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FIRST LINE TREATMENT BY CORTICOSTEROIDS IN SEVERE COVID-19 MANIFESTATIONS

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ABSTRACT

The SARS-CoV-2 pandemic has introduced the medical community to a lung disease heretofore unknown to most clinicians. Coronavirus disease 2019 (COVID-19) pneumonia, firstly reported in Wuhan, Hubei province, China, has rapidly spread around the world with high mortality rate among critically ill patients. In much of the discourse about COVID-19 lung disease, the more familiar clinical entity of ARDS has been used as the guiding paradigm. Reflecting on studies in ARDS, particularly that due to influenza, and on data from the SARS-CoV and MERS epidemics, many authorities, including within the discipline of infectious diseases, were initially passionate in their opposition to the use of corticosteroids for lung involvement in COVID-19.

Those patients usually underwent a stage of excessive inflammation before developing acute respiratory distress syndrome. In this study, we test the hypothesis that short-term, low-to-moderate-dose corticosteroids would benefit patients when used in the early phase of excessive inflammation, namely, the therapeutic window.

KEYWORDS: Corticosteroids,covid-19,SARS-CoV, ARDS, HRCT, GGO, HRCT, CRP,TNF.

INTRODUCTION

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). Despite the fact that COVID-19 patients have mild symptoms and signs in their early stage, about 8–30% of patients would eventually develop severe illness. Furthermore, the 28-day mortality rate of critically ill patients is over 60%. It thus calls for an urgent need to properly identify high-risk cases that are more likely to deteriorate and consequently impose necessary interventions in the early stage.[1,2]

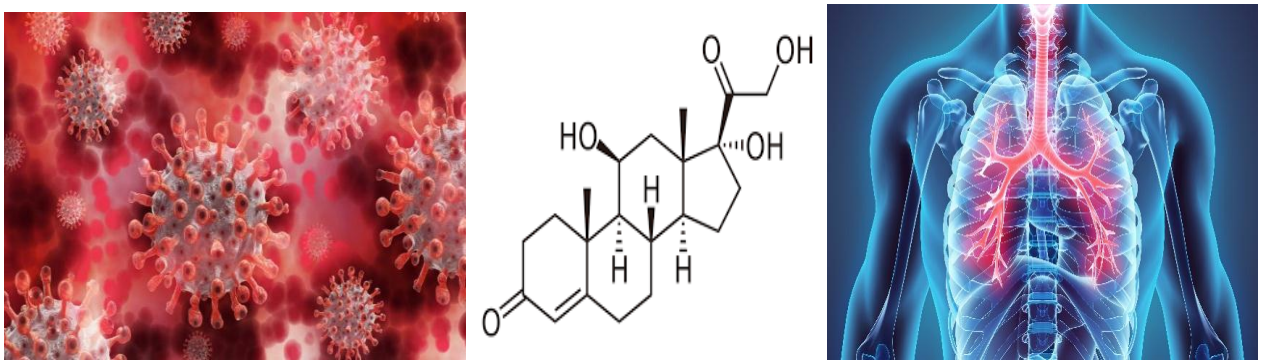


Figure-1: Covid, Steroid, Lungs.

The use of corticosteroids in the treatment of COVID-19 patients is controversial, considering the inconclusive or even adverse results of previous clinical studies on treating SARS-CoV, MERS-CoV, and other severe respiratory virus infections with corticosteroids.

Challenging analytical issues with these studies include the selection bias and confounders as physicians tend to use corticosteroids in more severe patients.[3-5] The study population of previous studies might not identify the subjects who could benefit from corticosteroids. According to the currently known molecular mechanisms and pathophysiology data on severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and influenza patients, critically ill patients usually undergo the following stages: virus invasion, immune activation, excessive inflammatory response, acute respiratory distress syndrome (ARDS), and, in the end, possible recovery or death.[6–11] Although corticosteroids can suppress the inflammatory response, using it too early may suppress the immune activation, thus weaken the viral clearance, while using it too late, the patient is probably too ill to be rescued, as excessive inflammation has progressed, causing ARDS as a result (Figure-2). The therapeutic window of the corticosteroids was presumed to be the early phase of excessive inflammation which varies from person to person and may change dynamically.

