95% CI: 65.5%–73.1%), respectively.[107]

DISCUSSION

COVID-19 not only changed the way we practice critical care but also forced us to reconsider resource allocation, staffing, and nonconventional strategies such as self-proning the awake patient in hopes of reducing the need for mechanical ventilation. Furthermore, the changing epidemiology and transmission forced critical care and researchers to rethink trial design, with a new adaptive platform trial not routinely performed before the COVID-19 pandemic.

However, some things do remain consistent over time. Respiratory failure due to COVID-19 seems to be consistent with prior cohorts of viral ARDS, with respect to mortality as well as

ventilator management. Lung-protective ventilation remains the mainstay of critical care and should not change based on the current available evidence. Sedation practices, similarly, deviated from clinical practice guidelines with benzodiazepine infusions leading to increased risk of delirium. Remembering the basics of critical care is important for improving outcomes, even in times of a global pandemic.

Pharmacologic therapies have rapidly evolved over time reducing morbidity and mortality for patients with respiratory failure from COVID-19. First and foremost, vaccinations have drastically reduced transmission and severity of illness. Corticosteroids have consistently demonstrated benefit with regards to mortality, whereas other medications such as remdesivir and tocilizumab have conflicting results but may reduce severity of illness.

The pandemic has taken a global toll, both from a health perspective and from an economic standpoint. Because vaccinations have become widespread in certain parts of the world, restrictions will be lifted, and life will begin to normalize for many. However, we cannot forget the lessons learned from this global pandemic. We need to maintain a public health infrastructure capable of responding rapidly with resources, train and maintain staff to respond with appropriate bed capacity, understand the importance of isolation precautions for infection prevention, and use research techniques such as randomized, embedded, multifactorial, adaptive platform (REMAP) to rapidly assess therapeutics to improve care and outcomes for our patients.

CLINICS CARE POINTS

- One in 4 patients hospitalized with COVID-19 become critically ill, with up to 80% of those requiring mechanical ventilation.
- In-hospital mortality varies, but with appropriate resources and capacity, can be as low as 12% in some cohorts.
- Long-term outcomes after COVID-19 remain poor, with 50% to 70% reporting persistent symptoms such as shortness of breath or fatigue.
- Acute respiratory failure from COVID-19 represents a similar spectrum of disease to other historical cohorts of viral ARDS.
- Corticosteroids remain the mainstay of treatment of COVID-19, although optimal dosing and duration remain unknown.

DISCLOSURE

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