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In Defense of Evidence-based Medicine for the Treatment of COVID-19 Acute Respiratory Distress Syndrome

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Severe acute respiratory failure from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease (COVID-19) has challenged intensivists worldwide with both increased severity of illness and quantity of patients. An extraordinary amount has been published about presentation, treatment, and outcomes of these patients in both medical journals and social media. Less than 6 months since the first reported case, a search for COVID-19 in PubMed finds more than 5,000 publications. Unfortunately, most of these reports are anecdotal, with few comparative, scientific studies among them. Similarly, Twitter and other social media platforms have been abuzz with anecdotes and "expert" advice as to how to care for these patients. Many of those pieces of advice have represented small-sample clinical experience or uncontrolled experiments, often without consent or regulatory oversight, with off-label uses of already-approved medications aimed at treating some mechanistic pathway or presumed pathophysiology extrapolated from a limited number of these patients. For example, on the basis of a case series of 21 patients published in a Chinese preprint (1), off-label use of the interleukin-6 receptor antagonist tocilizumab has been proposed to treat the "cytokine storm" that many have postulated causes the multisystem organ dysfunction seen with critically ill patients with COVID-19. Recently, off-label use of inhaled nitric oxide to prevent intubation and empiric anticoagulation or thrombolysis to treat the microthromboses seen in the lungs on autopsy (2) has also been proposed. Although many effective treatments start with similar postulates, these modalities can only demonstrate effectiveness, and thus become evidence-based treatments, in well-designed, placebo-controlled randomized trials. All too often in critical care, hypotheses based on mechanism and observation failed the test of the randomized trial.

The arguments on social media are based more in emotion than science. "We cannot just do nothing for these patients." As much as the "don't just stand there, do something" feeling is real, it is also likely dangerous to our patients. The prevailing evidence in critical care suggests that "doing less is more," as the more we try to interfere or disrupt the pathways of critical illness, the worse the patient outcomes. The inflammatory and coagulation cascades of critical illness are intertwined, complicated, and still poorly understood. To assume that we can target pathways in either or both cascades and improve the outcomes of our patients is naive and hubristic, as we have seen numerous times in the past with failed randomized trials of antiinflammatory and anticoagulant agents, such as anti-TNF (3), β-interferon (4), recombinant human activated protein C (5), and statins (6). Novel treatments must be studied in randomized controlled trials to truly understand both their benefits and their



risks (7), especially because recent data suggest about 95% of critical care trials fail to demonstrate benefit (8), rendering the pretest probability very low. Yet many of the past 30 years of failed critical care research hypotheses have been resurrected in hopes of providing novel COVID-19 treatments.

Although the desire to try to treat these patients with already approved drugs is understandable, what is less understandable is the desire in medical publications and on social media to abandon the principles of evidence-based critical care that we have established over the last 3 decades (9), because "I have never seen patients with ARDS act like this." Large, well-designed, multicenter randomized trials have set the foundation of an evidence-based practice of how to produce the best outcomes for critically ill patients. Abandonment of these principles in the face of this pandemic, without any supporting scientific data, simply because we are scared or

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overwhelmed, because we believe after a few months of anecdotal experience that we have recognized an entirely unique syndrome, or because we have not had time to conduct randomized controlled trials specifically in these patients, is clearly unacceptable. Outcomes of critically ill patients have improved steadily over the last 3 decades, not through the approval of new pharmacologic agents or by discovering some unique physiology in a new disease. Instead, improved outcomes are seen through understanding and implementing best practices derived via strong scientific evidence generated from well-designed randomized controlled trials into the routine care of critically ill patients. In other words, doing the things we do, and doing them well. Lung-protective ventilation with lower tidal volumes reduces mortality and shortens duration of ventilation in patients with ARDS (10), even those who have relatively preserved compliance (11), like that being seen early in the ARDS course of patients with COVID-19. In addition, randomized trials in ventilated patients without ARDS have also demonstrated improved outcomes with similar lung-protective ventilation strategies using tidal volumes around 6 ml/kg predicted body weight (12). Studies demonstrating benefit from higher tidal volumes in patients with higher compliance are nonexistent, and to think that after a few months of experience we have found a special population that we should ventilate differently than all others seems nonsensical. Similarly, higher levels of positive end-expiratory pressure (PEEP) (13) and prone positioning (14) have both been demonstrated to improve mortality in patients with severe ARDS, as defined by oxygenation and not lung compliance.

Maintaining other principles of good critical care, as demonstrated in large, multicenter randomized trials, will also improve outcomes in these critically ill patients with COVID-19, even if "COVID-19 is completely different from other intensive care unit syndromes." Conservative fluid management once out of shock and without renal failure increases time alive and free from ventilation (15). Although frequently more difficult in these patients, concurrently timed daily awakening and spontaneous breathing trials, with close monitoring at the patients' bedside and efficient extubation after 30 minutes, sometimes using low-dose dexmedetomidine, can successfully liberate these patients from the ventilator faster (16), making that ventilator available for the next critically ill patient. Checklists for placement of central lines (17) and other infection prevention strategies will decrease health care–acquired infections and reduce length of stay. Many have recommended avoiding noninvasive ventilation or high-flow nasal cannula because of risk of increasing aerosolization (18). However, these recommendations fail to reference any studies or supporting data demonstrating this to be the case in patients with COVID-19 and are contrary to both the Surviving Sepsis Campaign (19) and Australian and New Zealand Intensive Care Society Guidelines (20) for treating COVID-19, both of which recommend using these devices. Changing practice to avoid these oxygen-delivery devices has dramatically altered the care of patients with COVID-19, potentially to their detriment (21). In a pandemic that is projected to sicken millions and cause acute respiratory failure and critical illness in tens or hundreds of thousands, removing evidence-based respiratory support devices entirely from our arsenal of weapons to fight COVID-19 and intubating everyone "early" will certainly result in a losing battle.

