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 *Note: some of the data discussed below is in pre-print form that has not yet been peer-reviewed.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.

**Overall Treatment Reviews**


- A literature review of 1,315 English-language articles published through 25 March 2020 to evaluate potential drug therapies for the treatment of COVID-19, which included randomized controlled trials, case reports, case series, review articles and active ongoing clinical trials.
- The authors shared a few observations based on the literature review:
  1. There are no proven effective therapies for COVID-19; however, new information on SARS-CoV-2 virology is useful to identify potential drug targets.
  2. There are no data to support the efficacy of oseltamivir for the treatment of COVID-19.
  3. Corticosteroids are not recommended based on current evidence.
  4. ACE-inhibitors and angiotensin-receptor blockers should not be stopped in patients with COVID-19 based.
- Figure 1 depicts the virology of SARS-CoV-2 and mechanisms of proposed therapies. Table 1 of the article summarizes available therapies, including the agent target, dosing recommendations, contraindications, toxicities, major drug-drug interactions, and considerations for special populations.
- The authors respond to frequently asked questions related to clinical management of patients with COVID-19. One question that may be of particular interest is a response discussing strategies for determining whether COVID-19 patients should receive a specific therapy or traditional supportive care. The authors suggest prioritizing enrollment in available clinical studies for patients who are eligible. Considering experimental therapies in patient excluded from trials in setting of hypoxemia, pneumonia, or risk factors for progression to severe disease.
Hydroxychloroquine/chloroquine Containing Regimens


- Summary of data in clinical studies to date provided in table format (we have adapted this table and will continue to update on the DASON COVID-19 response page at this link).


- Multicenter, randomized, open-label study of HCQ vs standard of care (SOC) with 150 patients (75 HCQ+ SOC vs 75 SOC alone) [Stopped early after interim analysis]
  - Higher HCQ dose than other studies – loading dose of 400 mg TID for three days, followed by 400 mg BID for two (mild/moderate) or three weeks (severe)
  - 99% of patients had mild/moderate COVID-19, 1% had severe COVID-19
  - Mean day from disease onset to randomization was 16.6 days
  - 89% of patients received other medications prior to randomization and most continued other anti SARS-CoV-2 medications after randomization

- Primary endpoint:
  - 28-day negative conversion rate- no difference. Negative conversion rate for HCQ was 85.4% (95% confidence interval [CI], 73.8%, 93.8%), vs 81.3% (95%CI, 71.2% to 89.6%) in SOC group.
  - Similar rates of conversion to negative tests between groups at days 4, 7, 10, 14, or 21

- Secondary endpoints:
  - 28-day symptom improvement- no difference
  - Increased symptom improvement observed with HCQ after controlling for effects of concomitant medications: Hazard ratio, 8.83, 95%CI, 1.09 to 71.3
  - Faster normalization in CRP and recovery of baseline lymphocytopenia with HCQ, although overall improvement by 28 days was similar
  - Adverse events: higher with HCQ (20%) vs SOC (8.8%); 2 serious adverse events, both in HCQ group (1 disease progression, 1 upper respiratory infection)
    - most common AE was diarrhea (10% in HCQ group, 0% SOC)


- Parallel double-blind study assessing 2 different chloroquine doses (600 bid X 10 days or total 12g vs. 450 mg q12 x 1 day then 450 mg Q24 X 4 days or total 2.7g)
- Experience in first 81 patients described (of 440 target)
  - 41 high dose, 40 low dose
- All patients also received ceftriaxone + azithromycin (500 mg daily x 5 days)
  - ~90% also received oseltamivir (75 mg BID x 5 days)
- Stopped high dose arm early, owing to a higher mortality with the higher dosage (17%) by day 13 of follow-up.
- QTc >500 ms was 18.9% in high dose vs 11.1% low dose (p=NS)
- 2 patients in the high dose group had ventricular tachycardia prior to death, 1 in low dose group
- Only 22% of 27 patients with paired samples had negative respiratory viral load at day 4
Lane JCE, Weaver J, Kotska K et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid widespread use for COVID-19: a multinational, network cohort and self-controlled case series study. 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.04.08.20054551v1

- Used 14 sources of claims data or electronic medical records from Germany, Japan, Netherlands, Spain, UK, and USA to evaluate adverse events in almost 1 million adults initiating HCQ or sulfasalazine from 2000-2020 (for non-COVID-19 indications).
- Exposures evaluated:
  a. HCQ
  b. Sulfasalazine (control)
  c. HCQ + azithromycin
  d. HCQ + amoxicillin (control)
- No significant safety differences from short course HCQ compared to sulfasalazine (but long-term use associated with 65% increase in cardiovascular toxicity)
- The combination of HCQ + azithromycin was associated with a 15-20% increase in angina/chest pain and heart failure and two-fold risk of cardiovascular mortality in the first month

Tocilizumab
Tocilizumab, a monoclonal antibody against interleukin-6 (IL-6), has been used in the management of SARS-CoV-2 for the prevention of cytokine storm. IL-6 plays a key role in this inflammatory immune response which can result in rapid deterioration and death. Data from two small retrospective studies have attempted to evaluate outcomes associated with tocilizumab use in SARS-CoV-2 infection without control groups:


A retrospective study of 21 patients (4 critically ill and 17 severe) treated at two centers in Anhui, China between February 5 and February 14, 2020 evaluated tocilizumab use in severe or critical COVID-19 patients. A single intravenous tocilizumab dose of 400 mg was added to standard care which included lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy. A total of 15 patients (15/20, 75.0%) showed improvements in oxygen intake. CRP decrease with a return to normal in 84.2% (16/19) on the fifth day with CT scans showing absorption of lesions in 90.5% (19/21) after treatment. There were no reported deaths. A total of 19 patients (90.5%) were eventually discharged with no subsequent reports of pulmonary infection, deterioration of illness, or death.


This was a single-center, retrospective observational study of 15 patients who were treated with tocilizumab from January 27 to March 5, 2020 in Wuhan, China. Tocilizumab doses varied from 80 to 600 mg. The study population included two (13.3%) patients who were moderately ill, six (40.0%) patients with severe illness, and seven (46.7%) patients defined as critically ill. Both serum CRP and IL-6 levels were obtained before and after tocilizumab administration. Levels of CRP significantly decreased after tocilizumab administration from 126.9 (10.7 – 257.9) to 11.2 (0.02 – 113.7) mg/L (P < 0.01). IL-6 levels decreased in 10 (66.7%) of patients after an initial spike. However, four critically ill patients failed treatment and exhibited persistent and dramatic increases in IL-6 levels. Clinical stabilization or improvement was reported for 10 of 15 patients observed during this time period. Of note, a total of 8 patients also received corticosteroid therapy and repeated doses of tocilizumab were administered to 5 patients at varying time points.