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The Coronavirus Pandemic – At the Beginning of the Learning Curve



“In many ways, it is hard for modern people living in First World countries to conceive of a pandemic sweeping around the world and killing millions of people, and it is even harder to believe that something as common as Influenza could cause such widespread illness and death.”

These were the words used by the Charles River editors in their book titled “The 1918 Spanish Flu Pandemic: The History and Legacy of the World’s Deadliest Influenza Outbreak.”¹ Sadly, these words are once again relevant as the SARS-CoV-2 coronavirus finds its way around the globe. At the time of this writing, over 7.5 million cases of Coronavirus Disease 2019 (COVID-19) have been confirmed worldwide with close to 450,000 deaths; over 100,000 of these deaths occurring in the United States. During this time, traditional and social media have been bombarded with new information related to the pandemic. So too have professional and scientific journals. Unfortunately, submissions with appropriate studies and well-considered conclusions have been almost as frequent as documents full of speculation and bias, making it difficult to dissect useful information from the rest.

The experience of the AJMS has been no different. Since late January, the number of manuscript submissions has more than doubled. Under such circumstances, the editorial team has worked to identify high quality and relevant articles that provide new information or that complement rather than duplicate the published literature. Unfortunately, the rapidly changing nature of the pandemic, the breath of information available, and our interest in the quick dissemination of potentially useful knowledge conflicts with the inherent slower pace of manuscript publication (designed to ensure appropriate peer-review, opportunities for revision, and printing, for example), which may lead to the publication of redundant articles and even obsolete information. Nevertheless, consistent with the Journal’s mission, we hope that the process allows the readership to judge the impact of the pandemic and proposed interventions, while we contribute to the historic record about actions and missteps undertaken to address this crisis.

In this issue of the Journal, Huang et al report on the clinical characteristics and predictors of disease progression in patients with COVID-19 in the Jiangsu Province of China.² Notably, this manuscript focuses on 60 cases classified as severe. Not surprisingly, the investigators found that higher levels of troponin and the

application of noninvasive mechanical ventilation were predictors of disease progression, whereas higher lymphocyte count and early proning maneuvers were associated with improvement. On the other hand, the very low mortality rate described in such patients was unexpected. This might be related to the definition of severity used for inclusion in the study consisting of subjects with respiratory distress (respiratory rate >30/minute), hypoxemia (<93% hemoglobin oxygen saturation or oxygenation index <300 mm Hg), and respiratory failure requiring mechanical ventilation. Only 15% and 26.7% of patients included developed acute respiratory distress syndrome or respiratory failure, respectively, and APACHE prognostic scoring was not very high.

The article highlights several points that have emerged in the COVID-19 literature over the past 2 months including the observation that males, older individuals, and patients with co-morbidities have a worse prognosis. It also highlights the fact that during the early part of the pandemic, in their desperate search for effective interventions, clinicians have tried many and varied therapies for the disease based on information from treatment of other viral diseases and inferences from mechanisms of action. This approach may lead one to conclude that one therapy may be effective when it is not, or not effective when it might be. For example, Huang et al identified an association between the use of interferon with disease progression, a seemingly paradoxical finding considering the antiviral properties of the reagent. However, the authors do not tell us why or when only 20% of the patients received interferon. The interferon may have been tried later for patients who were very sick and less likely to respond to any additional therapy regardless. Interferon may, in fact, be an effective agent for the treatment for COVID-19 if given at the right time and severity of the disease. Only a prospective randomized clinical trial could determine this. The same could be said for other agents like hydroxychloroquine, antibiotics, cytokine inhibitors, immunoglobulin, corticosteroids, and other antivirals. Thus, the pandemic has again unearthed the almost primal but understandable need that providers experience when confronted with a dying patient in the absence of well-studied and proven interventions – do something now!

Another point highlighted by this manuscript is the usefulness of the proning maneuver. In contrast to the pharmacological interventions described above, this represents a physical maneuver that has been proposed to work in the treatment of the acute respiratory distress syndrome (ARDS) for over 30 years.³ It is now well known that COVID-19 may promote the development of ARDS, a condition characterized by relatively acute onset of hypoxemia and diffuse bilateral lung opacities on chest imaging resulting from noncardiogenic pulmonary edema and inflammation. As first described in 1967,⁴ the hypoxemia is refractory; in other words, it is severe and in those days it frequently required the implementation of mechanical ventilation to appropriately support the patient. Today, the availability of noninvasive ventilation,

high-flow ventilation, and other modalities limits, delays, and perhaps sometimes prevents the need for more aggressive interventions. However, in cases showing progression, clinicians often consider “salvage therapies” including unconventional ventilator modes, recruitment maneuvers, and extracorporeal membrane oxygenation. Proning is another one of these therapies.

Proning is proposed to improve ventilation-perfusion matching by reducing differences in ventral-dorsal transpulmonary pressures, thereby promoting a more homogeneous lung inflation. However, several clinical trials testing its effectiveness showed mixed results consisting of improvements in oxygenation, but little impact on mortality.³ A meta-analysis of studies conducted before 2013 suggested a benefit, but it was not until the PROSEVA study that a survival benefit was clearly identified in a prospective fashion; the study showed a 28-day mortality in the prone-positioning group of 16% when compared to 32.8% in the supine or control group.⁵ The strict nature of the diagnostic classification used for study inclusion, the complementary methods utilized, the length of the intervention and the experience of the staff and investigators involved in implementing the technique, among other factors, likely contributed to the outcome in that study. Proning, however, is not for every patient with refractory hypoxemia, as it requires a trained team to implement the maneuver safely. Further, contraindications include severe facial and neck trauma, elevated intracranial pressure, pelvic/spinal instability, hemoptysis or high probability of the patient requiring cardiopulmonary resuscitation. Nevertheless, experts suggest the use of proning in patients with moderate-to-severe ARDS and refractory hypoxemia, a position further supported by the American Thoracic Society⁶ and the Surviving Sepsis Campaign COVID-19 Panel.⁷ What is intriguing about the use of proning in COVID-19 patients is its early and successful implementation in hospitalized patients with progressive hypoxemia prior to instituting mechanical ventilation.⁸ This suggests that perhaps proning is most effective earlier than previously anticipated. Of course, the intrinsic characteristics of the inflammatory process triggered by SARS-CoV-2 might be responsible for the observed effect, rendering the intervention less likely to be generalized to other conditions. Further work will be required to determine the appropriate timing of proning in COVID-19 and its impact on mortality.

Finally, the reader should note that this issue of the Journal also includes a commentary about how the Coronavirus pandemic has again unveiled historical residues that promote healthcare disparities in the United States. In addition, we include letters that address COVID-19 related topics such as the controversy about hydroxychloroquine, the surge in methanol poisoning in Turkey, the impact on internal medicine trainees in the Caribbean, and questions remaining about retesting before going back to work, among others. Undoubtedly, much will be learned about SARS-CoV-2 and COVID-19 over the next months. Considering the ingenuity of our healthcare providers and scientists, such information is expected to lead to safe and effective means of prevention and treatment for a disease that has proven devastating to so many. In the meantime, public health measures like social distancing have proven useful around the globe and continue to remain the centerpiece of the fight against the pandemic. Hopefully, information accumulated during the next few months will serve to guide us well during the projected re-emergence of COVID-19 or that of another pandemic.

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