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Caring for the Critically Ill Patient with COVID-19

Matthew K. Hensley, MD, MPH, Hallie C. Prescott, MD, MSc

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 minorities12 but also between countries.13 Special populations, including patients with hematologic malignancy, have demonstrated unique host factors contributing to higher mortality14 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%)...
were admitted to the ICU, 25 (2.3%) underwent mechanical ventilation, and 2 (1.4%) died. 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 multorgan failure. 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). Half of the decedents (27/54) experienced a secondary infection. 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. 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. 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%). 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 H₂O (IQR 12–16), and median P/F ratio was 160 (IQR 114–220). In a subgroup of the first 1715 patients, as of May 30 2020, 865 (50.4%) were discharged from the ICU, 836 (48.7%) died, and 14 (0.8%) were still in the ICU. 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.

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, with nearly 70% of patients receiving mechanical ventilation, and in-hospital mortality ranging from 50% to 67%. Half of all patients received vasopressors, and median durations of ICU and mechanical ventilation were 14 and 10 days, respectively. By late March 2020, New York city became the epicenter of COVID-19 in the United States, yielding larger cohort studies. Of 1150 adults hospitalized with COVID-19 in New York city through April 1, 2020, 257 (22%) were critically ill. 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. 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. 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. Of the 373 critically ill patients, 320 (85.8%) received mechanical ventilation, and 81
| 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%)                 | 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%)                 | 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 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 ventilators31–33 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 equipment34 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 space39 proved to be the most important scarce 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 co-morbid 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%). 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). As would be expected, benzodiazepine infusion (OR 1.59 [95% CI: 1.33–1.91]) was associated risk of acute brain dysfunction. Despite guidelines 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. 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. 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 smartphones. Similarly, a single center case series found that family or friends were present in only one-third of deaths.

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. 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. 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. As further evidence emerged, significant heterogeneity of disease was observed, with varying compliance consistent with prior cohorts of patients with ARDS. 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.

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 aero-solization of SARS-CoV-2, and thereby drive the transmission of COVID-19 to health-care workers. This concern led many clinicians to electively intu-bate patients and initiate mechanical ventilation once oxygenation saturation could not be main-tained 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).75 Of the 50 patients who self-proned, 13 (24%) were intubated...
within 24 hours of arrival to the emergency room. 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. 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. 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 PaO2 increase 20% or greater during proning, with half of those nonsustained after resupination. 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 H2O and FiO2 0.6), whereas prone was feasible. 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 prone (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. Of 29 patients enrolled in a New York city hospital with respiratory failure due to COVID-19 between April 6, 2020 and April 14, 2020, 25 completed at least 1 hour of self-proning. 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.

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. 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.

**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 and randomized trials demonstrated no benefit with hydroxychloroquine. Since that time, numerous other agents have failed to show benefit, including Zinc and Vitamin C, convalescent plasma, sarilumab, lopinavir, interferon, canakinumab, and acalabrutinib. 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) (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). 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                                                                  |

(continued on next page)
| 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 vs 15 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 dose102 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, 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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**REFERENCES**

1. WHO coronavirus (COVID-19) Dashboard. Available at: https://covid19.who.int. Accessed July 2, 2021.
2. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and Forecast during an emergency Response. JAMA 2020;323(16):1545–6.
3. Harris GH, Baldisseri MR, Reynolds BR, et al. Design for implementation of a system-level ICU pandemic surge staffing plan. Crit Care Explor 2020;2(6):e0136.
4. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46(5):854–87.
5. Del Rio C, Maini PN. COVID-19-New Insights on a rapidly changing epidemic. JAMA 2020;323(14):1339–40.
6. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. Available at: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations. Accessed April 21, 2021.
7. CDC. COVID-19 and Your Health. Centers for Disease Control and Prevention; 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html. Accessed February 25, 2021.
8. Meng L, Qiu H, Wan L, et al. Intubation and ventilation amid the COVID-19 outbreak: Wuhan’s experience. Anesthesiology 2020;132(6):1317–32.
9. Sarma A, Calfee CS. Prone positioning in awake, nonintubated patients with COVID-19: necessity is the Mother of Invention. JAMA Intern Med 2020. https://doi.org/10.1001/jamainternmed.2020.3027.
10. Elharrar X, Trigui Y, Dols A-M, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxic acute respiratory failure. JAMA 2020;323(22):2336–8.
11. Oxygenation and ventilation. COVID-19 treatment guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/critical-care/oxygenation-and-ventilation/. Accessed April 21, 2021.
12. CDC. Community, work, and School. Centers for disease control and prevention. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/racial-ethnic-disparities/disparities-illness.html. Accessed April 21, 2021.

