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Influenza and COVID-19: Times Don't Get No Better

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The enormous human toll exacted by the coronavirus disease (COVID-19) pandemic has few precedents. Since the start of the outbreak, however, physicians have debated how novel the disease itself is. It is now conclusively established that, in its most severe form, COVID-19 meets the clinical definitions of acute respiratory distress syndrome (ARDS) (1, 2) and is appropriately treated with evidence-based protocols established for ARDS of other causes (3). Nevertheless, ARDS is a heterogeneous syndrome and not a single disease (4), and its course may vary by specific etiology (5). To date, rigorous comparisons of severe COVID-19 with other etiologies of ARDS have been lacking and discussions around disease heterogeneity in COVID-19 have proceeded largely without reference to high quality data. In this issue of *AnnalsATS*, Cobb and colleagues (pp. 632–640) supply some of that much needed data in the form of an analysis that compares patients admitted to the intensive care unit (ICU) with influenza and those admitted with severe COVID-19 at the same centers over roughly the same time period (6).

The authors report on 65 patients admitted to a medical ICU at two medical centers with COVID-19 and 74 patients admitted to a medical ICU with influenza over the period January 1, 2019, to April 15, 2020. Overall, patients with COVID-19 presented later after symptom onset. Both groups were older, predominantly male, and had similar rates of comorbidities with the exception of chronic obstructive pulmonary disease (COPD), which was more likely in the influenza group. Among intubated patients, disease severity measured by respiratory system compliance and the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen was similar in the two groups on presentation; however, patients with COVID-19 were more likely to meet a diagnosis of ARDS because of a greater incidence of bilateral infiltrates. Patients with COVID-19 were more likely to receive prone ventilation but were less likely to receive bilevel noninvasive positive-pressure ventilation than the influenza group. Despite all of these similarities, mortality was notably higher among patients with COVID-19. Specifically, in a multivariate analysis, COVID 19 was associated with a twofold increase in the rate of death, after adjusting for age, sex, the number of comorbidities, and sequential organ failure assessment score. This increased risk of mortality was true despite no increase in the need for mechanical ventilation, vasopressors, or renal replacement therapy in the COVID-19 group and an increased incidence of bacterial superinfection in the influenza group.

What should we make of these data? One clear lesson is that the sickest patients with both viral infections present similarly, confirming prior reports that although the size of the pandemic is unique, the clinical presentation is not. It is less clear, however, why patients with COVID-19 more frequently presented with bilateral infiltrates and why the risk of mortality was so much greater. Patients with COVID-19 presented later after symptom onset, which may have led to a more advanced pulmonary disease at the time of hospitalization. Markers of severity on Day 2 and Day 3 were also worse in patients with COVID-19, suggesting they became sicker during their ICU stay than the patients with influenza, and the proportion requiring ventilation for more than 7 days was higher in the COVID-19 group.

One seemingly compelling explanation for the disparity may be dismissed. Mortality in COVID- 19 was higher in early centers of the outbreak (7), suggesting that perhaps the availability of ICU resources contributed to the highly heterogeneous

reported outcomes. Cobb and colleagues, however, report no increase in the daily ICU census during the COVID-19 pandemic making that an unlikely explanation for their findings. More patients in the influenza group had bacterial pneumonia and so their more rapid improvement could reflect the availability of specific therapy in the form of antibiotics. Moreover, virtually all of the influenza group received antiviral medications but at the time of the study, remdesivir was only available in the context of a placebo-controlled trial. The most common specific therapy in the COVID-19 group was hydroxychloroquine, now known to be ineffective (8). It seems possible, therefore, that the higher mortality in COVID-19 reflects the more limited therapeutic options. Indeed, there was a higher rate of steroid use in the influenza group, reflecting both the low rate of steroid use in patients with COVID-19 at these centers at that time and, perhaps, the higher rate of COPD in the influenza group. Because the cases were gathered early in the outbreak, these data do not reflect any possible benefit of the now standard COVID-19 therapies of remdesivir and dexamethasone.

In addition to the availability of specific therapies, it is possible other treatment approaches varied between the two groups. In particular, sedation strategy and approach to ventilator liberation are known to contribute to the length of mechanical ventilation and may vary between patients with COVID-19 and patients without COVID-19 (9). Early on in the pandemic, there was also significant debate about

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whether COVID-19 respiratory failure was truly ARDS; however, there is no indication that the COVID-19 group did not receive evidence-based ARDS care on the basis of the similar driving pressures and high rates of proning in the COVID-19 group. In summary, this important work highlights both the severity of COVID-19 and the limited range of specific therapies, particularly early in the pandemic, while also confirming the overall similarity in the presentation of COVID-19 ARDS to other etiologies. It remains to be seen if the experience and therapeutics we have gained since those early days will improve outcomes in COVID-19, or if to quote Muddy Waters, the times don't get no better. ■

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

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Is Preoperative Exercise Training the New Holy Grail for Patients Undergoing Major Surgery?

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Surgical advances and postoperative care have improved recovery from most major surgeries. However, despite advances in perioperative care that have improved safety and accessibility for patients potentially at risk, there remains a group of patients who still have suboptimal recovery. Approximately 20–50% of patients undergoing surgery develop a postoperative complication with resulting increases in hospital length of stay and subsequent increases in overall healthcare costs. After surgery, patients also experience physical fatigue and periods of physical inactivity–induced loss of muscle mass, deconditioning, and poor quality of life (1). These complications occur predominantly in moderate- to high-risk patients who often present with modifiable risk factors.

An emerging body of evidence reports that the preoperative status of the patient has a critical impact on postoperative recovery (2, 3). Prehabilitation describes the process of enhancing preoperative functional capacity to enable patients to withstand the stress associated with a pending major procedure. Prehabilitation intervention may involve a single mode or be multimodal in addition to offering medical optimization concentrating on patient nutritional, psychological, and/or physical preoperative status, with the main aim of improving readiness for impending surgery.

In this issue of *AnnalsATS*, Assouline and colleagues (pp. 678–688) contribute to the growing body of evidence on the role of preoperative exercise (4). The authors report results of a systematic review with

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