

OPEN

Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019

Jesús Villar, MD, PhD¹⁻³; Marco Confalonieri, MD⁴; Stephen M. Pastores, MD, MACP, FCCP, FCCM⁵; G. Umberto Meduri, MD^{6,7}

Key Words: acute respiratory distress syndrome; coronavirus disease 2019; corticosteroids; intensive care unit; mechanical ventilation; mortality

CORONAVIRUS DISEASE 2019 ASSOCIATED ACUTE RESPIRATORY DISTRESS SYNDROME

In December 2019, pneumonia associated with the novel coronavirus disease 2019 (COVID-19) emerged in Wuhan, China. On March 14, 2020, the World Health Organization (WHO) declared the coronavirus outbreak a pandemic with confirmed cases in 127 countries. This unprecedented load on healthcare institutions is particularly overwhelming for ICUs and medical personnel treating mechanically ventilated patients. The occurrence rate of acute respiratory distress syndrome (ARDS) with COVID-19 infection varied

between 17% and 41% (1–3). ARDS may require weeks of mechanical ventilation (MV) and is associated with an unacceptably high mortality rate. Worldwide, thousands of patients are denied life-saving support for lack of mechanical ventilators. This is unprecedented global emergency without a workable solution. Thus, any intervention directed at decreasing duration of MV and mortality could have a great impact on public health and national security.

PROLONGED CORTICOSTEROID TREATMENT IN NONVIRAL ARDS

Corticosteroids have been off patent for greater than 20 years, they are cheap and globally equitable. Since the first clinical description of ARDS (4), corticosteroids are the most broadly used medication specifically targeted at treatment. Translational research has established a strong association between dysregulated systemic inflammation and progression (maladaptive repair) or delayed resolution of ARDS. In patients with ARDS, glucocorticoid receptor-mediated down-regulation of systemic and pulmonary inflammation is essential to restore tissue homeostasis and accelerate resolution of diffuse alveolar damage and extrapulmonary organ dysfunction. This can be significantly enhanced with prolonged low-to-moderate dose corticosteroid treatment (CST) (5). The recent publication of a large confirmatory trial (6) provides stronger evidence that prolonged low-to-moderate dose CST is effective and safe for nonviral ARDS (mostly caused by bacterial pneumonia and sepsis).

In 2017, the Corticosteroid Guideline Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) released guidelines for CST in critically ill patients including those with ARDS (5). The analysis to support the Task Force's recommendations was limited to nine randomized controlled trials (RCTs) that investigated methylprednisolone ($n = 322$) (7) and hydrocortisone ($n = 494$) treatment in ARDS for a duration of at least 7 days. The Task Force found moderate quality/certainty of evidence for a reduction in the duration of MV (mean difference, 7.1 d; 95% CI, 3.2–10.9 d) and improved

¹CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.

²Multidisciplinary Organ Dysfunction Evaluation Research Network (MODERN), Research Unit, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain.

³Keenan Research Center for Biomedical Science at the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada.

⁴Pulmonology Department University Hospital of Cattinara, Trieste, Italy.

⁵Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY.

⁶Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN.

⁷Memphis Veterans Affairs Medical Center, Memphis, TN.

Copyright © 2020 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Crit Care Expl 2020; 2:e0111