ICU capacity, ventilator supplies, and survival during the COVID-19 pandemic could all be increased today if the critical care community practiced the evidenced-based principles discovered over the last 3 decades. Innumerable randomized controlled trials have produced the robust knowledge necessary to care for patients with COVID-19 while we await high-quality evidence of whether any new therapies improve outcomes. Improving capacity and survival will be accomplished by using noninvasive ventilation or high-flow nasal cannulas to prevent intubation or reintubation. In the intubated patient, the use of lung-protective ventilation, PEEP, prone positioning if needed, a conservative fluid-management strategy, and paired awakening and spontaneous breathing trials have all been shown to improve outcomes.

In this time of increased work and uncertainty, many have forgotten everything that we do for our critically ill patients. Hopefully, this is because we do it so often that it becomes second nature and therefore is not thought of as special treatment. However, potentially worse, practitioners may not have forgotten but may be purposefully treating patients differently in their desire to feel like they "are doing something." Not giving a medication lacking high-quality evidence of benefit does not equal just standing there and doing nothing. To the contrary, providing evidence-based critical care is more than just doing something for our patients. It is providing them with the best possible chance of surviving without complications and not putting them at risk for poor outcomes from non–evidence-based care. "Fortune favors the bold," and we should boldly institute the evidence-based medicine we have been taught by the physician, nursing, and respiratory therapy giants that have come before us. It is our obligation, what our patients expect from us, and exactly what we owe them. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Xu X, Han M, Li T, Sun W, Wang D, Fu B, *et al*. Effective treatment of severe COVID-19 patients with tocilizumab [preprint]. ChinaXiv: 202003.00026v1. 2020 [2020 Apr 15]. Available from: http://www.chinaxiv.org/abs/202003.00026.

2 Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA,*et al*. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. *J Thromb Haemost* [online ahead of print] 8 Apr 2020; DOI: 10.1111/jth.14828.

3 Bernard GR, Francois B, Mira JP, Vincent JL, Dellinger RP, Russell JA, *et al*. Evaluating the efficacy and safety of two doses of the polyclonal anti-tumor necrosis factor-α fragment antibody AZD9773 in adult patients with severe sepsis and/or septic shock: randomized, double-blind, placebo-controlled phase IIb study. *Crit Care Med* 2014;42:504–511.

4 Ranieri VM, Pettilä V, Karvonen MK, Jalkanen J, Nightingale P, Brealey D, *et al*. Effect of intravenous interferon β-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: a randomized clinical trial. *JAMA* [online ahead of print] 17 Feb 2020; DOI: 10.1001/jama.2019.22525.

5 Liu KD, Levitt J, Zhuo H, Kallet RH, Brady S, Steingrub J, *et al*. Randomized clinical trial of activated protein C for the treatment of acute lung injury. *Am J Respir Crit Care Med* 2008;178:618–623.

6 Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, *et al*.; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014;370:2191–2200.

7 Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Chi-Chung Cheng V, *et al*. Infectious Disease Society of America guidelines on the treatment and management of patients with COVID-19 infection. 2020 [accessed 2020 Apr 16]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.

8 Harhay MO, Wagner J, Ratcliffe SJ, Bronheim RS, Gopal A, Green S, *et al*. Outcomes and statistical power in adult critical care randomized trials. *Am J Respir Crit Care Med* 2014;189:1469–1478.

9 Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Resp Crit Care Med* [online ahead of print] 30 Mar 2020; DOI: 10.1164/rccm.202003-0817LE.

10 Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.

11 Hager DN, Krishnan JA, Hayden DL, Brower RG; ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005; 172:1241–1245.

12 Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, *et al*.; IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013;369:428–437.

13 Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, *et al*. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865–873.

14 Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, *et al*.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.

15 Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, *et al*.; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564–2575.

16 Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, *et al*. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008;371:126–134.

17 Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, *et al*. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006;355:2725–2732.

18 Brown CA, Mosier JM, Carlson JN, Gibbs MA. Pragmatic recommendations for intubating critically ill patients with suspected COVID-19. *JACEP Open* [online ahead of print] 25 Mar 2020; DOI: 10.1002/emp2.12063.

19 Alhazzani W, Moller MH, Arabi YM, Loeb M, Gong MN, Fan E, *et al*. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med* [online ahead of print] 28 Mar 2020; DOI: 10.1007/s00134-020-06022-5.

20 Australian and New Zealand Intensive Care Society. ANZICS COVID-19 Guidelines. Melbourne: ANZICS; 2020 [accessed 16 Apr 2020]. Available from: https://www.anzics.com.au/wp-content/uploads/2020/03/ANZICS-COVID-19-Guidelines-Version-1.pdf.

21 Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, *et al*.; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185–2196.