13. Sorci G, Faivre B, Morand S. Explaining among-country variation in COVID-19 case fatality rate. Sci Rep 2020;10(1):18909.

14. Malard F, Genthon A, Brissot E, et al. COVID-19 outcomes in patients with hematologic disease. Bone Marrow Transplant 2020. https://doi.org/10.1038/s41409-020-0931-4.

15. Hensley MK, Bain WG, Jacobs J, et al. Intractable viremia in patients with acute respiratory distress syndrome caused by coronavirus disease 2019 (COVID-19) and prolonged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Replication in a chimeric antigen receptor-Modified T-Cell therapy Recipient: a case study. Clin Infect Dis 2021. https://doi.org/10.1093/cid/ciab072.

16. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.

17. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):934–43.

18. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13.

19. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708–20.

20. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020. https://doi.org/10.1016/S2213-2600(20)30079-5.

21. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020. https://doi.org/10.1001/jama.2020.5394.

22. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care Units in Lombardy, Italy. JAMA Intern Med 2020;180(10):1345–55.

23. Bhattacharjee P, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region - case series. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2004500.

24. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. JAMA 2020;323(16):1612–4.

25. Richardson S, Hirsch JS, Narasimhan M, et al. Prevalence of characteristics, Comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020. https://doi.org/10.1001/jama.2020.6775.

26. Petrelli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.

27. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395(10239):1763–70.

28. Ketcham SW, Bolig T, Molling DJ, et al. Causes and Circumstances of death among patients hospitalized with COVID-19: a retrospective cohort study. Ann ATS 2020. https://doi.org/10.1513/AnnalsATS.202011-1381RL. AnnalsATS.202011-1381RL.

29. Bravata DM, Perkins AJ, Myers LJ, et al. Association of intensive care Unit patient Load and demand with mortality rates in US department of Veterans Affairs hospitals during the COVID-19 pandemic. JAMA Netw Open 2021;4(1):e2034266.

30. Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia 2020. https://doi.org/10.1111/anae.15201.

31. Ranney ML, Griffeth V, Jha AK. Critical supply shortages — the need for ventilators and personal protective equipment during the Covid-19 pandemic. N Engl J Med 2020;382(18):e41.

32. Beitler JR, Mittel AM, Kallet R, et al. Ventilator sharing during an acute shortage caused by the COVID-19 pandemic. Am J Respir Crit Care Med 2020;202(4):600–4.

33. Tonetti T, Zanella A, Pizzilli G, et al. One ventilator for two patients: feasibility and considerations of a last resort solution in case of equipment shortage. Thorax 2020;75(6):517–9.

34. Kobokovich A. Ventilator Stockpiling and availability in the US. 2020. Available at: https://www.centerforhealthsecurity.org/resources/COVID-19/COVID-19-fact-sheets/200214-VentilatorAvailability-factsheet.pdf. Accessed April 30, 2021.

35. SCCM | consensus statement on multiple patients per ventilator. Society of critical care medicine (SCCM). Available at: https://sccm.org/Clinical-Resources/Disaster/COVID19/Advocacy/Joint-Statement-on-Multiple-Patients-Per-Ventilator. Accessed June 29, 2021.

