VIEWPOINTS

Perspectives on Cardiopulmonary Critical Care for Patients With COVID-19: From Members of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation

Bradley A. Maron [iD], MD; Mark T. Gladwin, MD; Sebastien Bonnet, PhD; Vinicio De Jesus Perez [iD], MD; Sarah M. Perman, MD, MSCE; Paul B. Yu [iD], MD, PhD; Fumito Ichinose [iD], MD

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), marks a global event that will permanently reshape implementation of intensive care medicine. As of June 4, 2020, there were 6 606 455 reported cases of COVID-19, including 388 556 fatalities spanning 215 countries and territories, although epidemiologic data remain incomplete. Early autopsy reports emphasize proximal airway and distal airspace involvement, including alveolar epithelial inflammation and capillary thickening. These processes appear to promote acute respiratory distress syndrome (ARDS) and increased susceptibility to cytokine storm, resulting in respiratory failure and circulatory collapse in severe cases. Cardiomyopathy (particularly myocarditis) and ventricular arrhythmia further complicate management. Indeed, the mortality among ventilated patients in the intensive care unit (ICU) is as high as 50%[1]; thus, critical care medicine has emerged as a central focus of the COVID-19 clinical spectrum. Here, critical care medicine and other matters of cardiopulmonary health important to the COVID-19 pandemic are discussed.

PATIENT ISOLATION AND PROTECTION OF HEALTHCARE WORKERS

Exposure to SARS-CoV-2 requires up to 14 days of quarantine, which significantly drains provider resources. Rational policies must balance the effort to reduce risk of virus transmission and quarantine with the supply chain analysis of current and future personal protective equipment (PPE) availability. This includes systems-based preparations that recognize and plan for the increased risk associated with aerosol-generating procedures (eg, endotracheal intubation, noninvasive positive pressure ventilation, high-flow oxygen therapy, jet nebulization, chest physiotherapy), including implementing droplet-level precautions under conditions in which PPE availability is limited. This also encompasses regular surgical masks on patients and providers in the inpatient and outpatient settings, 6-ft (1.8 m) distancing when possible, and gown-glove-hand washing with frequent sanitation of contact areas.

Patients who are being investigated, who are hospitalized and awaiting nasal swab sample collection

Key Words: COVID-19 ■ pulmonary heart disease ■ shock

and polymerase chain reaction–based testing, or who test positive for SARS-CoV-2 should be maintained in single-occupancy rooms with closed doors and under droplet contact precautions. If PPE resources are available, these patients can be managed with more rigorous aerosol transmission precautions in negative pressure isolation. The ideal management approach to confirmed COVID-19 cases is placement in specialized cohort units, which allows providers to maintain higher levels of protection for aerosol transmission using a PPE set that includes a fitted respirator mask (N95, FFP2) or a powered air-purifying respirator, gloves, gown, and eye protection (face shield or safety goggles). It is important to recognize that the techniques for doffing are as important as donning, since the PPE exterior may be contaminated (see https://www.cdc.gov/vhf/ebola/hcp/ppe-training/n95respirator_gown/donning_01.html). Unconventional but effective alternative methods to protect providers during intubation, such as using an aerosol box, have also been used when standard PPE availability is limited.[2]

CRITICAL CARE MEDICINE AND COVID-19

The cumulative incidence of out-of-hospital cardiac arrest has increased notably by approximately 60% during the pandemic in one Italian series, with 77% attributable to COVID-19.[3] Cardiopulmonary resuscitation during COVID-19 continues to focus on the provision of quality compressions, potentially with mechanical devices to limit resuscitation team size, and early first-pass success during intubation via video laryngoscopy. Standard advanced cardiac life support algorithms remain; however, guidelines have been updated to account for ensuring adequate PPE, minimizing the size of resuscitative teams, and providing strategies for prompt resuscitative measures in unique situations such as the proned patient or the patient with refractory hypoxemia. Because chest compression is considered to be an aerosol-generating procedure, recommendations have been made to decrease the number of cardiopulmonary resuscitation providers to minimize exposure and conserve PPE. Given the lack of data regarding outcomes for patients who suffer cardiac arrest after COVID-19 infection, early advanced care planning is necessary to establish appropriate goals of care. The decision regarding the appropriateness of beginning or continuing a resuscitation should be addressed by the medical team.[4]

