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REVIEW

Coronavirus disease 2019 respiratory failure: what is the best supportive care for patients who require ICU admission?

Daniel A. Sweeney and Atul Malhotra

Purpose of review

Currently, there is no cure for SARS-CoV-2 infection, yet hospital mortality rates for COVID-19 have improved over the course of the pandemic and may be due in part to improved supportive care in the ICU. This review highlights the evidence for and against various ICU supportive therapies for the treatment of critically ill patients with COVID-19.

Recent findings

Early in the pandemic, there was great interest in novel ICU supportive care, both for the benefit of the patient, and the safety of clinicians. With a few exceptions (e.g. prone ventilation of nonintubated patients), clinicians abandoned most of these approaches (e.g. early intubation, avoidance of high flow or noninvasive ventilation). Standard critical care measures, especially for the treatment of severe viral respiratory infection including acute respiratory distress syndrome (ARDS) were applied to patients with COVID-19 with apparent success.

Summary

In general, the COVID-19 pandemic reaffirmed the benefits of standard supportive care for respiratory failure and in particular, recent advances in ARDS treatment. Prone ventilation of nonintubated patients, an approach that was adopted early in the pandemic, is associated with improvement in oxygenation, but its impact on clinical outcome remains unclear. Otherwise, prone mechanical ventilation and avoidance of excessive tidal volumes, conservative fluid management, antibiotic stewardship and early evaluation for extracorporeal membrane oxygenation (ECMO) – basic tenants of severe respiratory infections and ARDS care – remain at the core of management of patients with severe COVID-19.

Keywords

mechanical ventilation, prone ventilation, severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2), supportive care

INTRODUCTION

In hospital and in particular ICU, mortality rates for patients with COVID-19 declined over the course of the pandemic [1,2,3▪,4]. Conceptually, this improvement in clinical outcomes may be a function of differences in patient characteristics, treatment and hospital system factors, or viral mutations.

CHANGES IN PATIENT CHARACTERISTICS DO NOT EXPLAIN THE IMPROVEMENT IN THE MORTALITY RATE

Two large retrospective studies addressed the question of whether shifting patient demographics including comorbidity burden could explain the improved survival rates for critically ill patients with COVID-19. One study led by Dennis *et al.* included 21 082 patients in England admitted between 1 March 2020 and 27 June 2020. The other study performed by Doidge and colleagues included 10 741 patients in England, Wales and Northern Ireland from 1 February 2020 to 31 July 2020. Both studies showed a similar improvement in mortality over the respective study time periods, before and after adjusting for baseline factors including age and comorbidities (mortality improvement after adjusting for risk factors of 8.9 and 11.2%, respectively).

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KEY POINTS

- Improvement in ICU supportive care over the course of the pandemic has likely contributed to a decline in mortality among hospitalized patients with COVID-19.
- Some supportive measures that were promoted during the pandemic (prone ventilation for nonintubated patients) may be beneficial whereas others (early intubation and avoidance of high-flow oxygen) proved either nonbeneficial or possibly harmful.
- Novel supportive measures, such as early intubation and avoidance of high-flow oxygen therapy proved either nonbeneficial or possibly harmful and have been abandoned. Prone ventilation for nonintubated patients continues to be administered despite lack of evidence of clinical benefit beyond improvement in oxygenation.
- Like other severe viral respiratory infections, standard critical care supportive measures and strategies for ARDS should be employed in the treatment of patients with severe COVID-19, including lung protective ventilation, prone ventilation, judicious use of empiric antibiotics, attentive fluid management, and early referral of select patients for ECMO.

MORTALITY RATE IMPROVED INDEPENDENTLY OF CHANGES IN HOSPITAL CAPACITY

Historically, hospital capacity strain has been shown to be associated with increased inpatient mortality and a similar effect was noted during the COVID-19 pandemic [5]. In a cohort study of 3143 critically ill patients admitted to 88 hospitals, the mortality risk was nearly two-fold higher [1.94, 95% confidence interval (CI) 1.46–2.59] during peak periods of ICU demand [6▪]. However, the mortality improvement over the course of the pandemic is likely unrelated to hospital capacity strain. In the study by Doidge and colleagues, analysis was stratified by time period (prepeak, peak, and postpeak periods) and the adjusted mortality improvement (11.2%) was noted when comparing patients from the prepeak and postpeak periods, thus excluding any hospital process effect that could have occurred during the time period of peak ICU admissions.

