Oval, N.P. ***IDSA. Issues Guidelines for the Treatment and Management of Patients with COVID-19.*** MPR, ***April*** 14, 2020

The IDSA highlighted that the guideline for COVID-19 management is a living document that will be frequently updated pending new data.
The coronavirus disease 2019 (COVID-19) pandemic caused by a novel strain of the viral family (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has highlighted the need for novel treatment options. However, novel treatments are often offered using non centralized data from small or anecdotal studies, with regimens for these treatments varying on an institutional basis. Therefore, the Infectious Disease Society of America (IDSA) has issued guidelines to aid in the treatment and management of patients with COVID-19.

A panel of 9 members from various disciplines in the field of infectious diseases used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method to develop 7 recommendations for the treatment of patients with COVID-19, all of which contain the caveat of use only in the context of patients receiving the identified treatment in the setting of a clinical trial.

Data from 2 randomized clinical trials showed that patients with confirmed COVID-19 with mild pneumonia or nonsevere infection who received hydroxycholorquine during hospitalization had a slightly higher percentage of clinical improvement (relative risk, 1.47; 95% CI, 1.02-2.11). Further, data from 4 studies on the combination of hydroxychloroquine and azithromycin demonstrated a 3.4% mortality rate among hospitalized patients and a lower rate of virologic failure. However, small sample sizes and sparse data on cointerventions and untreated cohorts significantly limit these findings.

In addition, the potential harms of this treatment are important to consider. Results from 2 studies demonstrated a significant QT prolongation in 10 of 95 patients who received combination hydroxychloroquine and azithromycin. A large cohort study also showed a hazard ratio of 2.71 vs 0.85 for sudden cardiac death among patients who received a 5-day course of azithromycin compared with no antibiotic or amoxicillin, respectively.

For these reasons, the IDSA panel made its first 2 recommendations: **patients who have been admitted to the hospital as a result of COVID-19 may receive hydroxychloroquine/chloroquine or combination hydroxychloroquine/chloroquine plus azithromycin only in the context of clinical trial.**

An intention-to-treat analysis using data from 1 randomized clinical trial and 2 case studies resulted in relative risks of 0.67 (95%, 0.38-1.17) and 0.78 (95% CI, 0.63-2.20) for treatment with lopinavir/ritonavir on mortality and clinical improvement, respectively. However, 14% of patients who received lopinavir/ritonavir did not complete the full 14-day course due to gastrointestinal adverse events (anorexia, abdominal pain, nausea, or diarrhea), including 2 serious adverse episodes of acute gastritis. Moreover, there are well-documented risks for hepatic injury, pancreatitis, QT prolongation, and multiple drug interactions from cytochrome P450 3A4 (CYP3A) inhibition with lopinavir/ritonavir treatment.

Therefore, **the panel recommended the use of lopinavir/ritonavir for patients with COVID-19 who are hospitalized, only in the context of clinical trials.**

No studies that focused exclusively on the use of corticosteroid treatment for patients with acute COVID-19 were found; therefore, indirect evidence from the SARS outbreak in 2003 and the Middle Eastern Respiratory Syndrome CoV (MERS-CoV) were considered. One such randomized clinical trial showed that viral loads of SARS-CoV-1 had delayed clearance linked to the use of corticosteroids. However, a subset of the same study also demonstrated that the use of steroids resulted in improvement in acute respiratory distress syndrome (ARDS). Findings from 2 larger trials, however, showed little to no effect among critically ill patients with pulmonary failure.

Based on the above data, the panel made its fourth and fifth recommendations: **the IDSA panel conditionally advises *against* the use of corticosteroids for the treatment of patients with COVID-19 pneumonia, but patients hospitalized due to ARDS as a result of COVID-19 should receive corticosteroid treatment only in the context of a clinical trial.** The panel noted, however, that patients receiving inhaled or systemic corticosteroids for other indications should continue to receive such treatment.

One study reported on the use of an interleukin (IL)-6 inhibitor, tocilizumab, for the treatment of patients with COVID-19. There were no deaths reported with this treatment, but the study did not include a control group or adjustments for confounding factors, making these results significantly uncertain. The study also did not demonstrate any serious adverse events, but previous data on tocilizumab have linked the medication to risks for serious infections, anaphylaxis, severe liver damage, hepatic failure, and intestinal perforation. Further, IL-6 has been established as having an inhibitory effect on cytochrome P450 systems, and as such, the use of tocilizumab may result in increased metabolism of medications that use this system.

Using this evidence, **the panel stated that among hospitalized patients with COVID-19, the use of tocilizumab is recommended only in the context of a clinical trial.**

Monoclonal antibodies against other respiratory viruses have been shown to be protective against hospitalization in specific high-risk populations. The panel identified a total of 2 case series reported on the use of convalescent plasma for the treatment of COVID-19. No deaths were reported among the study cohorts and no serious adverse reactions or safety events were noted. However, neither study adjusted for confounders, cotreatments, disease severity, or timing for plasma delivery relative to extubation.

The guidelines authors concluded that despite the limitations that the pandemic places on accruing vetted data from large clinical trials, "the recommendations were based on evidence from the best available clinical studies with patient-important endpoints…[and acknowledged] enrolling patients in [randomized clinical trials] might not be feasible for many frontline providers due to limited access and infrastructure. Should lack of access to clinical trials exist, we encourage setting up local or collaborative registries to systematically evaluate the efficacy and safety of drugs to contribute to the knowledge base. Without such evaluations we often attribute success to drugs and failure to [COVID-19]. During such a pandemic, barriers to conducting studies and enrolling patients in trials for already overburdened front line providers should be minimized while ensuring the rights and safety of patients." Of note, the IDSA panel

also highlighted that the COVID-19 guideline is a living document that will be frequently updated pending new data; they advised visiting the IbbDSA website for such updates.

Reference

Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Disease Society of America guidelines on the treatment and management of patients with COVID-19 infection. Updated April 11, 2020. Accessed April 13, 2020. https://.idsociety.org/COVID19guidelines