COVID-19, SARS CoV-2

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Coronavirus, SARS CoV-2, COVID-19

Recent Updates

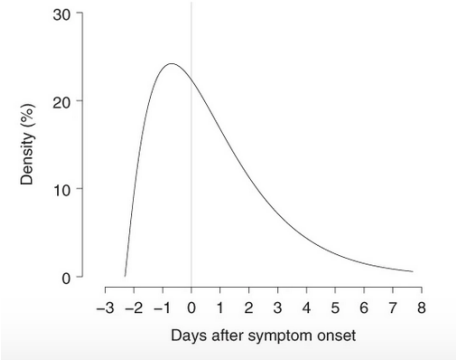
- Current IDSA Guidelines on COVID-19 serological testing here.
- Update on bacterial and fungal co-infections in hospitalized patients with COVID-19.
- Update and summary of studies on viral shedding (**See Transmission**/Viral shedding).
- Update on recently activated clinical trials (**See Comments**/Clinical trials of interest).
- Analysis of trial of convalescent plasma (**See Comments**/Convalescent plasma)
- We are beginning to divide COVID-19 material into sub-pages given the continually growing body of information:
    - Summary of vaccine development pipeline, see COVID-19, Prevention
        - Phase 3 trial enrollment announced 27 Jul 2020 for mRNA-1273 (Moderna/NIAID)
    - Complications in children and adolescents, see Multisystem Inflammatory Syndrome in Children (MIS-C)
        - Shock, with cardiac involvement, gastrointestinal symptoms, and significantly elevated markers of inflammation and positive serology for SARS CoV-2. Similar to Kawasaki disease and toxic shock syndrome and can be difficult to distinguish. MMWR 7 Aug 2020 early release.

Clinical Setting

- **Comprehensive review** of pathophysiology, transmission, diagnosis and treatment of COVID-19 in JAMA online 10 July 2020 doi:10.1001/jama.2020.12839.
    - Patient-oriented summary of the review here.
- SARS-CoV-2 (2019-nCoV) is a respiratory coronavirus that causes the disease COVID-19.
- Origins of the virus**:** SARS-CoV-2 emerged in late 2019 from live animal markets in Wuhan, China. Bats are the reservoir species (See Nat Microbiol 2020 Jul 28. doi: 10.1038/s41564-020-0771-4 for evolutionary history).

Transmission

- **Analysis of Diamond Princess COVID-19 outbreak** (MedRxIV, unpublished, not peer-reviewed) suggests that **aerosol inhalation** likely the dominant contributor to COVID-19 transmission.
    - **Cruise ship no sail order extended until 30 Sep 2020**: CDC press release, 16 Jul 2020. Avoid cruise ships, including river cruises: CDC HAN No. 430 (03/15/20): https://emergency.cdc.gov/han/2020/han00430.asp
- Efficient transmission in youth-centric overnight setting: Overnight camp, camper median age range 12 yrs, staff median age range 17: 44% positive in 11-17 yr age group. MMWR 31 Jul 2020
- **Transmission is highly efficient:**
    - **Droplet** is the primary mode of transmission is most settings.
    - **Airborne/aerosol** transmission possible, but probably not the primary mechanism in most settings (see JAMA 2020 Jul 13. doi: 10.1001/jama.2020.12458) with potential for transmission from aerosol generating procedures such as nasophayngeal swab sampling, intubation, invasive and non-invasive ventilation, nebulizers, high-flow oxygen nasal cannula, bronchoscopy.
    - **Highest transmission rates from close contacts** and within households (Clin Infect Dis. 2020. PMID: 32301964) but in most cases the exposure responsible for transmission is unknown (Science 10.1126/science.abb3221 (2020)).
    - **Fomite** transmission is possible but likely has is a minor role.
- **Maximum viral shedding begins 5-8 hours prior to onset of symptoms**, see figure below (He et al, Nature on line, 15 Apr 2020 (Figure 1c excerpt used with permission)