IMPROVEMENT IN ICU MORTALITY FOR PATIENTS WITH CORONAVIRUS DISEASE 2019 OCCURRED BEFORE DEXAMETHASONE AND REMDESIVIR THERAPY BECAME WIDELY PRESCRIBED

The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial began recruiting patients in the United Kingdom (UK) in April 2020 and the preliminary results of the beneficial effect of dexamethasone were not released until 16 June 2021 [7]. Although both studies involved patients from the UK, the trial by Dennis *et al.* did not include patients after 27 June 2020, whereas Doidge and colleagues report that their analysis involved 'few' patients who were admitted after the announcement of the RECOVERY trial results. In terms of remdesivir, the drug was approved for use in the UK by The Medicine and Healthcare products Regulatory Agency on 26 May 26 2020 but was approved for limited use and is also unlikely to explain the improved mortality seen in these two UK-based studies [8].

THERE IS NO EVIDENCE THAT VIRAL MUTATIONS LED TO IMPROVED OUTCOMES OVER THE COURSE OF THE PANDEMIC

SARS-CoV-2 is an RNA virus, which is naturally prone to having a high mutation rate. Most of these mutations are inconsequential – neither making the virus more pathogenic or more contagious. Since being established in April 2020, The COVID-19 genomics UK (COG-UK) consortium has been performing random genetic sequencing testing of positive samples in the UK. It was not until December, 2020– and after more than 100 000 viral genomes were sequenced – that the more transmissible B1.1.7 variant was identified in the UK [9]. Thus, it is unlikely that the SARS-CoV-2 genome changed significantly in the UK between February and July 2020 during which time the ICU mortality rates for patients with COVID-19 improved.

WHICH SUPPORTIVE ICU THERAPIES FOR THE TREATMENT OF CORONAVIRUS DISEASE 2019 ARE RESPONSIBLE FOR THE IMPROVED SURVIVAL RATES?

In the near absence of randomized, placebo-controlled trials, it is nearly impossible to identify exactly which individual therapies or practices are responsible for the improved clinical outcomes. Undoubtedly, critical care practice changed over the course of the pandemic. Early in the pandemic, much of the clinical decision-making was impacted by the potential unique characteristics of SARS-CoV-2 infection, a lack of understanding of transmission and the threat of outbreaks in the healthcare setting. Over time, similarities, rather than differences between COVID-19 and other more common respiratory viral illnesses, became more apparent, and thus there was a recommitment to high-quality critical care therapies for the treatment of severe viral pneumonia and ARDS. With few exceptions, we will detail how traditional critical therapies and approaches to hypoxic respiratory failure likely contributed to the overall improved survival rate amongst critically ill patients with COVID-19.

ABANDONMENT OF AN EARLY INTUBATION APPROACH TO PATIENTS WITH CORONAVIRUS DISEASE 2019; RETURN OF PREPANDEMIC CLINICAL JUDGEMENT TO DECIDE ON TIMING OF INTUBATION

At the beginning of the pandemic, many hospitals adopted a strategy of early intubation of patients with COVID-19 [10]. These policies were mostly born out the fear that high-flow nasal cannula would aerosolize SARS-CoV-2 and place healthcare workers at risk of infection [11]. In addition, experts initially argued that SARS-CoV-2 pneumonia was a unique viral pneumonia and advocated that early intubation would also prevent the theoretical risk of patient self-inflicted lung injury (PSILI) in select cases [12▪]. Over the course of the pandemic, guidelines shifted and epidemiological data suggested that an early intubation approach was replaced with traditional clinical judgement. Doidge *et al.* [3▪] described this trend when they compared patients with COVID-19 from the prepeak period (1 February 2021 to 28 March 2021), to post postpeak period (13 April to 31 July 2021). Compared with prepeak patients, patients in the postpeak period had a lower median PaO_2/FIO_2 ratio (−9.3, 95% CI −13.3 to 5.3), yet they were less likely to be treated with mechanical ventilation in the first 24 h of being admitted to the ICU (−32.7%, 95% CI −35.1 to −30.3%). It is also telling that the use of renal replacement therapy was employed less postpeak versus prepeak time periods (−8.4%, 95% CI −10.7 to −6.1%). Mechanical ventilation increases a patient's risk for acute kidney injury and the combination of mechanical ventilation and renal replacement therapy has been previously shown to increase mortality in critically ill patients [13]. Thus, the observed, unadjusted mortality improvement postpeak versus prepeak period (−10.0%, 95% CI −12.5 to −7.5%), may be due, in part, to clinicians reverting to the prepandemic approach to deciding whether a patient with a viral pneumonia and hypoxemia should be intubated [3▪,14▪]. Another retrospective study by Dupuis *et al.* [15] supports the assertion that early intubation may have resulted in increased mortality among critically ill patients with COVID-19; instead of renal failure as a possible cause, the authors note an association between secondary infections and early intubation. Analysis of 245 patients in 11 ICUs in France demonstrated that in cases of ICU-acquired pneumonia, bacteremia was significantly higher among patients with COVID-19 who were intubated early (defined as occurring during the first two calendar days of their ICU stay); moreover, a weighted model showed that early intubated patients had an increased 60-day mortality risk (hazard ratio 1.74, 95% CI 1.07–2.83).

