EDITORIAL

Acute respiratory distress syndrome and steroids in the shadow of coronavirus disease 2019

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The coronavirus disease 2019 (COVID-19) pandemic generated unprecedented efforts to find beneficial management strategies. These efforts include not only observational and experimental studies performed in the COVID-19 population but also attempts to gain new knowledge from previous studies and data on similar diseases (eg, influenza) or similar pathophysiological states (eg, septic shock or acute respiratory distress syndrome [ARDS]).

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Mammen et al[1] address the question of steroid use in ARDS, but the real clinical question is steroid use in severe COVID-19. As of the beginning of April 2020, we have no direct data answering such a pressing question, hence the attempt to use indirect evidence from studies on other diseases. Such a process requires intellectual endeavors to develop constructs and make assumptions, which also means relying on leaps of faith.

First, the paradoxically simplest issue is the use of steroids in ARDS. This clinical syndrome of significant hypoxia is defined by its timing (within a week of a known clinical insult), presence of bilateral pulmonary opacities, and exclusion of cardiac origin.[2] In its previous reiterations, the definition also included decreased lung compliance (measured as a ratio of tidal volume in response to applied pressure; a value less than 40 ml/cm H_2O is considered decreased). This criterion, although true, was dropped in the most recent definition of ARDS as not contributing to its predictive validity. The common triggering factors leading to ARDS include pneumonia, nonpulmonary sepsis, aspiration, pulmonary trauma, severe pancreatitis and burns, noncardiogenic shock, and transfusion-related acute lung injury.

In the last 2 months, I became aware of 2 groups performing parallel meta-analyses on steroid use in patients with ARDS. One of them presents its data in the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*).[1] Thankfully, these 2 groups are reaching effectively identical results and conclusions: the application of steroids in ARDS is likely associated with reduced mortality and shorter duration of ventilation at an acceptable expense of hyperglycemia and neuromuscular weakness.

However, the second issue, namely, how to apply this concept and data to the COVID-19 pandemic, is more relevant and prevalent in this turbulent time. The problems arise from the fact that bilateral infiltrates associated with hypoxia in the course of COVID-19 do not always equal ARDS. First, the possibility of myocardial dysfunction leading to cardiogenic pulmonary edema and mimicking ARDS is a simpler issue. More importantly, however, a similar picture may be present in the course of diffuse viral pneumonitis. The differentiation of pneumonitis from ARDS may not be simple. Helpful hints favoring ARDS include low pulmonary compliance, responsiveness to positive end-expiratory pressure and recruitment maneuvers, and a better response to prone positioning.[3] Relatively good compliance, with smaller ventilation-perfusion (V-Q) mismatch and a relatively weak response to recruitment maneuvers, increased positive end-expiratory pressure, and prone positioning, favors pneumonitis. Why is this important? Although the judgment of clinical experts through the last several decades fluctuated, current evidence points to the benefit of steroids in community-acquired pneumonia, septic shock, and ARDS.[4,5] There is, however, an important exception: low-quality data suggest that the use of steroids in the course of viral pneumonia may increase mortality.[6]

The issue of using or not using steroids in ARDS-like situations has thus many shades. The answer depends on the context. For "classic" ARDS observed in the majority of patients included in the past ARDS trials, the answer is likely yes. The answer for patients with an ARDS-like picture in the course of COVID-19 is more nuanced. Most recent guidelines providing advice

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on the management of COVID-19 reflect this dilemma suggesting not using steroids in patients with COVID-19 and respiratory failure but without ARDS and suggesting steroid use in mechanically ventilated adults with COVID-19 and ARDS. Both suggestions were made while recognizing low quality of evidence (low certainty, low confidence in the data) and practical difficulties in categorizing lung infiltrates as related to ARDS or not.[7]

This brings me to reflect on 2 issues. The first one is the perceived power of evidence-based medicine to tell us, clinicians, what to do. It seems that the most sophisticated ways of combining existing data yield results which depend almost completely on what data are available and how physicians interpret the clinical context. The second issue is more acute: we have gone through the outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), that is, 2 other coronavirus-related diseases. The number of patients with these conditions was relatively low, and the number of patients with influenza is much higher and thousands of people die of it every year. Yet, our knowledge of how to fight these viral diseases is very limited and even today we do not know if steroids are beneficial or harmful in their course. We cannot afford the same situation with COVID-19. Some innovative, adaptive-design randomized clinical trials are performed or planned as of now (unfortunately, there is an abundance of patients with severe presentation). Thanks to their innovative design, patients are offered tested interventions in different combinations so that almost every patient is receiving "something." This may alleviate ethical and emotional reservations about using "nothing" in the course of a potentially lethal disease. It is our shared responsibility to learn, once this pandemic progresses, if not only steroids but also antiviral drugs, hydroxychloroquine, azithromycin, interleukin-6 receptor antagonists, convalescent sera, anticoagulation, or many other proposed treatment candidates do more good than harm.[8]

It is often difficult to practice in the spirit of evidence-based medicine. Realizing how little confidence we may have in the existing data provokes anxiety. Nevertheless, decisions have to be made in face of uncertainty. Until new data arrive (within several weeks, I would hope), my own bottom line, when faced with COVID-19–related respiratory failure and a clinical picture suggestive of ARDS rather than "simple" viral pneumonia, is to use steroids at a reasonable dose, that is, 40 to 80 mg of methylprednisolone or its equivalent per day.

ARTICLE INFORMATION

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