Various scoring methods are available to prioritize scarce critical care services, but any decision to limit care should be made in advance of rapid clinical deterioration. This is important, as a subset of patients with COVID-19 present with mild hypoxia but quickly develop acute hypoxemic respiratory failure associated with the development of bilateral lung infiltrates. It is reasonable to offer supplemental oxygen via high-flow nasal cannula or noninvasive positive pressure ventilation in patients with mild hypoxemia; however, early intubation and mechanical ventilation may be necessary, as respiratory condition may worsen rapidly. In New York City, more than 30% of patients with COVID-19 who received invasive mechanical ventilation did not need supplemental oxygen during the first 3 hours after presenting to the emergency department.[5] Of the 393 patients with COVID-19 admitted to 2 New York City hospitals, 130 patients (33.1%) developed severe respiratory failure requiring mechanical ventilation. It is important to note that the field is evolving continuously, and approaches to limit intubation and mechanical ventilation are being considered. Many centers have adapted a strategy of earlier prone positioning in non–mechanically ventilated patients compared with usual care and, similarly, a low threshold to use high-flow oxygen and noninvasive ventilation with appropriate aerosol-transmission precautions.

Given the risk of viral transmission via aerosolization, advanced PPE such as an N95 mask/face shield or powered air-purifying respirator should be used in a negative pressure room when administering high-flow oxygen, noninvasive ventilation, or performing endotracheal intubation. The Surviving Sepsis Campaign Guidelines for the Management of Critically Ill COVID-19 Patients[6] recommends intubation using video-guided laryngoscopy to decrease the risk of aerosol exposure by maintaining distance from the patient's mouth. Furthermore, it is recommended that a designated team of specialists with expertise in endotracheal intubation be responsible for handling intubations to minimize the time and attempts required to secure the airway.

Controversy persists regarding the optimal timing of intubation in COVID-19, in part because of the heterogeneous cardiopulmonary clinical spectrum associated with this disease and data lacking from gold-standard randomized trials. Some clues on lung subphenotypes have emerged; for example, findings from one retrospective analysis of 70 suspected patients with COVID-19 admitted to the ICU showed that estimated lung weight does not correlate with lung compliance in this population.[7] Others have shown static compliance in COVID similar to observations in non–COVID-19 patients with similar respiratory clinical phenotype.[8] Overall, there remains a pressing need for point-of-care tools to predict respiratory failure in patients with COVID-19.

MANAGING ARDS IN PATIENTS WITH COVID-19

We recommend adhering to long-standing and proven principles of ARDS management, particularly relative to mechanical ventilation: (1) titrate FiO_2 to a goal oxyhemoglobin saturation of 92% to 96%, (2) low tidal volume ventilation (4–6 mL/kg of predicted body weight) with positive end-expiratory pressure (PEEP) >10 cm H_2O while maintaining plateau pressure <30 cm H_2O, and (3) conservative fluid management if vasopressors are not required.[1] Different strategies to titrate PEEP have been implimented in clinical practice, such as using low and high ARDSnet PEEP tables for body mass index <40 kg/m^2 versus >40 kg/m^2, respectively,[9] titrating to static compliance, or using pressure-volume loop contour to guide decision making, mindful that atypical pressure-volume loops/compliance curves have been observed anecdotally in patients with COVID-19. Personalized approaches to determining PEEP are likely to hinge on better characterizing the relationship between focal and nonfocal ARDS relative to lung compliance (recruitability).[10] The exact ventilator mode (ie, pressure-limited versus volume-cycled assist-control) is less important provided that a sufficient inspiratory:expiratory ratio and appropriate lung-protective low tidal volume are achieved.