36. Arabi YM, Azoulay E, Al-Dorzi HM, et al. How the COVID-19 pandemic will change the future of critical care. Intensive Care Med 2021;47(3):282–91.
37. Hester TB, Cartwright JD, DiGiovine DG, et al. Training and Deployment of medical Students as respiratory therapist Extenders during COVID-19. ATS Scholar 2020;1(2):145–51.
38. Martin L. Shortage of ICU Providers Who Operate Ventilators Would Severely Limit Care During COVID-19 Outbreak. Society of critical care medicine (SCCM). Available at: https://sccm.org/getattachment/About-SCCM/Media-Relations/ Final-Covid19-Press-Release.pdf?lang=en-US. Accessed June 20, 2021.
39. Williams D, Lawrence J, Hong Y, et al. Tele-ICUs for COVID-19: a Look at national prevalence and characteristics of hospitals providing Telementive care. J Rural Health 2020. https://doi.org/10.1111/jrh.12524.
40. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med 2020;8(5):506–17.
41. Supady A, Curtis JR, Abrams D, et al. Allocating scarce intensive care resources during the COVID-19 pandemic: practical challenges to theoretical frameworks. Lancet Respir Med 2021;9(4): 430–4.
42. Chopra V, Flanders SA, O'Malley M, et al. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med 2020. https://doi.org/10.7326/M20-5661.
43. Writing Committee for the COMEBAC Study Group, Morin L, Savale L, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA 2021;325(15):1525–34.
44. Huang C, Huang L, Wang Y, et al. 6-month outcomes of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397(10270): 220–32.
45. Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open 2021;4(5):e2111417.
46. Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA 2020;323(24):2466–7.
47. Culture of Health Program. National Academy of medicine. Available at: https://nam.edu/programs/culture-of-health/. Accessed June 29, 2021.
48. Gross CP, Essien UR, Pasha S, et al. Racial and ethnic disparities in population-level Covid-19 mortality. J Gen Intern Med 2020;35(10):3097–9.
49. Kanter GP, Segal AG, Groeneveld PW. Income disparities in access to critical care services. Health Aff 2020;39(8):1362–7.
50. Wiley Z, Ross-Driscoll K, Wang Z, et al. Racial and ethnic differences and clinical outcomes of COVID-19 patients presenting to the emergency department. Clin Infect Dis 2021. https://doi.org/10.1093/cid/ciab290.
51. U.S. Census Bureau QuickFacts: United States. Available at: https://www.census.gov/quickfacts/table/US/PST045219. Accessed May 14, 2021.
52. Vahidy FS, Nicolas JC, Meeks JR, et al. Racial and ethnic disparities in SARS-CoV-2 pandemic: analysis of a COVID-19 observational registry for a diverse US metropolitan population. BMJ Open 2020;10(8):e039849.
53. Marra A, Ely EW, Pandharipande P, et al. The ABCDEF bundle in critical care. Crit Care Clin 2017;33(2):225–43.
54. Liu K, Nakamura K, Katsukawa H, et al. ABCDEF bundle and supportive ICU practices for patients with coronavirus disease 2019 infection: an International point prevalence study. Crit Care Explorations 2021;3(3):e0353.
55. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. Lancet Respir Med 2021. https://doi.org/10.1016/S2213-2600(20)30552-X.
56. Barr J, Fraser GL, Puntিলlo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41(1):263–306.
57. Valley TS, Schutz A, Nagle MT, et al. Changes to visitation Policies and communication practices in Michigan ICUs during the COVID-19 pandemic. Am J Respir Crit Care Med 2020;202(6):883–5.
58. Gattinoni L, Coppola S, Cressoni M, et al. Covid-19 does not Lead to a “typical” acute respiratory distress syndrome. Am J Respir Crit Care Med 2020. https://doi.org/10.1164/rccm.202003-0817LE.
59. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020. https://doi.org/10.1001/jama.2020.6825.
60. Chiumello D, Busana M, Coppola S, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. Intensive Care Med 2020;46(12): 2187–96.
61. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46(6): 1099–102.
62. Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med 2020. https://doi.org/10.1164/rccm.202004-1163LE.
63. Hernandez-Romieu AC, Adelman MW, Hockstein MA, et al. Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. Crit Care
64. Maley JH, Winkler T, Hardin CC. Heterogeneity of acute respiratory distress syndrome in COVID-19: “typical” or not? Am J Respir Crit Care Med 2020; 202(4):618–9.