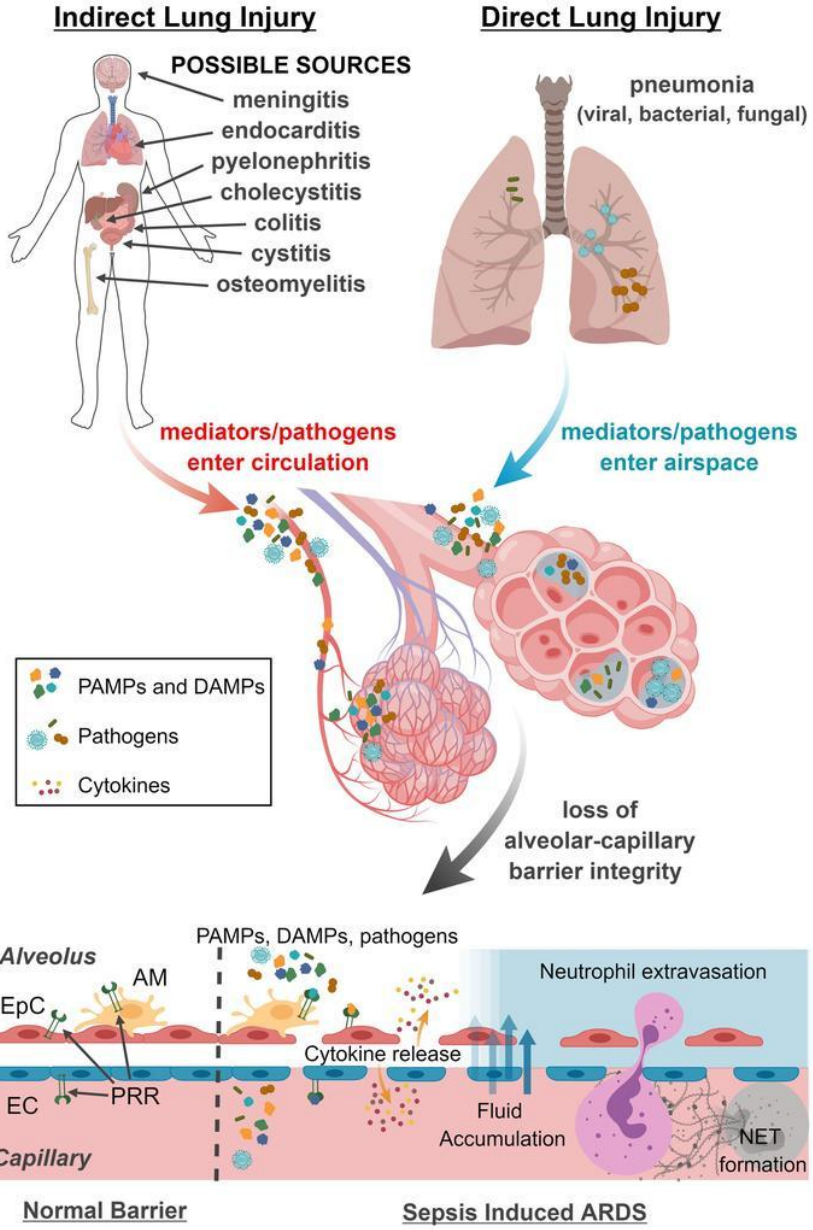


Figure-2. Schema of the pathogenesis of virus-induced ARDS. Balancing virus clearance and host immune response is critical. The early phase of the excessive inflammation is presumed to be the therapeutic window of the corticosteroids.[6–11] Abbreviation: ARDS, acute respiratory distress syndrome.