- **Mean incubation time is estimated to be ~5 days after exposure** (range 4.1 - 7.0 days, but as short as 36 hours. Transmission can occur from an infected person who is asymptomatic (prior to onset of symptoms; see above)
- **Viral shedding** (References: Nature. 2020;581(7809):465-469; Lancet Infect Dis. 2020;20(5):565-574; van Kampen, et al, pre-print and not peer reviewed):
    - Careful studies of COVID-19 patients with mild-to-moderate disease (more than 90% of cases) have shown that infectious virus could not be isolated after more than 8 days of symptoms. Viral loads in asymptomatic and symptomatic individuals at time of diagnosis are similar; some evidence shows less likelihood of transmission to contacts of asymptomatic individuals. Robust data from patients with severe or critical COVID-19 show the duration of infectious virus shedding ranged from 0 to 20 days (median 8 days) after symptom onset. The probability of detecting infectious virus dropped below 5% after 15 days. Implications from these latter data are for hospital inpatient infection control. Severe or critical patients typically require 30 or more days of hospitalization and prolonged home convalescence; these data have no implications for return to work or the community for typical patients. For mildly ill patients, shedding of viral RNA assayed by RT-PCR from saliva and nasopharyngeal secretions is at peak value on the day of symptom onset, remains high for approximately 6 days, declines significantly in the second week of illness, and usually ceases by day 14. The maximum duration of positive nasopharyngeal PCR testing in several large series is 43 days from symptom onset and 28 days from symptom resolution; 19% of

patients are PCR positive 2 weeks after symptom resolution. One outlier case of viral RNA shedding for 95 days following symptom onset has been reported in a patient with prolonged illness.

Prevention / Isolation

- **Prevention measures**
  - Systematic review and meta-analysis (Lancet, published online June 1, 2020) of **social distancing, N95 respirators, surgical masks, eye protection** in community and healthcare settings indicates that each provides a level of protection against COVID-19**.**
  - **Frequent handwashing** (alcohol-based sanitizer and/or soap and water)
  - Sanitize common surfaces (see cautions regarding improper use of disinfectant and cleaning products in MMWR June 5, 2020 early release)
  - **Community responsibility**
    - **Social distancing** (1m somewhat protective, at least 6 feet / 1.8 meter preferred)
    - **WEAR A FACE MASK IN PUBLIC WHEN IN THE PRESENCE OF OTHERS**: Protective of yourself and others by preventing spread of nasal/respiratory droplets
    - **AVOID CROWDS, CONGESTED PLACES, particularly indoor spaces (restaurants, bars, churches), which continue to be transmission focal points**
  - Respiratory hygiene, i.e., cover nose and mouth when sneezing or coughing
  - Avoid touching eyes, nose, mouth
  - Consult Federal, State and local guidance for reopening and containment measures in specific situations
- **Home Care & Ending Self Isolation**. See CDC Clinical Care Interim Guidance 20 Jul 2020.
  - For persons COVID-19 positive **and** symptomatic who were directed to self-care at home (or hotel, dormitory), isolation may be discontinued:
    - After 10 days from symptom onset **and** after 24 hours from fever resolution (without use of fever-reducing medication) **and** other symptoms have improved
  - For persons who remain asymptomatic after a positive RT-PCR for SARS CoV-2:
    - After 10 days from date of positive test
  - Test-based strategy no longer recommended to determine when to end home isolation (except in specific situations, i.e., immunocompromised)
- **Healthcare Personnel**
  - **Personal protective equipment (PPE) when caring for a patient with COVID-19**
    - Patients **not** undergoing aerosol generating procedures**:** N95 respirator preferred, surgical mask acceptable; face shield, gown, gloves
    - **Patient undergoing nasopharyngeal swab, aerosol generating procedures:** N95 respirator or PAPR, face shield, gown, gloves
  - **Return to work** after COVID-19: see CDC interim guidance 17 Jul 2020
    - Mild / moderate illness: 10 days from symptom onset + 24 hours from resolution of fever (without fever-reducing meds) + improved symptoms
    - Severe illness: 20 days from symptom onset + 24 hours from resolution of fever (without fever-reducing meds) + improved symptoms
- **Vaccine development pipeline**: see COVID-19, Prevention for summary of vaccine development and clinical trials.