These collective metrics are important for increasing mean arterial pressure across both inspiration and expiration that may improve oxygenation and prevent lung injury, respectively. In patients with persistent hypoxemia unresponsive to low tidal volume ventilation and appropriate PEEP, a trial of prone ventilation and inhaled pulmonary vasodilators (eg, inhaled nitric oxide) could be considered. Refractory hypoxemia may warrant venovenous extracorporeal membrane oxygenation as a bridge to recovery.

For patients with septic shock (ie, hemodynamic collapse attributable to COVID-19 or associated superinfection), we recommend a conservative fluid resuscitation strategy with crystalloids to prevent exacerbating lung edema, and inotropic support as indicated. Use of vasopressors should be considered if patients fail to maintain mean arterial pressure >60 mm Hg. For patients with refractory shock, a trial of low-dose corticosteroids (hydrocortisone 200 mg daily, often supplemented with oral fludrocortisone) may also improve central and peripheral blood pressure. Treatment with dexamethasone may be considered in patients with the appropriate indications. Managing the respiratory status of patients with septic shock in COVID-19 may be complicated by nosocomial ventilator-associated pneumonia (aerobic gram-negative rods and *Staphylococcus aureus*) and the fact that approximately 13% of patients use renal replacement therapy.[5]

Several reports have shown some efficacy for use of systemic corticosteroids or experimental therapies such as convalescent plasma, favipiravir, inhaled nitric oxide, or tocilizumab in patients with COVID-19.[11] One recently reported randomized double-blind, clinical trial showed that remdesivir for 10 days shortened the recovery time in hospitalized COVID-19 patients with lower respiratory tract infection compared to placebo.[12] A number of clinical trials are under way to determine the efficacy of these potential treatments for COVID-19. A list of ongoing clinical trials in COVID-19-ARDS is provided in Table 1. Based on the results of a clinical trial that showed remdesivir shortened the time to recovery in some patients, the US Food and Drug Administration issued an emergency use authorization for remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.[13] However, given the lack of definite evidence and the potential complications associated with these medications, we recommend against their routine use at the time of this writing. Nonetheless, physicians should consider enrolling patients in ongoing clinical trials if this is an available option.

RESOURCE MANAGEMENT

A major challenge during epidemic disease "surge" is the potential for limited ventilators to meet demand. Scoring systems have been developed based on experience from the H1N1 epidemic and have recently been updated and published.[14] These simple scoring systems use the Sequential Organ Failure Assessment tool[15] and other widely available models to establish long-term probability of survival to generate a numerical score, which can be used to prioritize rare resources and limit subjective and possibly biased assessments. Many states are considering legislation to limit liability for providers shouldered with these tragic decisions.

MYOCARDIAL INJURY: IMPLICATIONS ON ICU CARE

An increase in circulating markers of myocardial injury is reported in 7.2% to 27.8% of patients with COVID-19 and correlates positively with disease severity including need for mechanical ventilation and biochemical measures of heart failure (eg, N-terminal pro-B-type natriuretic peptide).[16,17] Elevated cardiac troponin-T was associated with an 11.7-fold increase in mortality risk in one series,[18] is predictive of malignant arrhythmias, and increased more frequently in patients with COVID-19 with existing ischemic heart disease, hypertension, or cardiomyopathy.[19,20]

Table 1. Selected Clinical Trials Actively Recruiting Patients With COVID-19 and ARDS

