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Perspective

Corticosteroids in the treatment of severe COVID-19 lung disease: The pulmonology perspective from the first United States epicenter

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A B S T R A C T
The SARS–CoV–2 pandemic has introduced the medical community to a lung disease heretofore unknown to most clinicians. In much of the discourse about COVID-19 lung disease, the more familiar clinical entity of acute respiratory distress syndrome (ARDS) has been used as the guiding paradigm. Reflecting on studies in ARDS, particularly that caused by influenza, and on data from the SARS-CoV and MERS epidemics, many authorities, including those within the discipline of infectious diseases, were initially passionate in their opposition to the use of corticosteroids for lung involvement in COVID-19. The voice of the pulmonology community—the community of lung experts—has continued to be among the quietest in this conversation. Herein we offer our perspective as academic pulmonologists who encountered COVID-19 in its first United States epicenter of New York City. We encourage a conceptual separation between early COVID-19 lung involvement and ARDS. We draw on history with other immune cell-mediated lung diseases, on insights from the SARS-CoV experience, and on frontline observations in an attempt to allay the skepticism towards corticosteroids in COVID-19 lung disease that is likely to persist even as favorable study results emerge.

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As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic first swept across the globe in the first quarter of 2020, the management of the associated clinical entity termed coronavirus disease 2019 (COVID-19) became the subject of institutional recommendations (Massachusetts General Hospital, 2020), societal guidelines (Bhimraj et al., 2020), and position statements (Russell et al., 2020). Because acute respiratory failure (ARF) in COVID-19 is triggered by a viral pathogen, it is understandable that the discussion of this potentially devastating illness has centered on its infectious disease and epidemiologic implications. However, as pulmonologists who treated severe COVID-19 patients in the first United States epicenter of New York City, we believe that something important has been under-emphasized in this discourse. At the “heart” of COVID-19 is a lung disease, and a question that has still not been raised often enough is – what exactly is the nature of the lung disease caused by SARS-CoV-2? More specifically, when progression to lung involvement appears, what would one see under the microscope in a section of lung tissue? This hypothetical question is of utmost importance because frontline experience indicates that reversal of COVID-19 lung disease and avoidance of prolonged invasive mechanical ventilation (IMV) is pivotal. All too frequently, the features of lung involvement in severe COVID-19 have been conflated with the acute respiratory distress syndrome (ARDS), a clinically defined entity intended to correspond to the histological lung injury pattern known as diffuse alveolar damage (DAD). The correlation between ARDS and pathological DAD is highly imperfect (Thille et al., 2013), and ARDS has a number of well-described mimics among diffuse lung diseases with acute presentations (Schwarz and Albert, 2004). The importance of differentiating ARDS from its mimics is that, unlike DAD, many histological patterns in the mimic category are exquisitely corticosteroid-sensitive. Early in the pandemic, it was recognized that the physiological behavior of COVID-19 lung disease is often distinct from that typically encountered in ARDS/DAD (Gattinoni et al., 2020). To the trained eye of a pulmonologist,
the thoracic imaging appearance of early COVID-19 lung disease is less reminiscent of corticosteroid-resistant ARDS/DAD and more reminiscent of corticosteroid-sensitive substrates such as organizing pneumonia (OP), acute eosinophilic pneumonia (AEP), and vasculitis (Hani et al., 2020; Nencic et al., 2012). Although both influenza and coronavirus infect respiratory epithelial cells, there is histopathological evidence from the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV) epidemic to suggest that the former has a more dramatic propensity than the latter for catastrophic lung injury in the form of DAD (Ng et al., 2006). Clinicoanatomical differences between COVID-19 lung disease and influenza are likewise emerging to support the histopathological observations (Tang et al., 2020). This is consistent with our clinical experience with COVID-19. Figure 1 depicts the chest radiographs (CXR) of three representative patients with COVID-19 admitted to the intensive care unit (ICU) of our institution; each row of the panel corresponds to a single patient. The CXRs on the left (panels A, C, E) were obtained on the day of ICU admission while the CXRs on the right (panels B, D, F) were obtained less than 24 h later. In each case, the only pharmacological intervention these patients received between the two CXRs that could account for a dramatic improvement in lung consolidation within such a short period of time is a single 1 g “pulse” dose of methylprednisolone. This type of radiographic behavior is decidedly uncharacteristic of ARDS/DAD but is quite characteristic of the corticosteroid-sensitive ARDS/DAD mimics mentioned above. While caring for scores of severe COVID-19 lung disease patients and repeatedly witnessing a striking clineroanradiographic response to pulse corticosteroids, we were disheartened by the initial negativity towards corticosteroids expressed by, among others, our infectious disease colleagues (Massachusetts General Hospital, 2020; Bhimraj et al., 2020; Russell et al., 2020). Although benefit suggested by recent observational (Fadel et al., 2020) and (preliminary) clinical trial (Horby et al., 2020) results has led to guideline revisions in favor of corticosteroids (Bhimraj et al., 2020), many skeptics have not relented since the early months of the pandemic. Opposition to corticosteroid use for COVID-19 lung disease typically rests on one or both of the following arguments:

a Corticosteroids are an ineffective pharmacotherapy for ARDS, most notably ARDS secondary to influenza
b Corticosteroid use has been associated with harm in the SARS-CoV epidemic as well as during the outbreak of the middle eastern respiratory syndrome (MERS) caused by another coronavirus