EARLIER RECOGNITION OF ACUTE RESPIRATORY DISTRESS SYNDROME AND MORE WIDESPREAD USE OF EVIDENCE-BASED VENTILATORY STRATEGIES FOR THE TREATMENT OF SEVERE CORONAVIRUS DISEASE 2019 RESPIRATORY FAILURE

Prior to the SARS-CoV-2 pandemic, evidence-based guidelines and expert opinion recommended a number of supportive interventions for the treatment of severe respiratory failure and ARDS, including lung protective ventilation, prone ventilation, conservative fluid management, and to a lesser degree, open lung ventilation, minimizing driving pressure, neuromuscular blockade, and early referral for extracorporeal membrane oxygenation (ECMO) in the setting of refractory hypoxemia [16,17].

Nonetheless, prepandemic observational studies revealed that ARDS remained underrecognized and compliance with accepted treatment strategies were not uniformly adopted. In a prospective study involving 459 ICUs in 50 countries, it was noted that severe ARDS was recognized in 78.5% (95% CI 44.8–81.8%) of cases and that prone ventilation, a therapy shown in the Prone Positioning on Mortality in Patients with Severe and Persistent Acute Respiratory Distress Syndrome (PROSEVA) Trial to have a mortality benefit, was only administered in 16.3% (95% CI 13.7–19.2%) of these patients [18,19]. Early in the SARS-CoV-2 pandemic, deliberation amongst clinicians regarding whether COVID-19 pneumonia was associated with an 'atypical' ARDS may have further obfuscated the urgency to apply standard ARDS ventilatory strategies [20]. Overall, the application of ARDS ventilatory therapies during the pandemic, including prone mechanical ventilation, eventually surpassed historic rates in numerous reports. A retrospective multicenter study from Italy involving patients admitted between 24 February and 14 July 2020 revealed that 77% of patients with COVID-19 and severe ARDS underwent prone ventilation [21]. As the pandemic progressed, it is likely that inexperience with prone ventilation – a recognized barrier to its use – has been replaced with expertise and thus broader application of this therapy [22]. In another natural history study of the management of 633 patients in the UK with COVID-19 the application of prone positioning, along with higher positive end-expiratory pressure (PEEP) and the use of neuromuscular blockade increased significantly over the time course of the study (1–26 March 2020 versus 27 March to 9 April 2020). Whether broader application of standard ARDS respiratory supportive therapy resulted in improved outcomes over the course of the pandemic remains unproven but the overall mortality of 43.3% observed in this study (in the setting of only 50% of patients receiving prone ventilation) was higher compared with other studies in which prone ventilation was applied in more than 70% of patients with COVID-19 [23].

ANTIMICROBIAL STEWARDSHIP, JUDICIOUS FLUID MANAGEMENT, AND EXTRACORPOREAL MEMBRANE OXYGENATION CONSIDERATION FOR SEVERE CASES REPRESENT ESSENTIAL SUPPORTIVE CARE FOR PATIENTS WITH CORONAVIRUS DISEASE 2019

