DASON COVID-19 Weekly Treatment Literature Update 6/26/2020
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The following summarizes key literature pertaining to treatment of COVID-19 during the past week.
*Note: some of the data discussed below is in pre-print form that has not yet been peer-reviewed. We have noted some discrepancies in some of this data, and final printed versions may ultimately differ from what is shown here. We will update as soon as possible; caution is advised when interpreting this literature.

NIH Treatment Guidelines Update
Based on the results shared in the pre-print of the RECOVERY trial (discussed below), dexamethasone has been added to the NIH treatment guidelines.

Dexamethasone is **recommended** for patients who are mechanically ventilated or who require supplemental oxygen
Dexamethasone is **NOT** recommended for COVID-19 patients who do not require supplemental oxygen

The dexamethasone summary can be found at this link:  
https://www.covid19treatmentguidelines.nih.gov/dexamethasone/

The full guidelines is available at this link:  

New Literature This Week
Brief on “Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report”
Authors: RECOVERY Collaborative Group (This version posted June 22, 2020 is not certified by peer review)

This article is a preliminary report from the larger RECOVERY clinical trial (Randomized Evaluation of COVid-19 thErapY) in the United Kingdom investigating whether treatment with either lopinavir-ritonavir, hydroxychloroquine, corticosteroids, azithromycin, convalescent plasma or tocilizumab prevents death in patients with COVID-19.1 The low-dose dexamethasone arm was halted based on the trial Steering Committee assessment that a sufficient number of patients were enrolled to establish whether or not the drug had meaningful benefit.

The results have been posted by medRxiv, as a preprint. Based on this preliminary data, the Public Health Service in the UK included dexamethasone in national recommendations and on June 25th the NIH added dexamethasone to the COVID Treatment Guidelines.2

In brief, 2,104 patients were randomly allocated to receive usual care plus dexamethasone 6mg once daily (PO or IV) for up to 10 days (or discharge if sooner, median treatment was 6 days) were compared to 4,321 patients concurrently allocated to usual care. Overall, 21.6% of the patients receiving dexamethasone died and 24.6% allocated to the usual care died within 28 days (age-adjusted rate ratio [RR] 0.83; 95% CI 0.74-0.92; p<0.001). The largest benefit was seen in the patients receiving invasive mechanical ventilation, where mortality in the dexamethasone group was 29% vs 40.7% in the usual care group (RR 0.65, 95% CI 0.51-0.82). There was also a
benefit in the oxygen only group (which included non-invasive ventilation) where the mortality in the dexamethasone group was 21.5% vs 25% (RR 0.80, 95% CI 0.70-0.92). This benefit was not seen in the patients who were not requiring oxygen and in fact, mortality was higher in the patients receiving dexamethasone although this did not reach statistical significance.

A few questions remain before we can make a blanket recommendation to give this treatment to any patient with COVID-19 who requires oxygen or needs mechanical ventilation. Some of these questions may be answered after the normal peer review process occurs. We have a few comments about this preliminary report as we begin to think about considering this treatment for our patients.

First, patients were excluded if the treating clinician considered dexamethasone to be definitely needed or contraindicated. Further demographic details are not available regarding these excluded patients. If there were a large proportion of patients with ARDS or respiratory failure receiving steroids, these factors may have been important contributors to the end outcome. Therefore, before starting dexamethasone, clinicians should review patient’s medical history and assess the potential risks and benefits of administering corticosteroids to the patient.

A second note is that 83% of the mechanical ventilation group were under 70 years old, compared to 55% in the oxygen only group and 43% in the no oxygen group. Another way to describe the difference, the mechanical ventilation group were on average 10 years younger. In supplemental material, the investigators also showed an analysis of the effect of dexamethasone on mortality by age and there was a significant benefit in those patients <70 (RR 0.64; 95% CI 0.52-0.78) but not in those ≥70. While the primary analysis between respiratory support groups was age-adjusted, these age effects are important to note before we generalize to our population in the ICU in the US. We know that older age is a risk factor for more severe disease and as highlighted in the NIH treatment guidelines, more complete analysis is needed to determine the effect of dexamethasone in particular age groups.

Thirdly, we know there are 2 phases of COVID-19, with the first largely driven by the viral infection and the second driven by the host immune response. It is in this second phase where we think immunomodulators such as corticosteroids may have a beneficial impact. In this study they showed there was a significant benefit when the steroids were given >7 days since symptom onset (RR 0.68, 95% CI 0.58-0.80) and no benefit if given before, reinforcing this idea that immunomodulators may have greatest benefit in this second phase of illness. The mechanical ventilation group also had symptoms for 7
days longer than the no oxygen group, or a median of 13 days. These findings should help us as we think about timing and patient-related factors for immunomodulator administration in COVID.

Based on preliminary data available, there is clearly a role for dexamethasone in some COVID-19 infected patients. As the data are further analyzed and reviewed, details will emerge regarding the ideal patient population and timing of administration. The ongoing work will also provide information on toxicities.

One of the largest remaining questions is whether alternate steroids could be used in place of dexamethasone. This is a particular concern as dexamethasone supplies have dwindled since the press release earlier in June. As stated in the NIH treatment guidelines2, it is unknown if other steroids will have similar effect, but the NIH does provide dose equivalencies for prednisone, methylprednisone and hydrocortisone for facilities considering this option.

We will continue to provides updates as more data and analyses are available.

References:

Treatment Summary Tables
The remdesivir summary table with the information of published studies to date can be found at this link: https://dason.medicine.duke.edu/summary-recent-clinical-data-use-remdesivir-covid-19

The hydroxychloroquine summary table is available at this link: https://dason.medicine.duke.edu/summary-recent-clinical-data-use-hydroxychloroquine-and-chloroquine-covid-19

The tocilizumab summary table with the information of published studies to date can be found at this link: https://dason.medicine.duke.edu/summary-recent-clinical-data-use-tocilizumab-covid-19