65. Sjoding MW, Admon AJ, Saha AK, et al. Comparing clinical Features and outcomes in mechanically ventilated patients with COVID-19 and the acute respiratory distress syndrome. Ann Am Thorac Soc 2021. https://doi.org/10.1513/AnnalsATS.202008-1076OC.

66. Bain W, Yang H, Shah FA, et al. COVID-19 versus non-COVID ARDS: comparison of Demographics, Physiologic Parameters, Inflammatory Biomarkers and clinical outcomes. Ann ATS 2021. https://doi.org/10.1513/AnnalsATS.202008-1026OC.

67. Bos LDJ, Paulus F, Vlaar APJ, et al. Subphenotyping acute respiratory distress syndrome in patients with COVID-19: consequences for ventilator management. Ann Am Thorac Soc 2020;17(9):1161–3.

68. Constantin J-M, Jabaudon M, Lefrant J-Y, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Med 2019;7(10):870–80.

69. Iwashyna TJ, Boehmer A, Capecelatro J, et al. Variation in aerosol Production across oxygen Delivery Devices in spontaneously breathing Human Subjects. medRxiv 2020;2020. https://doi.org/10.1101/2020.04.15.20066688. 04.15.20066688.

70. Nickson C, MD JI, Young P. "Silent hypoxaemia" and COVID-19 intubation. Life in the Fast Lane • LITFL. 2020. Available at: https://litrfl.com/silent-hypoxaemia-and-covid-19-intubation/. Accessed July 9, 2021.

71. Lee YH, Choi K-J, Choi SH, et al. Clinical significance of timing of intubation in critically ill patients with COVID-19: a multi-center retrospective study. J Clin Med 2020;9(9). https://doi.org/10.3390/jcm9092847.

72. Dupuis C, Bouadma L, de Montmollin E, et al. Association between early invasive mechanical ventilation and day-60 mortality in acute hypoxic respiratory failure related to coronavirus disease-2019 pneumonia. Crit Care Explorations 2021; 3(1):e0329.

73. Pandya A, Kaur NA, Sacher D, et al. Ventilatory mechanics in early vs late intubation in a cohort of coronavirus disease 2019 patients with ARDS. Chest 2021;159(2):653–6.

74. Papoutsi E, Giannakoulis VG, Xourgia E, et al. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. Crit Care 2021;25(1):121.

75. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159–68.

76. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED’s experience during the COVID-19 pandemic. Acad Emerg Med 2020;27(5):375–8.

77. Sartini C, Tresoldi M, Scarcellini P, et al. Respiratory Parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care Unit. JAMA 2020; 323(22):2338–40.

78. Thompson AE, Ranard BL, Wei Y, et al. Prone positioning in awake, nonintubated patients with COVID-19 hypoxemic respiratory failure. JAMA Intern Med 2020;180(11):1537–9.

79. Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. JAMA 2020;323(18):1839–41.

80. Hemodynamics. COVID-19 treatment guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/critical-care/hemodynamics/. Accessed May 24, 2021.

81. Kazory A, Ronco C, McCullough PA. SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA 2020;324(21):2165.

82. Comparison of two fluid-management strategies in acute lung Injury | NEJM. Available at: https://www.nejm.org/doi/full/10.1056/nejmoa062200. Accessed May 24, 2021.