Community-onset bacterial coinfections in hospitalized patients with COVID-19 has proven to be exceedingly rare. In a cohort of 1705 patients hospitalized with COVID-19 in 38 Michigan hospitals, the rate of confirmed community-onset coinfections was 3.5% yet the majority (56.6%) of patients were prescribed empiric antibiotics [24]. However, once hospitalized, patients with COVID-19 frequently suffered from hospital-acquired infections (HAIs). In a study of 774 patients admitted to 8 Italian hospitals between 20 February 2020 and 20 May 2020, 46% of patients were diagnosed with a HAI, with empiric broad spectrum antibiotics prescribed at the time of admission being a risk factor for acquisition of a HAI (hazard ratio 0.61, 95% CI 0.44–0.84) [25]. Although this study did not identify steroids or immunomodulator therapy as a risk factor for HAIs, other studies have shown both therapies to be both associated with an increased risk of bacterial and fungal HIAs. This pattern of excessive antibiotic use at the onset of admission followed by immune modulating treatments and subsequent increased risk for HAIs, is one in which antimicrobial stewardship can be most helpful at multiple points during a patient's hospital stay. Indeed, an antimicrobial stewardship intervention aimed at reducing unnecessary empiric antibiotic use in patients admitted with a diagnosis of COVID-19 resulted in a 32.5% absolute reduction in antibiotic prescriptions [26]. In this single-center study of 506 patients, the stewardship intervention did not impact clinical outcomes, which suggests a lack of harm with reduced antibiotic use.

Although not yet systematically studied, optimal fluid management strategies for patients with severe COVID-19 are likely to mirror current approaches for critically ill patients suffering from viral respiratory failure. For example, in the minority of cases in which patients with COVID-19 develop septic shock, current COVID-19 guidelines recommend resuscitation with fluids and vasoactive agents guided by dynamic measures in a similar manner to sepsis caused by other infectious agents [27,28]. In patients with COVID-19 and ARDS, it is advantageous to avoid pulmonary edema, and thus a conservative fluid management approach is recommended. Fluid status is particularly challenging to predict in patients with COVID-19 as it will vary depending upon comorbidities, when in the course of their viral illness they present, and with what predominant symptoms. For example, a patient presenting with several days of malaise and gastrointestinal symptoms may be hypovolemic, whereas a patient with concomitant coronary artery disease may be relatively hypervolemic and require early diuresis. Thus, judicious fluid management, guided by dynamic measures and further aided by point-of-care ultrasound, is a key component of COVID-19 supportive care.

Despite limited supportive data from the pandemic, ECMO is recommended by several expert guideline committees for the treatment of severe COVID-19 and ARDS refractory to conventional therapies including lung protective ventilation and prone ventilation therapies [27,29]. A meta-analysis of four studies from China conducted early in the SARS-CoV-2 pandemic showed no difference in mortality when comparing ECMO versus conventional therapy (94.1 vs. 70.9%, respectively; odds ratio 2.00, 95% CI 0.49–8.16), thus leading to concerns that ECMO may not be beneficial in the treatment of severe COVID-19 [30]. However, there are limitations to this analysis, including an extremely high mortality rate in the conventional therapy arm and the relatively small number of patients who received ECMO therapy across the 4 studies (17 of the 234 total patients). More recently, analysis of a data from the Extracorporeal Life Support Organization (ELSO) Registry, including 1035 patients with COVID-19, most of whom were diagnosed with ARDS, revealed an estimated in-hospital mortality 90 days after ECMO initiation of 37.4% (95% CI 34.4–40.4) [31▪]. This mortality rate is remarkably similar to the 60-day mortality rate (35%) of patients with ARDS who were treated in the largest randomized controlled trial to date of ECMO for ARDS, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial [32]. Although the role of ECMO in patient management is controversial, the prevailing opinion, largely based on the EOLIA trail results, is that ECMO should be considered in select patients with ARDS, and thus should be offered to patients with ARDS secondary to COVID-19. Deciding, which patients, refractory to conventional ARDS treatment, will benefit from ECMO is crucial. At this time, the ELSO COVID-19 interim patient selection guidelines for ECMO are based on data derived from non-COVID-19 patients [33]. Consistent with these guidelines, the ELSO registry-based COVID-19 study identified a number of risk factors associated with increased mortality among patients treated with ECMO, including advanced age and chronic respiratory disease [31▪].

NONINTUBATED PATIENTS WITH CORONAVIRUS DISEASE 2019 DEMONSTRATE IMPROVED OXYGENATION BUT EVIDENCE OF CLINICAL OUTCOME BENEFIT IS LACKING