DOI: 10.1097/CCE.0000000000000111

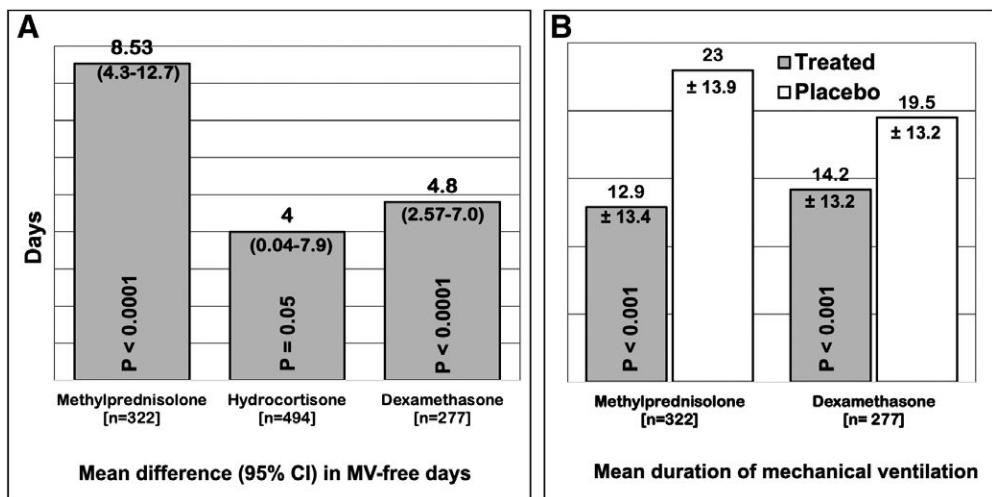


Figure 1. Randomized trials investigating prolonged corticosteroid treatment (CST) in acute respiratory distress syndrome (ARDS) ($n = 1,093$): impact (treated vs control) on (a) duration ventilator dependence and ventilator-free days. Data obtained from prior meta-analysis (randomized controlled trials [RCTs] 9; $n = 816$) used for the Corticosteroid Guideline Task Force of the Society of Critical Care Medicine and European Society of Intensive Care Medicine released guidelines for CST in critically ill patients including those with ARDS (5), with the addition of the new DEXA-ARDS RCT ($n = 277$) (6). **A**, Mean difference and 95% CI for increase in mechanical ventilation (MV)-free days by day 28 (7). The reduction in duration of MV in the four RCTs investigating methylprednisolone treatments was strikingly similar (methylprednisolone vs control: 10.4 ± 19.2 vs 20.2 ± 26.6 , $p = 0.051$; 10.6 ± 2.9 vs 21.2 ± 2.2 , $p < 0.001$; 18.6 ± 24.4 vs 27.3 ± 26.6 , $p = 0.43$; and 27.3 ± 26.6 vs 14.1 ± 1.7 , $p = 0.006$) (7). **B**, Mean (sd) difference in methylprednisolone treatment versus control (-10.10 ; -13.12 to 7.08 ; $p < 0.001$) and dexamethasone versus control (-5.3 ; -8.4 to -2.2 ; $p = 0.0009$).