Clinical Manifestations

- **Mean incubation time is estimated to be ~5 days after exposure** (range 4.1 - 7.0 days), but as short as 36 hours.
- 25-50% of cases may be **asymptomatic or minimally symptomatic** (Euro Surveill. 2020 Mar;25(10). doi: 10.2807/1560-7917.ES.2020.25.10.2000180).
- **Presentation / symptoms**:
    - Common presenting signs and symptoms (See CDC listing of symptoms):
        - headache, arthralgias / myalgias, fatigue. fever. cough, shortness of breath, loss of taste and/or smell, nausea / vomiting, diarrhea, sore throat, "fuzzy thinking", delirium
    - One week to 10 days prodrome, which may progress to difficulty breathing at any time, often in the second week.
    - Average 8 days to development of dyspnea and average 9 days to onset of pneumonia/pneumonitis.
    - Key presentation vitals (at triage): temp > 38ºC (30.7%), O_2 sat < 90% (20.4%), heart rate > 100 beats/min (43.1%)
    - Approximately 15% of patients will develop severe disease with 5% requiring mechanical ventilation.
- **Associated co-morbidities / risk factors**
    - Most common: hypertension (56.6%), obesity (41.7%), diabetes (33.8%)
    - **Risk factors** for:
        - **Severe disease**: older age, diabetes, cardiovascular disease, chronic lung disease, obesity, cancer. At any age if underlying condition (MMWR ahead of print, 03/31/20)
        - **Poor prognosis**: older age (> 65 years), high SOFA score & d-dimer >1mcg/mL (retrospective cohort study, Lancet online ahead of print, 03/11/20)
        - **Death**: male, older age, diabetes, severe asthma, black and South Asian ethnicity (Nature online 8 Jul 2020)(analysis based on 17 million adults); obesity (BMI ≥ 35)(Eur J Endocrin online 9 Jul 2020)
- **Other manifestations**, often associated with severe disease: myocarditis, heart failure, myocardial infarction; stroke; thromboembolic events; acute kidney injury; ARDS, multiple organ failure
- **Complications in children and adolescents,** see Multisystem Inflammatory Syndrome in Children (MIS-C)
- **Clinical Course**
    - **Mild / moderate illness** (outpatient). Illness may be prolonged, even in healthy younger adults. Among 170 symptomatic adults surveyed from Mar-Jun 2020, 35% (20% in the 18-34 yr age group) had not returned to a usual state of health 14-21 days from positive RT-PCR for SARS CoV-2. MMWR 24 Jul 2020.
- **Mortality** (JAMA online 10 July 2020 doi:10.1001/jama.2020.12839**)**
    - U.S. death rates shown in the table below:

Age (Yrs)	Death rate/1000
<18	0.4
18-29	1.1
30-39	3.5
40-49	8.6
50-64	29.7
65-74	105.0

75-84	210.5
85+	304.9

Testing / Diagnostics

- **Review of COVID-19 diagnostic testing:** JAMA. 2020 May 6. doi: 10.1001/jama.2020.8259. Epub ahead of print
- **Testing Recommendations** (updated July 17, 2020): see https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html.
    - Individuals with signs or symptoms consistent with COVID-19
    - Asymptomatic individuals with recent known or suspected exposure to SARS-CoV-2 to control transmission
    - Asymptomatic individuals without known or suspected exposure to SARS CoV-2 in special settings that can lead to rapid spread (e.g., long-term care facilities, correctional/detention facilities, homeless shelters, congregate work or living settings)
    - Selected individuals being tested to determine resolution of infection (e.g., test-based strategy for early return to work for healthcare providers, immunocompromised patients)
    - Individuals being tested for purposes of public health surveillance for SARS-CoV-2
- **RT-PCR and nucleic acid amplification tests**
    - For diagnosis of active COVID-19 infection (See IDSA Guidelines at https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics; excellent review of current state of diagnostic testing in Ann Intern Med 2020;172:726;
    - **Specimen**: upper respiratory nasopharyngeal (NP) swab preferred (see CDC interim guidelines (above) and JAMA 2020 Mar 11. doi: 10.1001/jama.2020.3786 for yields of different specimen types).
    - **Test kits**: The U.S. FDA has issued Emergency Use Application (EUA) letters for a growing list of SARS CoV-2 / COVID-19 diagnostic tests. Accuracy and/or reliability remains highly variable. See FDA for current details: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations
- **Antigen tests**
    - Antigen tests detect viral protein fragments of proteins from samples collected from the nasal cavity using swabs.
    - The utility of this approach compared to PCR-based testing in diagnosis of COVID-19, its advantages (rapid turnaround being a major one) and disadvantages (less sensitivity), are a work in progress.
- **Serological (Antibody) testing**
    - IDSA Guidelines on COVID-19 serological testing here.
    - Cochrane review of serological testing here.