Study Name	Identifier	Duration	Treatment	Primary End Point
DEXA-COVID19 (Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19)	NCT04325061	60 d	Dexamethasone	Mortality at 60 d
SevCov (Sevoflurane in COVID-19 ARDS)	NCT04355962	28 d	Sevoflurane×48 h	Composite mortality and organ failure
COVIDORNASE (Efficacy and Safety of Aerosolized Intra-tracheal Dornase Alfa Administration in Patients With COVID19-induced ARDS)	NCT04355364	7 d	Dornase-alfa	Improvement in ARDS severity
ICAR (Polyvalent Immunoglobulin in COVID-19 Related ARds)	NCT04350580	28 d	Human immunoglobulin	Ventilatory-free days
MACoVIA (MultiStem Administration for COVID-19 Induced ARDS)	NCT04367077	28 d	MultiStem (stem cell agent)	Ventilatory-free days
RUXCOVID-DEVENT (Assessment of Efficacy and Safety of Ruxolitinib in Participants With COVID-19-Associated ARDS Who Require Mechanical Ventilation)	NCT04377620	28 d	Ruxolitinib	Mortality
BREATHE (A Study to Assess the Efficacy and Safety of Gimsilumab in Subjects With Lung Injury or Acute Respiratory Distress Syndrome Secondary to COVID-19)	NCT04351243	43 d	Gimsilumab	Mortality
LEAF-4L7520/4L6715 (A Study of Trans Crocetin in Patients With Acute Respiratory Distress Syndrome Due to COVID-19 Disease)	NCT04378920	24 h	LEAF-4L6715	Proportion of patients with 25% of PaO_2:FiO_2 ratio
Valsartan for Prevention of Acute Respiratory Distress Syndrome in Hospitalized Patients With SARS-COV-2 (COVID-19) Infection Disease	NCT04335786	14 d	Valsartan	First occurrence of ICU admission, mechanical ventilation, or death
STROMA-CoV2 (Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS)	NCT04333368	7 d	Human MSC	Increase in PaO_2:FiO_2 ratio from baseline to day 7
CoDEX (COVID-19-associated ARDS Treated With Dexamethasone: Alliance Covid-19 Brasil III)	NCT04327401	28 d	Dexamethasone	Ventilator-free days
COMBATCOVID19 (COlchicine in Moderate-severe Hospitalized Patients Before ARDS to Treat COVID-19)	NCT04363437	2 mo	Colchicine	Percentage of patients requiring supplemental oxygen beyond 8 L nasal cannula
Fibrinolytic Therapy to Treat ARDS in the Setting of COVID-19 Infection	NCT04357730	48 h		PaO_2:FiO_2 improvement from pre- to post intervention
The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients	NCT04321616	3 wk	Remdesivir Hydroxychloroquine	In-hospital mortality
MP-C19 (Methylprednisolone for Patients With COVID-19 Severe Acute Respiratory Syndrome)	NCT04323592	28 d	Methylprednisolone	Death or ICU admission or invasive mechanical ventilation
NOSARSCOVID (Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19)	NCT04306393	48 h	Inhaled nitric oxide	Change of arterial oxygenation at 48 h from enrollment
NoCovid (Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19)	NCT04305457	28 d	Inhaled nitric oxide	Reduction in the incidence of patients with mild/moderate COVID-19 requiring intubation and mechanical ventilation

ARDS indicates acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICU, intensive care unit; MSC, mesenchymal stromal cells; and SARS-CoV, severe acute respiratory syndrome coronavirus.

Furthermore, a meta-analysis (N=341 patients) showed that a standardized mean difference in cardiac troponin-I of 25.6 ng/L corresponded to an increase in ICU admission, ARDS, or mortality.[21] Serial measurements are helpful in determining clinical risk and prognosis, although standardized guidelines are lacking at present.

Type 2 myocardial infarction from decreased oxygenation and hemodynamic stress accompanying ARDS in COVID-19 has been reported[22]; myocarditis attributable to cytokine storm and associated T-helper 1 and 2 cell response such as that seen previously with SARS-CoV infection; or myocarditis attributable to either direct involvement or infection of myocardial tissues by SARS-CoV-2. Some of the same factors driving type 2 myocardial infarction may also increase risk of true acute coronary syndromes in patients with COVID-19, the management of which is challenging because of concern about contagion and provider safety, and ECG mimicry of infarct attributable to myopericarditis.[23] Recently proposed guidelines suggest that computed tomographic coronary angiography may permit expedited evaluation for both acute coronary syndrome and myocarditis