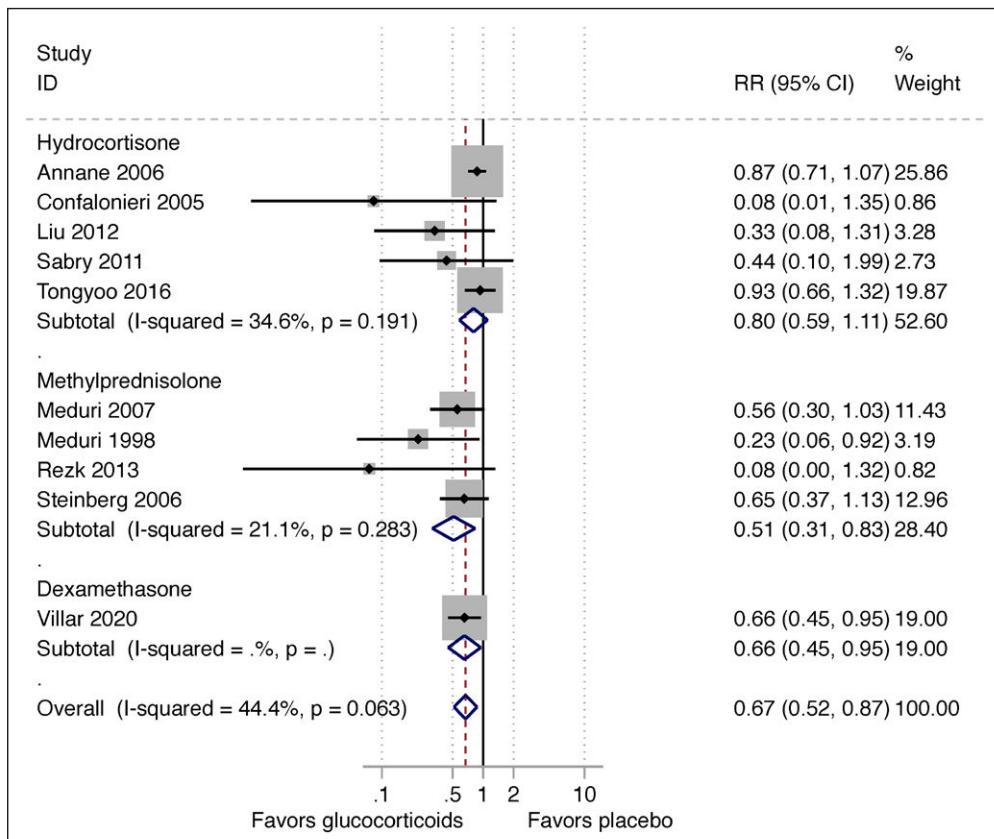


Figure 2. Hospital mortality for patients randomized before day 14 of acute respiratory distress syndrome in randomized trials investigating prolonged corticosteroid treatment. ID = identification, RR = relative risk.

survival (relative risk, 0.64; 95% CI, 0.46–0.89) and therefore made a conditional recommendation for methylprednisolone treatment (5). The high benefit/risk (therapeutic index) associated with the intervention supported their recommendation. Except for transient hyperglycemia (mostly within the 36 hr following an initial bolus), CST was not associated with increased risk for neuromuscular weakness, gastrointestinal bleeding, or nosocomial infections (very low certainty evidence) (5). Importantly, the survival benefit observed during hospitalization persisted after hospital discharge with follow-up observations extending up to 60 days (6, 8, 9), 4 months (10), 6 months (11), or 1 year (limit of measurement) (12). However, most trials were less than 100 patients and performed before the implementation of lung-protective MV. A larger confirmatory RCT in patients receiving low tidal volume (LTV) ventilation was missing.

Clinical investigators in Spain recently completed a large confirmatory RCT (Efficacy Study of Dexamethasone to Treat the Acute Respiratory Distress Syndrome [DEXA-ARDS]) enrolling 277 patients with moderate-to-severe ARDS and receiving LTV ventilation (6). Early administration of dexamethasone for 10 days led to a significant reduction in duration of MV (mean difference, 5.9 d; 95% CIs, 2.7–9.1 d) and all-cause mortality (mean difference, 15.3%; 95% CIs, 4.9–25.9%), without increasing rate of complications. This latest RCT provided consistent evidence similar to what was observed in the previous meta-analyses. The aggregate data from 10 RCTs ($n = 1,093$) clearly demonstrate that CST is associated with a sizable reduction in duration of MV and hospital mortality. **Figures 1** and **2** show the impact of prolonged CST on reduction of ventilator dependence and hospital mortality (number needed to save one life is seven). Canadian investigators are working on an updated meta-analysis.

SUPPORTING ARGUMENTS FOR CONSIDERING USE OF CORTICOSTEROID TREATMENT IN COVID-19 ARDS

Dysregulated Systemic Inflammation (Cytokine Storm) and CST

The dysregulated inflammation and coagulation observed in COVID-19 (13) is similar to that of multifactorial medical ARDS, where ample evidence has demonstrated the ability of prolonged CST to down-regulate inflammation-coagulation-fibroproliferation and accelerate disease resolution (14). Additionally, the CT findings of ground-glass opacities (15) and the histological findings of hyaline membrane and inflammatory exudates (16) are compatible with corticosteroid-responsive inflammatory lung disease. A recent study (2) showed that COVID-19 is associated with a cytokine elevation profile that is reminiscent of secondary hemophagocytic lymphohistiocytosis, a condition responsive to CST.

The WHO statement (17) of not recommending the routine use of corticosteroids for treatment of viral pneumonia outside clinical trials relies on incomplete evidence. If the evidence favors the use of corticosteroids in nonviral ARDS, why does the WHO not recommend CST for COVID-19-associated ARDS? There are

limitations on the evidence approach used by WHO to reach a categorical decision with potentially serious public health repercussions. The WHO's brief argument to support the recommendation is mainly based on the risk of decreased viral clearance reported in one observational study (18) and inconclusive evidence from retrospective observational studies without a predesigned study protocol and subjected to confounding (imbalances in baseline characteristics and postbaseline time-dependent patient differences that influence the decision to prescribe corticosteroids), and hidden bias (19). A more recent high-quality meta-analysis found a high correlation between CST and potential confounders for measured outcomes, such as disease severity and comorbid illnesses. Therefore, confounding by indication is likely to be a significant bias in studies which only provided unadjusted effect estimates. Additionally, time to hospitalization, antiviral use, presence of respiratory failure prior to corticosteroids, and the rationale for corticosteroid use or treatment regimen were sparsely reported across studies (20). What "kills" COVID-19 patients is dysregulated systemic inflammation. There is no evidence linking delayed viral clearance to worsened outcome in critically ill COVID-19 patients, and it is unlikely that it would have a greater negative impact than the host own "cytokine storm" (13).