We hypothesized that short-term, low-to-moderate-dose corticosteroids therapy in the therapeutic window would most likely benefit the patients. In the study, our first step is to identify possible markers for this therapeutic window; the second step was to demonstrate that patients within the therapeutic window veritably benefit from corticosteroids therapy; the third step was to verify that corticosteroids therapy within the treatment window could also benefit the patients in the validation cohort.

Case Description: The two patients are residents of Wuhan City and both had exposure to patients with confirmed severe COVID-19.

Case 1: A 41-year-old man with no smoking history was admitted on February 11, 2020 and the duration from onset of syndromes to admission was 5 days. He was from a family clustering of COVID-19 and his parents and grandmother died from COVID-19. He presented dyspnea and fever with maximum body temperature of 40.0°C. He reported poor appetite without diarrhea and had chronic sinusitis. Laboratory tests results and treatment information are demonstrated in Tables. The patient had leukocytopenia with lymphocytopenia and had an increased C-reaction protein (CRP) and interleukin (IL)-6. He received antiviral treatment including arbidol, hydroxychloroquine, and ribavirin. Wide-spectrum antibiotics (moxifloxacin and imipenem) were used to prevent secondary infections. Other therapies included relieve coughing and phlegm, immunomodulatory, antioxidant, and nutritional support. At admission, he required high-flow oxygen therapy (flow rate 10 L/Min) through a face mask, and his pulse oxygen saturation was 90%. He did not receive mechanic ventilation or noninvasive ventilation during hospitalization. The first day after his admission, the fever persisted, and dry cough and dyspnea worsened. Chest high-resolution computed scan (HRCT) was performed and showed a rapid progression of diffuse ground-glass opacities (GGO) and consolidations compared to those performed before admission. Methylprednisolone (40 mg twice daily, intravenously) was administered for 4 days and then discontinued. After corticosteroids were given, his body temperature decreased to normal and the syndromes improved. HRCT showed obvious absorption of GGO and consolidations by March 26, 2020, he was discharged.