83. Muscedere DJ. Nebulized Furosemide for pulmonary Inflammation in intubated patients with COVID-19 - a Phase 2/3 study. clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT04588792. Accessed May 23, 2021.

84. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;382(25):2411–8.

85. Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 Days in hospitalized patients with COVID-19: a randomized clinical trial. JAMA 2020;324(21):2165.

86. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral drugs for Covid-19 - Interim WHO Solidarity trial results. N Engl J Med 2021;384(6):497–511.

87. Thomas S, Patel D, Bittel B, et al. Effect of high-dose Zinc and Ascorbic Acid Supplementation vs usual care on symptom length and reduction among Ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Netw Open 2021;4(2):e210369.
88. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. N Engl J Med 2021; 384(7):619–29.

89. Sanofi. Regeneron shut down Kevzara trial in COVID-19 after finding no benefit for ventilated patients. FiercePharma. Available at: https://www.fiercepharma.com/pharma/sanofi-regeneron-s-kevzara-trial-covid-19-comes-to-a-screaming-halt-after-no-benefit-found. Accessed May 25, 2021.

90. Novartis provides update on CAN-COVID trial in hospitalized patients with COVID-19 pneumonia and cytokine release syndrome (CRS). Novartis. Available at: https://www.novartis.com/news/media-releases/novartis-provides-update-can-covid-trial-hospitalized-patients-covid-19-pneumonia-and-cytokine-release-syndrome-crsv. Accessed May 25, 2021.

91. Update on CALAVI Phase II trials for Calquence in patients hospitalised with respiratory symptoms of COVID-19. Available at: https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-calavi-phase-ii-trials-for-calquence-in-patients-hospitalised-with-respiratory-symptoms-of-covid-19.html. Accessed May 25, 2021.

92. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384(8):693–704.

93. Cano EJ, Fuentes XF, Campioli CC, et al. Impact of corticosteroids in coronavirus disease 2019 outcomes: systematic review and meta-analysis. CHEST 2021;159(3):1019–40.

94. Corticosteroids for COVID-19. Available at: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Corticosteroids-2020.1. Accessed May 25, 2021.

95. Mishra GP, Mulani J. Corticosteroids for COVID-19: the search for an optimum duration of therapy. Lancet Respir Med 2021;9(1):e8.

96. Beigel JH, Tomaszek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — Final report. N Engl J Med 2020;383(19):1813–26.

97. Therapeutic management. COVID-19 treatment guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/. Accessed May 26, 2021.

98. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med 2021;384(16):1503–16.

99. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor Antagonists in critically ill patients with Covid-19. N Engl J Med 2021;384(16):1491–502.

100. Bilaloglu S, Aphinyanaphongs Y, Jones S, et al. Thrombosis in hospitalized patients with COVID-19 in a New York city health system. JAMA 2020; 324(8):799–801.

101. Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy Findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Ann Intern Med 2020;173(4):268–77.

102. ASH guidelines on Use of anticoagulation in patients with COVID-19 - Hematology.org. Available at: https://www.hematology.org/443/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19. Accessed May 26, 2021.

103. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, et al. Effect of intermediate-dose vs Standard-dose prophylactic anticoagulation on Thrombotic events, Extracorporeal Membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care Unit: the INSPIRATION randomized clinical trial. JAMA 2021;325(16):1620–30.

104. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. J Am Coll Cardiol 2020;76(1):122–4.

105. Interim Presentation of ATTACC, ACTIV-4a & REMAP-CAP. ATTACC. https://www.attacc.org/presentations. [Accessed 26 May 2021]. Accessed.

106. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2034577.

107. Moghadas SM, Vilches TN, Zhang K, et al. The impact of vaccination on COVID-19 outbreaks in the United States. medRxiv 2021. https://doi.org/10.1101/2020.11.27.20240051.

108. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 2020;324(13):1317–29.

109. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on Days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020;324(13):1307–16.