We contend that there are grounds to reconsider both premises. We have already mentioned the pitfalls of automatically subsuming severe COVID-19 lung disease under the rubric of ARDS, including ARDS in the setting of influenza, as the two viruses likely differ with respect to clineroanradiological and histological behavior in the lung (Hani et al., 2020; Tang et al., 2020). Unfortunately, for reasons that are apparent, most of our understanding of the histopathology of COVID-19 lung disease—as is the case with SARS-CoV—has been based on results of autopsies. This is extremely problematic because lung tissue obtained from patients with terminal lung failure, whether occurring early or late in the clinical course, is likely to reveal a predominance of DAD obscuring the original substrate. Nevertheless, from a number of reports describing the postmortem (Nicholls et al., 2003; Zhang et al., 2020) and even antemortem (Tian et al., 2020; Pogatchnik et al., 2020) lung findings in both SARS-CoV and COVID-19 lung disease there emerges a signal for two corticosteroid-sensitive patterns: hyperpopulation of the lung by immune cells (e.g., macrophages, lymphocytes) and filling of alveolar spaces by immature connective tissue plugs (i.e., OP). These findings support the hypothesis that, at least in the early stages, COVID-19 does not cause bland DAD as influenza is apt to do, but rather ignites a proliferation of immune cells in the lung that are part of the aberrant immune system activation that is being increasingly recognized as a feature of severe COVID-19 (Mehta et al., 2020). Laboratory research in SARS-CoV has also implicated dysregulated lung immune cell activity in the pathogenesis of lung disease (Yoshikawa et al., 2009). OP may be the first step COVID-19 lung disease takes towards lung injury, but like immune cell infiltration of the lung, OP is highly responsive to corticosteroids. In fact, observing as dramatic an improvement in dense lung consolidation within 24 h of corticosteroid therapy in patients with ARF as that illustrated in Figure 1 conjures up in the pulmonologist’s mind only the most uniquely corticosteroid-sensitive causes of ARF such as OP, AEP, vasculitis, and very few others.

Critics of corticosteroid treatment of COVID-19 lung disease correctly point out that it has been an ineffective therapeutic strategy for influenza ARDS (Bruun-Buissin et al., 2011). We agree but contend that this is a flawed comparison. In the lungs of susceptible hosts destined for ARF, influenza causes rapid evolution of DAD, and the resultant ARDS is indeed expected to be corticosteroid-resistant. If left unaddressed, COVID-19 lung disease is likewise capable of progression to ARDS/DAD at which point the window for corticosteroid therapy is lost, and ARDS-specific management strategies such as prone positioning and extracorporeal support supplant pharmacotherapy. If ARDS/DAD sets in, one is faced with a medically untreatable lung condition with mortality approaching 50% in severe cases (Fan et al., 2018). For this reason, from the pulmonologist’s perspective, it is imperative to control COVID-19 lung disease with a potent broad-spectrum immunomodulatory agent like corticosteroids before its escalation to ARDS/DAD. Based on clinical experience with COVID-19 and other lung diseases, we are, in turn, pessimistic that narrowly focused immunomodulators exemplified by interleukin-6 antagonists can effectively arrest immune dysregulation in the lung.