Treatment

Primary Regimens

- **See also Critical Care Considerations, below**
- **Patients with hypoxia**

    - Remdesivir (U.S. FDA Emergency Use Authorization 05/01/2020) (See Comments and provider Fact Sheet). Randomized trial demonstrating efficacy (for possible remdesivir drug-drug interaction, see Remdesivir)
        - Adult dosing (wt > 40 kg): 200 mg IV loading dose on day 1, then 100 mg IV daily maintenance dose
            - Infuse each dose over 30-120 min
            - 5 day course if not on ventilation/ECMO. If no clinical improvement at 5 days, extend to 10 days
            - 10 day course for patients on mechanical ventilation/ECMO
        - Pediatric dosing (wt 3.5 - 40 kg): 5 mg/kg loading dose on day 1, then 2.5 mg/kg maintenance dose
            - 5 day course if not on ventilation/ECMO. If no clinical improvement at 5 days, extend to 10 days
            - 10 day course for patients on mechanical ventilation/ECMO
    - **Dexamethasone** (see Comments)
        - 6 mg once daily IV or po x 10 days for patients on supplemental oxygen or receiving mechanical ventilation
        - **Do not use** in patients who do not require supplemental oxygen or mechanical ventilation: no benefit, possible harm (**see Comments**).
    - **No other therapies are of proven efficacy: enrollment in a randomized clinical trial, if available, is strongly encouraged**
        - IDSA Guidelines on Treatment and Management of Patients with COVID-19
        - NIH COVID-19 Treatment Guidelines.
- **Patients without hypoxia**
    - Supportive care

Alternative Regimens

- None

Critical Care Considerations

- **Critical illness, hospitalized in ICU, on mechanical ventilation**. **For suuggested interventions** see NIH COVID-19 Treatment Guidelines
    - **Fluids**: balanced crystalloids
    - **Pressors**: norepi > vasopression/epi; cardiogenic shock - dobutamine; not dopamine
    - **Steroids**:
        - Refractory shock: consider low dose hydrocortisone
        - Dexamethasone: see **Primary Regimens** above
    - **Anti-inflammatory**: acetaminophen and/or ibuprofen
    - **Anti-thrombolytic therapy guidelines here**
    - **Antiviral therapy for SARS CoV-2**: Remdesivir (See Primary Regimens, above)
    - **Co-infection** (Lancet Microbe online 24 Apr 2020, Cleve Clin J Med online May 2020)
        - Bacterial and fungal co-infection
            - Meta-analysis of 28 studies (22 from China, 2 US, 1 UK, I Spain, 1 Singapore, 1 Thailand) with 3448 hospitalized patients between 12/25/19 and 3/31/20 (Clin Microbiol Infect 220; Jul 22;S1198-743X(20)30423-7): Overall bacterial infection rate of 7.1% with 3.5% of patients infected at presentation and with 15.5% of patients developing secondary bacterial infections over the course of illness. Rates of

infection in critically ill patients and fatal cases were 8.1% and 11.6%, respectively. 71% of patients received systemic antibacterial therapy. Most common bacterial species (n=41 total) identified in infected patients were Mycoplasma spp. (29.3%), Haemophilus influenzae (19.5%), Pseudomonas aeruginosa (12.2%), Enterobacteriaceae (30%).
        - Single center study of 4267 hospitalized patients in New York City between 3/1/20 to 4/28/20 (Infect Control Hosp Epidemiol 2020; Jul 24, 1-13. doi: 10.1017/ice.2020.368): Overall bacterial and fungal infection rate of 3.6% with respiratory only infection in 46%, blood only in 40%, both in 14%. 95% of patients with positive respiratory cultures were intubated. The fatality rate in patients with bacterial or fungal co-infection was 57% with 28% still in hospital at the time of publication. Most common isolates were Staphylococcus aureus (44% respiratory, 30% blood, Pseudomonas aeruginosa (16% respiratory, 6% blood), Klebsiella spp. (10% respiratory, 3% blood), Enterobacter spp. (8% respiratory, 3% blood), E. coli (4% respiratory, 7% blood), S. epidermidis (12% blood), Streptococcus spp. (12% blood), and Enterococcus spp. (7% blood). There was 8 cases of candidemia and 1 case of pulmonary aspergillosis. 71% of COVID-infected patients, whether co-infected or not, received antimicrobial therapy. A significant decline in antimicrobial susceptibility of Enterobacteriaceae was observed.
    - **Empiric antimicrobial therapy:**
        - Reasonable to consider but data above suggest bacterial co-infection occurs only in a minority of patients
        - If initiated, re-evaluate at 2-3 days and adjust or discontinue antimicrobials, as appropriate, based on clinical status and microbiology.