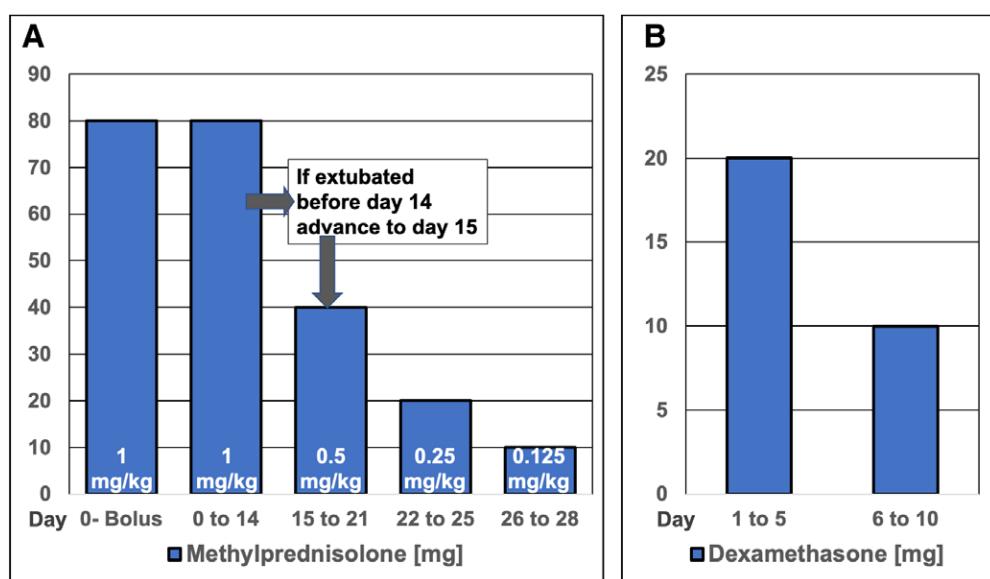


Figure 3. Corticosteroid treatment protocols: methylprednisolone and dexamethasone. **A**, Methylprednisolone treatment. The dosage is adjusted to ideal body weight and round up to the nearest 10 mg (i.e., 77 mg round up to 80 mg). Day 0, IV bolus (80 mg in 50 cc normal saline) over 30 min. Day 0-to-ICU discharge: infusion is obtained by adding the daily dosage to 240 cc of normal saline and run at 10 cc/hr. If necessary, infusion can be changed to bolus every 6 hr (1/4 daily dose) or in the last 6 d very 12 hr (1/2 daily dose). Five days after the patient can ingest medications, methylprednisolone is administered orally in one single daily equivalent dose. Enteral absorption of methylprednisolone, and likely other corticosteroids, is compromised for days after extubation. If between days 1 to 14, the patient is extubated, the patient is advanced to day 15 of drug therapy and tapered according to schedule. Monitor anti-inflammatory response with daily measurements of C-reactive protein levels in addition to severity scores of acute respiratory distress syndrome and multiple organ dysfunction. Rapid tapering can be associated with reconstituted systemic inflammation in the presence of suppressed adrenal function with worsening lung physiology and increased mortality risk (28). Urgent reinstitution of corticosteroid treatment is necessary to be followed after improvement by slow tapering. **B**, Dexamethasone treatment. Patients in the dexamethasone group received an IV dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. Treatment was maintained for a maximum of 10 d after randomization or until extubation (if occurring before day 10). An updated protocol mandates to give dexamethasone for a maximum of 10 d after randomization, independently of the intubation status. This protocol does not mandate further tapering for few days to minimize the risk for reconstituted systemic inflammation.