because of limited availability of cardiac magnetic resonance imaging and exposure risk of catheterization laboratory staff with coronary angiography.[24] In some settings, routine thrombolytic therapy is proposed if access to percutaneous coronary intervention is limited or problematic.[25] A clinical trial assessing early prophylactic medical management of acute coronary syndrome using dual antiplatelet therapy, atorvastatin 40 mg, and low-dose rivaroxaban (2.5 mg daily) in hospitalized patients with COVID-19 is ongoing (NCT04333407).

Systemic hypotension is common in COVID-19 (≈50%), although data profiling cardiac dysfunction in hemodynamically unstable patients are lacking or mixed. In one series of 24 critically ill patients including 82% with shock, echocardiographic left ventricular wall motion abnormalities were not observed.[26] High-quality echocardiographic data are limited by prone positioning of some ICU patients as well as protocols to protect sonographers, suggesting potential value for point-of-care ultrasound (NCT04339998). In exceptional cases, persistent cardiogenic shock has necessitated the use of biventricular mechanical circulatory support. High-dose intravenous immune globulin and high-dose corticosteroids were reported to reverse COVID-19 myocarditis in one case[27]; however, high-dose corticosteroids are not routinely advised because of prolonged viremia and increased mortality observed

with treatment in SARS-CoV-1. Colchicine to prevent myocarditis, cytokine storm, mechanical ventilation, or mortality is being tested currently (NCT04355143, NCT04326790, NCT04350320, NCT04375202, NCT04328480, NCT04360980, and NCT04322682).

Given the dual role of membrane angiotensin-converting enzyme (ACE)-2 serving as the entry protein for SARS-CoV-2 and preserving endothelial barrier function in acute lung injury, there is uncertainty about whether ACE inhibitor or angiotensin receptor blocker medications, which may increase ACE-2 expression, should be continued, discontinued, or initiated in acute COVID-19 illness. Clinical data are mixed, with reports of increased mortality with inpatient use of an ACE inhibitor in one series[18] and decreased mortality with an ACE inhibitor or angiotensin receptor blocker in another,[28] both retrospective studies with multiple confounders. In one recent cross-sectional observational study involving 12 594 patients, the use of ACE inhibitors or angiotensin-receptor blockers was not associated with COVID-19 test positivity.[29] Current guidelines reflect equipoise with respect to initiating or discontinuing these medications, acknowledging that hypotension or shock may dictate practice. Several trials proposing randomization to cessation or initiation of these medications have been announced (NCT04338009, NCT04353596, NCT04351581, NCT04330300, NCT04338009, NCT04340557, NCT04345406, NCT04335786, NCT04364893). A list of pivotal clinical trials in COVID-19 is provided in Table 2.

Table 2.   **Selected Pivotal Clinical Studies in Patients With COVID-19**

PMID Number	Trial Identifier	Medication	Design/Patients (N)	Duration	Primary End Point	Results
32339248	NCT04323527	High-dosage chloroquine diphosphate (CQ): 600 mg twice daily×10 d Low-dosage CQ: 450 mg twice daily×4 d	Parallel, double-masked, randomized, phase IIb N=81	13 d	↓ Lethality by ≥50% in the high-dosage group vs low-dosage group	39.0% in the high-dosage vs 15.0% in low-dosage group
32187464	ChiCTR2 000029308	lopinavir-ritonavir (400–100 mg) twice daily×14 d	Randomized, controlled, open-label trial N=199	Median 16 d	Time to clinical improvement (improvement of 2 points on an ordinal scale or discharge from the hospital)	No significant difference in end point between treatments
32379955	…	Hydroxychloroquine 600 mg twice on day 1, then 400 mg daily for a median of 5 d vs patients not treated with hydroxychloroquine	Observational study involving patients admitted to the hospital N=1376	Median follow-up= 22.5 d	Composite of intubation or death in a time-to-event analysis	Hazard ratio for treated patients vs nontreated patients 1.04; 95% CI, 0.82–1.32
32356627	…	Prescription for ACE inhibitor or ARB vs no prescription for these medications	Population-based case-control study N=6272			No association between ACE inhibitor or ARB rx and COVID-19

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; and COVID-19, coronavirus disease 2019.

