Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Etoposide for Cytokine Storm Because of Coronavirus Disease 2019

To the Editor:

We have read with interest the article published in *CHEST* (January 2021) by Patel et al[1] in which the authors present a single case of cytokine storm due to coronavirus disease 2019 (COVID-19) treated with etoposide. The authors claim that this is the first report of a severe acute respiratory syndrome coronavirus 2-related hyperinflammatory state treated with topoisomerase II inhibitor etoposide. However, we previously reported on 11 patients with COVID-19 who presented with hyperinflammation treated with etoposide as salvage therapy.[2] In our experience, just one to two doses of etoposide (50-150 mg/m^2) were clinically effective and resulted in a significantly decreased need for intubation in the majority of patients from a selected cohort with alarming Pao_2/Fio_2 ratios, commonly under 150. We advocate for administering etoposide to patients with biochemical alterations suggestive of severe hyperinflammation (ferritin levels >1000 ng/mL and/or IL-6 values >50 pg/mL), acute respiratory distress syndrome (defined by Pao_2/Fio_2 <300), and failure of previous treatment with methylprednisolone (or dexamethasone) plus tocilizumab or anakinra. After treatment, we observed a rapid and nearly 200% overall improvement of Pao_2/Fio_2 ratios; >80% of the patients finally could be discharged home. We also observed three cases of profound leukopenia. However, hepatotoxicity was not relevant in our series. All patients had received methylprednisolone and interleukin inhibitors before etoposide, which could have been potential confounders in the interpretation of results. At present, etoposide is offered to patients who present with cytokine storm release syndrome resembling that of hemophagocytic lymphohistiocytosis, in which corticoid plus interleukin inhibitor treatment fails to improve the clinical course, as part of our institutional therapeutic protocol for COVID-19. The currently ongoing clinical trial[3] that started on May 8, 2020 will likely contribute to evaluate the safety and efficacy of etoposide in these patients.

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Response

To the Editor:

We would like to thank Delgado-Lopez et al for their response to our original manuscript.[1] We agree with the sentiment echoed by the writers that, after failure of various antiinflammatory-like corticosteroids and biologic therapies (anti IL-6, anti-IL-1), etoposide has a role in selective patients who still have laboratory and clinical data suggestive of hyperinflammatory syndromes.[1,2] Although the authors have reported on eleven patients with coronavirus disease 2019 who were treated with etoposide as salvage therapy in June 2020, our initial submission was in April 2020 at which time none of the publications had reported any such cases. We are, however, very happy to see the results from the authors' case series reporting similar outcomes as ours. We, like the authors, await the result of the ongoing clinical trial NCT04356690,[3] which will shed more light on the safety and efficacy of etoposide in coronavirus disease 2019.

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Immortal Time Bias in Comparing Late vs Early Intubation in Patients With Coronavirus Disease 2019

To the Editor:

I read with great interests on the study by Pandya et al[1] in *CHEST* (February 2021), in which they compared the difference between late vs early intubation of patients with coronavirus disease 2019. They found that late intubation was associated with longer length of stay in ICU and duration of mechanical ventilation than the early intubation group. Although it is plausible that the late intubation group may experience prolonged periods of hypoxia that result in pathophysiologic derangements such as hypoxemia and multiorgan dysfunction, the finding may also be attributable to the immortal time bias.[2] Immortal time bias refers to a distortion that modifies an association between an exposure and an outcome, caused when a cohort study is designed so that follow up includes a period of time in which participants in the exposed group cannot experience the outcome and are essentially "immortal."

In the present study, the time from admission to intubation is the immortal time, in which the outcome of mortality cannot occur. When the length of stay in ICU was calculated from admission, this immortal time is attributed inappropriately to the effect of intubation. As a result, the length of stay is prolonged in the late intubation group. A potential solution to the immortal time bias is to reset the time zero of follow up to the time