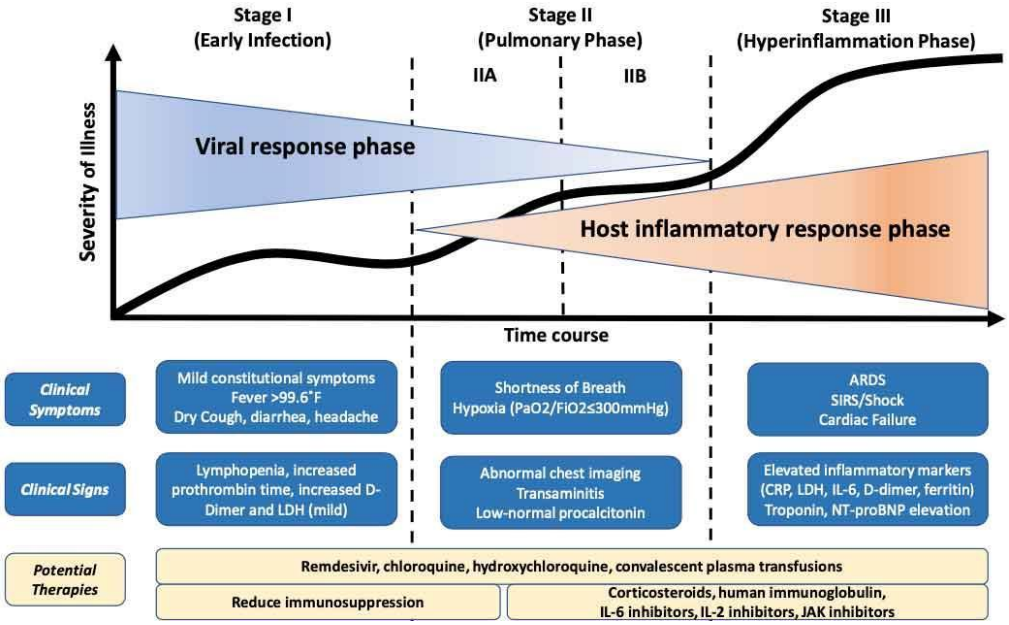


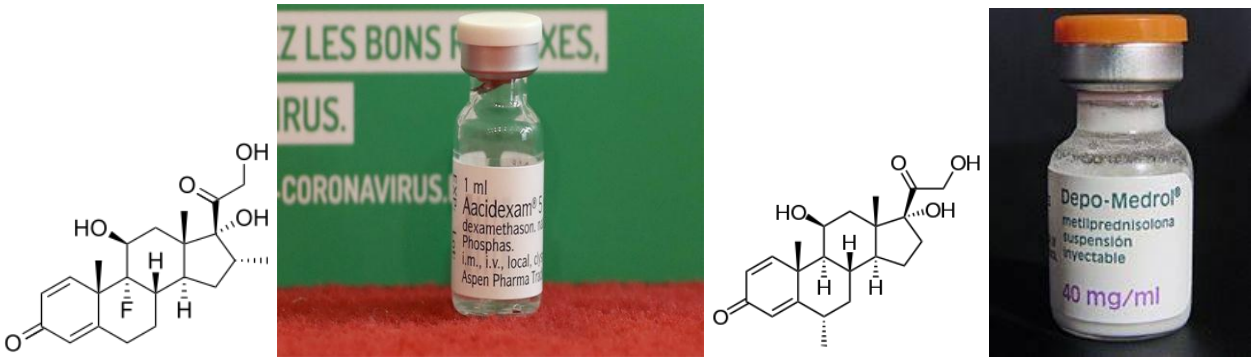
Figure-3: Biochemical pathway of Covid respiratory syndrome.

Case 2: A 73-year-old man with no smoking history was admitted to another hospital on February 8, 2020 and the duration from onset of syndromes to admission was 10 days. He stayed in that hospital for 15 days with persistent fever and worsening dyspnea, then transferred to the hospital on February 23, 2020. He also presented dyspnea, dry cough, and fever with maximum body temperature of 40.0°C. He reported poor appetite without diarrhea and denied having any chronic diseases.The patient had an increased count of white blood cell, an increased CRP, and an elevated D-Dimer. The concentrations of tumor necrosis factor (TNF)-α, IL-1β, and IL-6 were elevated. The antiviral treatments he received were similar to case 1 except for arbidol (Umifenovir). Meropenem was used to prevent secondary infections. At admission, he required high-flow oxygen therapy and his pulse oxygen saturation was 95%.

The fever persisted, and dry cough and dyspnea worsened on the first day after his admission. HRCT was performed, showing diffused GGO and a subpleural consolidation with air trapped in the left upper lung. The initial dosage of methylprednisolone was 40 mg twice daily for 3 days, then tapered to 40 mg per day for 3 days; after that, oral dosage was maintained 8~16 mg per

day for 14–17 days and discontinued. After giving him corticosteroids, the syndromes improved and HRCT showed an improved status (Fig. 2). By March 29, 2020, he was still hospitalized.

Treatment: The treatment of COVID-19 is a great challenge for clinicians and no pharmacological therapy has been proven effective yet. The mainstay of treatment is supportive care. Clark Russell and his colleagues summarized the available clinical evidence on corticosteroid therapy in severe COVID-19.[4-6] Middle East respiratory syndrome (MERS)and influenza against corticosteroid use in 2019 novel coronavirus pneumonia, except in the setting of a clinical trial.[6,7] The main potential risks associated with corticosteroids usage include secondary infections, long-term complications, and delayed virus clearance. In addition, the administration of corticosteroids did not show an advantage to decrease mortality, plus, patients receiving corticosteroids were more likely to require mechanical ventilation, vasopressors, renal replacement therapy and stay in intensive care unit (ICU) longer.[6,7]



DexamethasoneMethylprednisolone
Figure-4: Corticosteroids for Covid.