Prone ventilation for the treatment of nonintubated patients was sparsely studied prior to the SARS-CoV-2 pandemic; a handful of studies, mostly conducted in patients with pneumonia showed that prone positioning of patients improved oxygenation [34]. Since the onset of the pandemic, prone ventilation for the treatment of patients with COVID-19 has become more commonplace, due in part to the limited capacity of healthcare systems to provide mechanical ventilation. A preprint review and meta-analysis (including 15 single arm studies) and a more recent 'rapid review' (including 29 studies, only 1 reported data from a control group) reveal a potential benefit from prone ventilation for the treatment of nonintubated patients with COVID-19, albeit tempered by a great amount of uncertainty [35,36]. Taken together, these reviews show that patient oxygenation improves with prone positioning, but evidence of clinical benefit is lacking. Although one retrospective study (105 patients) reported that prone ventilation of nonintubated patients reduced the risk of intubation (adjusted hazard ratio, 0.30; 95% CI, 0.09–0.96), these results have not been consistently replicated [37▪]. And although prone ventilation appears to be well tolerated, adverse events were not consistently documented across studies. Understanding the effects of prone ventilation on nonintubated patients is further challenged by the fact that not all patients can tolerate prone positioning and the amount of time in the prone position varied across studies. Despite these shortcomings, prone ventilation of nonintubated patients with COVID-19 is worthy of future study considering its potential benefit, apparent favorable safety profile and minimal cost.

CONCLUSION

Clinical outcomes for critically ill patients with COVID-19 have improved over the course of the pandemic independent of shifting patient demographics, viral variants, ICU capacity stress, or the subsequent widespread use of therapies, such as dexamethasone or remdesivir. Thus, the honing of supportive critical care strategies for the treatment of severe COVID-19, particularly ARDS, is likely responsible for this observed clinical improvement. Indeed, the pandemic has largely reaffirmed widely accepted but often neglected proven therapies for ARDS. The decision to intubate a patient with COVID-19 should be based on clinical judgement rather than dictated by an early intubation protocol. It is worth emphasizing that prone ventilation of nonintubated patients improves oxygenation but meaningful clinical outcome benefit is lacking. Instead, patients with severe COVID-19 should receive standard supportive therapies, such as lung protective ventilation, prone ventilation, judicious use of empiric antibiotics, attentive fluid management and possible ECMO in select cases.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
▪ of special interest
▪▪ of outstanding interest

1. Ciceri F, Ruggeri A, Lembo R, *et al.* Decreased in-hospital mortality in patients with COVID-19 pneumonia. Pathog Glob Health 2020; 114:281–282.
2. Dennis JM, McGovern AP, Vollmer SJ, Mateen BA. Improving survival of critical care patients with coronavirus disease 2019 in England: a national cohort study, March to June 2020. Crit Care Med 2021; 49:209–214.
3. ▪ Doidge JC, Gould DW, Ferrando-Vivas P, *et al.* Trends in intensive care for patients with COVID-19 in England, Wales, and Northern Ireland. Am J Respir Crit Care Med 2021; 203:565–574.

After adjusting for important risk factors and independent of improved therapies, the outcomes of critically ill patients with COVID-19 improved over the early course of the pandemic.

4. Horwitz LI, Jones SA, Cerfolio RJ, *et al.* Trends in COVID-19 risk-adjusted mortality rates. J Hosp Med 2021; 16:90–92.

5. Eriksson CO, Stoner RC, Eden KB, *et al.* The association between hospital capacity strain and inpatient outcomes in highly developed countries: a systematic review. J Gen Intern Med 2017; 32:686–696.

6. ▪ 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:e2034266.

This study shows how critically ill patients with COVID-19 who were treated in the ICU during peroids of increased COVID-19 ICU demand had increased mortality risk compared with patients treated during periods of low-COVID-19 ICU demand.

7. RECOVERY Collaborative Group. Horby P, Lim WS, *et al.* Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021; 384:693–704.

8. MHRA issues a scientific opinion for the first medicine to treat COVID-19 in the UK [press release]. 26 May 2020.

9. Wise J. Covid-19: new coronavirus variant is identified in UK. BMJ 2020; 371:m4857.

10. Goyal P, Choi JJ, Pinheiro LC, *et al.* Clinical characteristics of Covid-19 in New York City. New Engl J Med 2020; 382:2372–2374.

11. Haymet A, Bassi GL, Fraser JF. Airborne spread of SARS-CoV-2 while using high-flow nasal cannula oxygen therapy: myth or reality? Intensive Care Med 2020; 46:2248–2251.

12. ▪ Gattinoni L, Chiumello D, Caironi P, *et al.* COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020; 46:1099–1102.

A frequently cited article promoting the idea that severe COVID-19 pneumonia has two phenotypes and that some patients should not receive traditional lung preventive ventilation.

13. Hepokoski ML, Malhotra A, Singh P, Crotty Alexander LE. Ventilator-induced kidney injury: are novel biomarkers the key to prevention? Nephron 2018; 140:90–93.