In a recent commentary regarding the use of corticosteroids in contemporary severe viral epidemics (such as severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, or influenza), coauthored by a member of the WHO panel on clinical management for 2019 novel coronavirus (2019-nCoV), it states that there are "conclusive data" to expect that patients with COVID-19 ARDS will not benefit from corticosteroids (21). This interpretation is biased and without evidence-based support (22). First, their "conclusive" statement rested on only four small studies without including results from another 25 publications (19). Six of the 10 studies in the referenced meta-analysis did not describe the CST used (23). Second, they ignored the positive findings of two large studies (5,327 patients with severe acute respiratory syndrome [SARS] [24] and 2,141 patients with influenza H1N1 pneumonia [25]) that evaluated the impact of time, dose, and duration of CST and reported a significant reduction in mortality with dosage and duration similar to the one recommended by SCCM and ESICM Task Force (5). In the SARS study, after adjustment for possible confounders, CST was

safe and decreased the risk for death by 47% (hazard ratio [HR], 0.53; 95% CI, 0.35–0.82) (24). In the H1N1 study, 1,055 patients received corticosteroids and 1,086 did not receive it. Subgroup analysis among patients with $\text{PaO}_2/\text{FiO}_2$ less than 300 mm Hg (535 vs 462 mm Hg), low-to-moderate-dose CST significantly reduced both 30-day mortality (adjusted HR [aHR], 0.49; 95% CI, 0.32–0.77) and 60-day mortality (aHR, 0.51; 95% CI, 0.33–0.78) (25).

Early Evidence and Recommendations From Those on the Frontline in China and Italy

Early evidence from few observational studies on COVID-19 ARDS is available. In a recent report in 84 COVID-19 patients with ARDS from a single center in Wuhan, China, the administration of methylprednisolone (dosage similar to protocol recommended by the SCCM and ESICM Task Force [5]) was associated with reduced risk of death (HR, 0.38; 95% CI, 0.20–0.72; $p = 0.003$) (3). In a letter to Lancet “On the use of corticosteroids for 2019-nCoV pneumonia,” Shang et al (22) provide a compelling argument from intensivists in the frontline of the outbreak in China that deserves consideration. The letter includes a summary of the expert consensus statement on the use of corticosteroids in 2019-nCoV pneumonia from the Chinese Thoracic Society. Finally, the Italian National Institute for the Infectious Diseases “L. Spallanzani” released updated recommendations for COVID-19 clinical management that included the use of methylprednisolone or dexamethasone for COVID-19-associated ARDS (26).

In conclusion, this is a critical moment for the world, in which even industrially advanced countries have rapidly reached ICU saturation and intensivists are forced to make difficult ethical decisions that are uncommon outside war zones. Although there is a wide divergence of opinion in the literature on whether corticosteroids should be used in patients with COVID-19, the two largest studies on H1N1 and SARS ($n = 7,568$) (25, 27) lend support to its use. However, the lack of sufficient evidence is not tantamount with negating the plausible efficacy of corticosteroids in COVID-19-associated ARDS. The stronger evidence for nonviral ARDS, the early reports from China, and the recommendations from the frontlines of China and Italy should be considered. Inconclusive clinical evidence should not be a reason for abandoning CST in COVID-19-associated ARDS. RCTs are in progress (NCT04273321, NCT04244591, NCT04325061, and NCT04323592) and results will not be available for months. Until then, there is no justification based on available evidence and professional ethics to categorically deny the use of CST in severe life-threatening “cytokine storm” associated with COVID-19 in hospitals not involved in a RCT. **Figure 3** shows the protocols most commonly used in patients with nonviral ARDS RCTs.

This material is the result of work supported with the resources and use of facilities at the Memphis VA Medical Center.

Dr. Villar is funded by grants from the Instituto de Salud Carlos III, Madrid, Spain (CB06/06/1088, PI16/0049), the European Regional Development's Funds, and the Asociación Científica Pulmón y Ventilación Mecánica. Canary Islands, Spain. Dr. Meduri received support for article research from the Veteran Administration. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Address requests for reprints to: G. Umberto Meduri, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Memphis Veterans Affairs Medical Center (111), 1030 Jefferson Avenue Suite room #CW444, Memphis, TN 38104. E-mail: gmeduri@uthsc.edu

The contents of this commentary do not represent the views of the U.S. Department of Veterans Affairs or the U.S. Government.