From the early days of the pandemic to the present, skeptics have referred to existing corticosteroid studies in SARS-CoV and MERS cohorts (Stockman et al., 2006), citing their inconclusive nature and the harm some of them have demonstrated. Although methodologically flawed, this body of literature is far more robust than that which has postulated the use of corticosteroids in pulmonary medicine, including pulse dose, for certain diffuse lung diseases, a practice that is readily applied even to novel entities such as e-cigarette or vaping product-use associated lung injury (EVALI) that lack any evidence base (Layden et al., 2020). Many of the studies labeled inconclusive were never intended to specifically examine the role of corticosteroids. If one restricts the view to just those English-language studies designed to investigate corticosteroid regimens, an overall optimistic picture emerges, particularly considering that the survival figures include critically ill patients (Table 1) (Fowler et al., 2003). The most discouraging study in this group is a retrospective analysis of critically ill MERS patients showing a very high mortality with no survival advantage attributable to corticosteroids (Arabi et al., 2018). It is worth considering that corticosteroids were administered based on clinicians’ discretion with a median of three days into ICU stay at a median dose of methylprednisolone equivalents of 60 mg, which is very different from the 1 g of methylprednisolone administration on the day of ICU arrival and continued for three days that has been our practice with severe COVID-19 lung disease. This study, along with another from the SARS-CoV era (Lee et al., 2004), implicated corticosteroids in the persistence of viral RNA. However, to our knowledge, prolonged viral RNA detection has yet to be linked to adverse clinical outcomes in coronavirus syndromes. Studies of SARS-CoV patients found an association between corticosteroid
Figure 1. Depicted are chest radiographs belonging to three different patients admitted to the intensive care unit of our institution with acute respiratory failure due to confirmed COVID-19 infection. Each row corresponds to a single patient’s imaging. Chest radiographs in the left column (panels A, C, E) represent those obtained at time of intensive care unit entry. Chest radiographs in the right column (panels B, D, F) were obtained fewer than 24 h following the initial studies. The improvement in dense lung consolidation between earlier and later films is striking. The only intervention received by these patients capable of producing such a dramatic change over this time period was a single 1 g dose of methylprednisolone. Radiographic resolution was mirrored by improvement in oxygenation in all three cases.
administration and psychosis (Lee et al., 2004) and joint osteonecrosis (Griffith et al., 2005). Nor is a surprising complication of corticosteroid therapy, both have management options, and each is a reasonable price to pay for reversal of potentially lethal ARF.

In summary, as pulmonologists who managed acute lung failure in the epicenter of COVID-19 in the United States, we urge—based on observations and analysis presented herein—our infectious disease colleagues to consider the following suggestions:

1. Avoid automatic equation of severe COVID-19 lung disease with ARDS because COVID-19 lung disease, at least in its pre-catastrophic stage, is unlikely to correspond to a predominance of DAD histology and thus should be viewed through the prism of pharmacotherapy rather than the prism of ARDS/DAD management, which is devoid of proven pharmacotherapeutic options.

2. As a corollary to item 1, revisit the basis for residual opposition to the use of corticosteroids for severe COVID-19 lung disease given the primacy of prompt, effective lung-targeted treatment in this disease and the mechanistic plausibility that it involves indirect, treatable, immune-mediated lung pathology rather than direct viral injury or DAD.

3. ARF requiring invasive mechanical ventilation is the main source of morbidity and mortality in severe COVID-19. For this reason, and in light of well publicized shortages of mechanical ventilators caused by the pandemic, avoidance of IMV or shortening its duration is a priority. As corticosteroids may plausibly have a role in achieving this endpoint in an immune-mediated lung disease, their use should be encouraged even at the expense of anticipated adverse effects, including prolongation of viral RNA detection, which may have no bearing on important clinical outcomes (Zha et al., 2020).

4. Pulse-dose administration of corticosteroids has been in use by the pulmonary community for decades for the treatment of acute lung diseases with an immunologic basis—a practice supported by observational rather than clinical trial data. Experience indicates that it is the fastest way to exert an immunosuppressive effect on the lung, and responses can be evident immediately. The side effect profile of this approach is sufficiently comparable to lower dose regimens to justify the stated advantages (Ho et al., 2003).

Table 1

| Syndrome | Country | Design | N<sup>a</sup> | Critically Ill<sup>b</sup> | Pulse<sup>c</sup> | Survival<sup>d</sup> |
|----------|---------|--------|---------------|---------------------|-----------------|-------------------|
| Ho et al. (2003) | SARS | China | R | 72 | 12 (17%) | 17 (24%)<sup>f</sup> | 68 (94%) |
| Chen et al. (2006) | SARS | China | R | 268 | 121 (45%) | None | 243 (91%) |
| Sung et al. (2004) | SARS | China | P/D | 132 | 37 (283) | 107 (81%) | 117 (89%) |
| Lau et al. (2004) | SARS | China | P/D | 68 | 15 (22%) | 30 (44%) | 65 (96%) |
| Arabi et al. (2018) | MERS | Saudi Arabia | R | 151 | 151 (100%) | None | 34 (23%) |

O = observational; P = prospective; R = retrospective.
<sup>a</sup> Number of corticosteroid recipients in each study.
<sup>b</sup> At any point during study period.
<sup>c</sup> Absolute number of pulse corticosteroid recipients and percentage of total who received pulse dosing.
<sup>d</sup> Survival to hospital discharge.
<sup>f</sup> In the non-pulse arm of this study, 44 of 55 patients (80%) received pulse dose steroid rescue.

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