14. ▪ Tobin MJ. Basing respiratory management of COVID-19 on physiological principles. Am J Respir Crit Care Med 2020; 201:1319–1320.

Excellent editorial discussing how basic physiology should guide the decision to intubate a patient with severe COVID-19.

15. Dupuis C, Bouadma L, de Montmollin E, *et al.* Association between early invasive mechanical ventilation and day-60 mortality in acute hypoxemic respiratory failure related to coronavirus disease-2019 pneumonia. Crit Care Explor 2021; 3:e0329.

16. Amato MBP, Meade MO, Slutsky AS, *et al.* Driving pressure and survival in the acute respiratory distress syndrome. New Engl J Med 2015; 372:747–755.

17. Papazian L, Aubron C, Brochard L, *et al.* Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care 2019; 9:69.

18. Bellani G, Laffey JG, Pham T, *et al.,* LUNG SAFE Investigators, ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016; 315:788–800.

19. Guerin C, Reignier J, Richard JC, *et al.,* PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013; 368:2159–2168.

20. Tobin MJ. Pondering the atypicality of ARDS in COVID-19 is a distraction for the bedside doctor. Intensive Care Med 2021; 47:361–362.

21. Langer T, Brioni M, Guzzardella A, *et al.* Prone position in intubated, mechanically ventilated patients with COVID-19: a multicentric study of more than 1000 patients. Crit Care 2021; 25:128.

22. Klaiman T, Silvestri JA, Srinivasan T, *et al.* Improving prone positioning for severe acute respiratory distress syndrome during the COVID-19 pandemic. An implementation-mapping approach. Ann Am Thorac Soc 2021; 18:300–307.

23. Patel BV, Haar S, Handslip R, *et al.,* United Kingdom COVID-ICU National Service Evaluation. Natural history, trajectory, and management of mechanically ventilated COVID-19 patients in the United Kingdom. Intensive Care Med 2021; 47:549–565.

24. Vaughn VM, Gandhi TN, Petty LA, *et al.* Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalized with coronavirus disease 2019 (COVID-19): a multihospital cohort study. Clin Infect Dis 2021; 72:e533–e541.

25. Grasselli G, Scaravilli V, Mangioni D, *et al.* Hospital-acquired infections in critically ill patients with COVID-19. Chest 2021. [Epub ahead of print]

26. Pettit NN, Nguyen CT, Lew AK, *et al.* Reducing the use of empiric antibiotic therapy in COVID-19 on hospital admission. BMC Infect Dis 2021; 21:516.

27. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov. [Accessed 12 June 2021]

28. 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). Crit Care Med 2020; 48:e440–e469.

29. COVID-19 Clinical management: living guidance [13 June 2021]. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. [Accessed 12 June 2021]

30. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): pooled analysis of early reports. J Crit Care 2020; 58:27–28.

31. ▪ Barbaro RP, MacLaren G, Boonstra PS, *et al.,* Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet 2020; 396:1071–1078.

The most complete description of the ECMO experience during the pandemic; identified risk factors for increased mortality among patients with COVID-19 who were treated with ECMO.

32. Combes A, Hajage D, Capellier G, *et al.,* EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. New Engl J Med 2018; 378:1965–1975.

33. Shekar K, Badulak J, Peek G, *et al.,* ELSO Guideline Working Group. Extracorporeal Life Support Organization Coronavirus Disease 2019 Interim Guidelines: a Consensus Document from an International Group of Interdisciplinary Extracorporeal Membrane Oxygenation Providers. ASAIO J 2020; 66:707–721.

34. Touchon F, Trigui Y, Prud'homme E, *et al.* Awake prone positioning for hypoxaemic respiratory failure: past, COVID-19 and perspectives. Eur Respir Rev 2021; 30:. 210022.

35. Reddy MP, Subramaniam A, Lim ZJ, *et al.* Prone positioning of nonintubated patients with COVID-19 - a systematic review and meta-analysis. medRxiv 2020. [Epub ahead of print]

36. Weatherald J, Solverson K, Zuege DJ, *et al.* Awake prone positioning for COVID-19 hypoxemic respiratory failure: a rapid review. J Crit Care 2021; 61:63–70.

37. ▪ Jagan N, Morrow LE, Walters RW, *et al.* The POSITIONED Study: prone positioning in nonventilated coronavirus disease 2019 patients-a retrospective analysis. Crit Care Explor 2020; 2:e0229.

This retrospective analysis of patients with COVID-19 from a single center is notable for the fact that it suggests the use of prone ventilation conferred a mortality benefit.