REFERENCES

- Chen N, Zhou M, Dong X, et al: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020; 395:507–513
- Huang C, Wang Y, Li X, et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497–506
- Wu C, Chen X, Cai Y, et al: Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020 Mar 13. [online ahead of print]
- Ashbaugh DG, Maier RV: Idiopathic pulmonary fibrosis in adult respiratory distress syndrome. Diagnosis and treatment. *Arch Surg* 1985; 120:530–535
- Annane D, Pastores SM, Rochwerg B, et al: Guidelines for the diagnosis and management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2017; 45:2078–2088
- Villar J, Ferrando C, Martínez D, et al: Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. *Lancet Respir Med* 2020; 8:267–276
- Meduri GU, Bridges L, Shih MC, et al: Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: Analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med* 2016; 42:829–840
- Confalonieri M, Urbino R, Potena A, et al: Hydrocortisone infusion for severe community-acquired pneumonia: A preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171:242–248
- Tongyoo S, Permpikul C, Mongkolpun W, et al: Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: Results of a randomized controlled trial. *Crit Care* 2016; 20:329
- Meduri GU, Headley AS, Golden E, et al: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 1998; 280:159–165
- Steinberg KP, Hudson LD, Goodman RB, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1671–1684
- Meduri GU, Golden E, Freire AX, et al: Methylprednisolone infusion in early severe ARDS: Results of a randomized controlled trial. *Chest* 2007; 131:954–963
- Mehta P, McAuley DF, Brown M, et al: COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395:1033–1034
- Meduri GU, Annane D, Chrousos GP, et al: Activation and regulation of systemic inflammation in ARDS: Rationale for prolonged glucocorticoid therapy. *Chest* 2009; 136:1631–1643
- Tang L, Zhang X, Wang Y, et al: Severe COVID-19 pneumonia: Assessing inflammation burden with volume-rendered chest CT. *Radiology: Cardiothoracic Imaging* 2020; 2:e200044
- Xu Z, Shi L, Wang Y, et al: Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; 8:420–422
- World Health Organization: Coronavirus Disease 2019 (COVID-19): Situation Report—54. Available at: <https://www.who.int/docs/default-source/coronavirus/situation-reports/20200314-sitrep-54-covid-19.pdf1>. Accessed March 14, 2020
- Arabi YM, Mandourah Y, Al-Hameed F, et al: Corticosteroid therapy for critically ill patients with the Middle East Respiratory Syndrome. *Am J Respir Crit Care Med* 2018; 197:757–767

19. Delaney JW, Pinto R, Long J, et al: The influence of corticosteroid treatment on the outcome of influenza A(H1N1)pdm09-related critical illness. *Crit Care* 2016; 20:75
20. Lansbury LE, Rodrigo C, Leonardi-Bee J, et al: Corticosteroids as adjunctive therapy in the treatment of influenza: An updated cochrane systematic review and meta-analysis. *Crit Care Med* 2020; 48:e98–e106
21. Russell CD, Millar JE, Baillie JK: Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020; 395:473–475
22. Shang L, Zhao J, Hu Y, et al: On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet* 2020; 395:683–684
23. Ni YN, Chen G, Sun J, et al: The effect of corticosteroids on mortality of patients with influenza pneumonia: A systematic review and meta-analysis. *Crit Care* 2019; 23:99
24. Long Y, Xu Y, Wang B, et al: Clinical recommendations from an observational study on MERS: Glucocorticoids was benefit in treating SARS patients. *Int J Clin Exp Med* 2016; 9:8865–8873
25. Li H, Yang SG, Gu L, et al; National Influenza A(H1N1)pdm09 Clinical Investigation Group of China: Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. *Influenza Other Respir Viruses* 2017; 11:345–354
26. Nicastri E, Petrosillo N, Bartoli TA, et al: National institute for the infectious diseases “L. Spallanzani”, IRCCS. Recommendations for COVID-19 clinical management. *Infect Dis Rep* 2020; 12:8543
27. Chen RC, Tang XP, Tan SY, et al: Treatment of severe acute respiratory syndrome with glucocorticoids: The Guangzhou experience. *Chest* 2006; 129:1441–1452
28. Meduri GU, Bridges L, Siemieniuk RAC, et al: An exploratory reanalysis of the randomized trial on efficacy of corticosteroids as rescue therapy for the late phase of acute respiratory distress syndrome. *Crit Care Med* 2018; 46:884–891