PULMONARY CIRCULATORY DISEASE

It is recognized increasingly that a subset of patients with COVID-19 demonstrate severe hypoxemia despite near normal lung mechanics. Recent data from dual-energy computed tomographic imaging show striking perfusion defects attributed to morphologic abnormalities in pulmonary arteries,[30] providing an anatomic correlate to impaired hypoxic pulmonary vasoconstriction suspected clinically.[31] Attenuated hypoxic pulmonary vasoconstriction is suspected to cause intrapulmonary shunting, leading to a severe reduction in the pulmonary venous oxygenation, poor oxygen delivery, and organ dysfunction.

Akin to the 2004 SARS-CoV-1, pulmonary hypertension has been reported in patients with COVID-19, possibly via in situ microthrombosis, gross thrombosis, or luminal embolism.[32] This could explain an inverse correlation between plasma D-dimer concentration and clinical outcomes and the potential beneficial effects of anticoagulant therapies suggested by preliminary data sets,[33] as well as data from one autopsy series reporting deep vein thrombosis in 7 of 12 (58%) patients.[32] The wider implications of pulmonary hypertension on right ventricular function includes cor pulmonale in a subset of ICU patients, although the prevalence of end-stage right heart failure across COVID-19 cohorts is not clear.[34] Nonetheless, thrombolytic agents should not be considered for routine management of patients with COVID-19 outside of clinical trials, and data profiling pulmonary vascular involvement in this syndrome remains forthcoming.

FUTURE PERSPECTIVES

Critical research is needed to clarify the totality of factors underlying hypoxemia in COVID-19, role of inhaled vasodilators, implementation of computed tomographic imaging for disease staging, and timing and appropriateness of noninvasive ventilation. This is particularly important because of wide-ranging clinical practice patterns that dominate management currently. Because COVID-19 is a rapidly evolving crisis with no end in sight at the time of this writing, we anticipate reporting further updates on our effort in critical care and cardiopulmonary medicine in the near future.

ARTICLE INFORMATION

Affiliations

From the Division of Cardiovascular Medicine (B.A.M., P.B.Y.), Brigham and Women's Hospital and Harvard Medical School, Division of Pulmonary, Allergy, and Critical Care and Heart, Lung, Blood, and Vascular Medicine Institute University of Pittsburgh, PA (M.T.G.); Pulmonary Hypertension Research Group, CRIUCPQ Laval University, Quebec, Canada (S.B.); Division of Pulmonary and Critical Care Medicine Stanford University, Stanford, CA (V.D.J.); Department of Emergency Medicine University of Colorado School of Medicine, Denver, CO (S.M.P.); and Anesthesia Center for Critical Care Research, Department of Anesthesia, Critical Care, and Pain MedicineAnesthesia Center for Critical Care Research, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA (F.I.)

REFERENCES

1. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, 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;8:475–481.
2. Canelli R, Connor CW, Gonzalez M, Nozari A, Ortega R. Barrier enclosure during endotracheal intubation. *N Engl J Med*. 2020;382:1957–1958.
3. Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, Klersy C, Palo A, Contri E, Ronchi V, et al. Out-of-hospital cardiac arrest during the Covid-19 outbreak in Italy. *N Engl J Med*. 2020. [Epub ahead of print].
4. Edelson DP, Sasson C, Chan PS, Atkins DL, Aziz K, Becker LB, Berg RA, Bradley SM, Brooks SC, Cheng A, et al. Interim guidance for basic and advanced life support in adults, children, and neonates with suspected or confirmed COVID-19: from the Emergency Cardiovascular Care Committee and Get With the Guidelines®-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration with the American Academy of Pediatrics, American Association for Respiratory Care, American College of Emergency Physicians, The Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists: Supporting Organizations: American Association of Critical Care Nurses and National EMS Physicians. *Circulation*. 2020 141:e933-e943.
5. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR Jr, Nahid M, Ringel JB, et al. Clinical characteristics of COVID-19 in New York City. *N Engl J Med*. 2020;382:2372–2374.
6. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, Oczkowski S, Levy MM, Derde L, Dzierba A, et al. Surviving sepsis campaign:

guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;8:e440–e469.

7. Bos LD, Paulus F, Vlaar APJ, Beenen LFM, Schultz MJ. Subphenotyping ARDS in COVID-19 patients: consequences for ventilator management. *Ann Am Thorac Soc*. 2020 May 12 [epub ahead of print].

8. Ziehr D, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, Hibbert KA, Thompson BT, Hardin CC. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. *Am J Respir Crit Care Med*. 2020;201:1560–1564. [epub ahead of print].

9. Bime C, Fiero M, Lu Z, Oren E, Berry CE, Parthasarathy S, Garcia JGN. High positive end-expiratory pressure is associated with improved survival in obese patients with acute respiratory distress syndrome. *Am J Med*. 2017;130:207–213.

10. Schultz MJ. High versus low PEEP in non-recruitable collapsed lung tissue: possible implications for patients with COVID-19. *Lancet Respir Med*. 2020;8:e44.

11. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020 Apr 13 [epub ahead of print].

12. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. Remdesivir for the treatment of COVID-19 - Preliminary Report. *N Engl J Med* 2020. [Epub ahead of print].

13. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382:2327–2336.

14. White DB, Lo B. A framework for rationing ventilators and critical care beds during the COVID-19 pandemic. *JAMA*. 2020;323:1773. [epub ahead of print].

15. Jentzer JC, van Diepen S, Murphree DH, Ismail AS, Keegan MT, Morrow DA, Barsness GW, Anavekar NS. Admission diagnosis and mortality risk prediction in a contemporary cardiac intensive care unit population. *Am Heart J*. 2020;224:57–64.

16. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020:e200950.

17. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506.

18. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020:e201017.

19. He XW, Lai JS, Cheng J, Wang MW, Liu YJ, Xiao ZC, Xu C, Li SS, Zeng HS. [Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48:E011.

20. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.

21. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. *Prog Cardiovasc Dis*. 2020 Mar 10 [epub ahead of print].

22. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol*. 2020 Mar 27. [epub ahead of print].

23. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020 Mar 27 [epub ahead of print].

24. Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, Cooper JT, Chahal CAA. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm*. 2020:S1547-5271(20)30422-7.

25. Daniels MJ, Cohen MG, Bavry AA, Kumbhani DJ. Reperfusion of STEMI in the COVID-19 era-business as usual? *Circulation*. 2020;141:1948–1950.

26. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, et al. COVID-19 in critically ill patients in the Seattle region-Case series. *N Engl J Med* 2020;382:2012-2022.

27. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J*. 2020 Mar 16 [epub ahead of print].

28. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin ii receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126:1671–1681.

29. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med*. 2020;382:2441–2448.

30. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, Li MD, Witkin A, Rodriguez-Lopez JM, Sheppard JO, et al. Hypoxaemmia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. *Lancet Infect Dis*. 2020:S1473-3099(20)30367-4.

31. Rello J, Storti E, Belliato M, Serrano R. Clinical phenotypes of SARS-CoV-2: implications for clinicians and researchers. *Eur Respir J*. 2020;55:2001028.

32. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med*. 2020:M20–M2003.

33. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18:1094–1099.

34. Creel-Bulos C, Hockstein M, Amin N, Melhem S, Truong A, Sharifpour M. Acute cor pulmonale in critically ill patients with Covid-19. *N Engl J Med*. 2020;382:e70.