On the other hand, several studies supported the use of corticosteroids at low-to-moderate doses in patients with virus infection. Reports showed that the proper use of corticosteroids could reduce the mortality of critically ill SARS patients and shorten their hospital stay without causing secondary infections and other complications.[8] Furthermore, low-to-moderate doses of corticosteroids were also associated with reduced mortality in patients with influenza A (H1N1) viral pneumonia when oxygen index was lower than 300 mmHg.[9] Recently, Song et al. reported that methylprednisolone treatment might be beneficial for patients with COVID-19 who developed acute respiratory distress syndrome (ARDS).[10]

The clinical course of COVID-19 is not to be fully characterized. Zhang et al. reported that about 17% of patients with severe illness may quickly progress to ARDS. Among them, 11% of patients worsened in 1~2 weeks and died of multiple organ failure. In our cases, patient 1 was admitted on the fifth day from onset.[11] The disease course and chest HRCT abnormalities progressed rapidly. A study reported that the pathological findings of COVID-19 were interstitial mononuclear inflammatory infiltrating, pulmonary edema, and hyaline membrane formation, suggesting early phase of ARDS. So, timely and appropriate use of corticosteroids could be considered to attenuate cytokine-related lung injury and prevent ARDS development.[12] For patient 2, when he was transferred to our hospital, the clinical course was exceeding 20 days and HRCT showed a prominent consolidation with bilateral involvement. The clinical characteristics, disease course, and radiological findings demonstrated a subacute process, resembling secondary organizing pneumonia (SOP).[13] The total durance of corticosteroids was 25 days and he showed a favorable response to corticosteroid treatment. However, is the treatment durance appropriate? Do such "organizing pneumonia"-like abnormalities in HRCT progress or relapse after corticosteroids discontinued? What extent or degree will the interstitial abnormalities be left in the lung? How long will it take for lung functions to recover? All these clinical questions remain our concerns. A long-term follow up is indeed needed to monitor the serial pulmonary functions and HRCT appearances. Cytokine release syndrome (CRS) contributing to multiorgan dysfunctions has been widely discussed in the pathogenesis of COVID-19 for the plasma levels of proinflammatory cytokines, particularly IL-6, IL-1β, and TNF-α, were markedly increased in ICU patients.[14] Pathogenic T cells and inflammatory monocytes released a considerable amount of interleukin 6, which was associated with the severity and outcome of the disease and was therefore believed to play a major role in inciting the cytokine storm. Xu and his colleagues reported 21 cases diagnosed as severe or critical COVID-19.

CONCLUSION

COVID-19 has an initial period characterized by cough and fever, followed after around 8 days in approximately 20% of patients by the development of dyspnoea with pulmonary infiltrates in about 10%. Approximately a quarter of patients admitted to hospital developed acute respiratory distress syndrome (ARDS) after a median of 10.5 days after symptom onset. *In-vitro* models suggest that there is impaired interferon production and other anti-viral innate immune responses to experimental

rhinovirus and influenza infection in both asthma and COPD, and this could potentially increase susceptibility to viral infections including COVID-19. However, not all studies have replicated these findings. For instance, a study of the response of asthmatic children to natural colds, including some due to coronavirus, showed an appropriate innate response. These contrasting results may reflect the heterogeneity in innate immune responses between individuals and/or variability in the response to different viruses. Surprisingly, the prevalence of chronic respiratory disease among patients with SARS and COVID-19 appears to be lower than among the general population. This is not the case for other chronic diseases and leads us to hypothesize that lung disease, patients' behavior or, more likely, their treatment may have some protective effective. Sadly, patients with underlying lung disease who develop COVID-19 and are hospitalized have worse outcomes, with a case fatality rate of 6.3% compared to 2.3% overall in China. These individuals may have less reserve to cope with the pulmonary effects of severe infection or their immunopathological abnormalities may make them more susceptible to developing pulmonary inflammation and ARDS.

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