Comments

- **Remdesivir**
    - **Efficacy demonstrated** in one placebo-controlled randomized trial.
        - Superior to placebo in shortening time to recovery in hospitalized adults (N Engl J Med online 22 May 20): Randomized, double-blind, placebo controlled trial of 1059 patients (NCT04280705) sponsored by NIAID found that patients that remdesivir treated patients had a median time to recovery of 11 days compared to 15 days for patients who received placebo ($p<0.001$). The odds of clinical improvement, a secondary outcome, were higher in the remdesivir group at the day 15 visit, than in the placebo group (odds ratio for improvement, 1.50; 95% CI, 1.18 to 1.91; P = 0.001; 844 patients). Results also suggested a survival benefit, with a 14-day mortality rate of 7.1% for the group receiving remdesivir versus 11.9% for the placebo group (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04; 1059 patients). Rates of adverse events were similar. Subgroup analysis suggested benefit across multiple subgroups with the notable exception of patients receiving mechanical ventilation or ECMO, suggesting a lack of efficacy in those with advanced disease.
    - Efficacy of 5-day and 10-day courses of Remdesivir similar for patients with severe COVID-19 not requiring mechanical ventilation (N Engl J Med, May 27, 2020, doi: 10.1056/NEJMoa201530) (JAMA 2020)
    - Press release from Gilead: greater clinical improvement in patients with moderate COVID-19 (pneumonia "without reduced oxygen levels") who were treated with remdesivir for 5 days compared to standard of care.
    - Guidance from NIH, in times of drug shortages, remdesivir should be prioritized for use in hospitalized patients who require supplemental oxygen but who are not on high-flow oxygen,

noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)

- **Dexamethasone**
  - **Efficacy demonstrated** in an open-label, randomized controlled trial:
    - The RECOVERY trial (see N Engl J Med. 2020 Jul 17. doi: 10.1056/NEJMoa2021436) an open-label, randomized controlled trial comparing dexamethasone, 6 mg once daily for up to 10 days (n= 2104) to usual care (n=4321) found lower 28-day mortality in dexamethasone-treated patients (22.9%) compared to usual care (25.7%) (age adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.75 to 0.93; P<0.001). Dexamethasone reduced deaths in patients receiving invasive mechanical ventilation (29.3% vs. 41.4%, RR 0.64 [95% CI 0.51 to 0.81), and in patients receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%, RR 0.82 [95% CI 0.72 to 0.94]). Dexamethasone did not reduce mortality in patients not receiving respiratory support at randomization (17.8% vs. 14.0%, RR 1.19 [95% CI 0.91 to 1.55]). Dexamethasone was associated with fewer hospital days (median 12 days vs. 13 days) and a greater probability of discharge within 28 days (rate ratio 1.10 [95% CI 1.03 to 1.17]), which was greatest for those receiving mechanical ventilation at baseline. For patients not on mechanical ventilation at baseline, the risk for progression to the pre-specified composite secondary outcome of invasive mechanical ventilation or death was lower in dexamethsone-treated patients (risk ratio 0.92 [95% CI 0.84 to 1.01]); the effect was greater for patients receiving oxygen at randomization.

- **Convalescent plasma**
  - **Efficacy unproven.**
  - FDA issued a hold on Emergency Use Authorization (EUA) approval, and 24 hrs later issued the EUA(!), based on the 35,322 patient, non-randomized, non-controlled study described below.
  - Pre-print, not peer-reviewed, uncontrolled, non-randomized trial of 35,322 hospitalized patients with COIVD-19 found that earlier use (within 3 days versus > 4 days after diagnosis) of convalescent plasma and administration of plasma with higher antibody titers (stratified into low, medium, and high) were associated with improved 7-day and 30-day mortality. Although these results are encouraging, there are numerous limitations to the study that preclude a definitive assessment of efficacy of convalescent plasma for treatment of COVID-19. These include, first and foremost, its non-randomized observational design and lack of a control group; secular changes in mortality over the course of the study; heterogeneity of patients who were enrolled; use of concomitant medications that could have affected outcome; and uncertain generalizability to current standard of care therapies with Remdesivir and dexamethosone.
  - Small, under-powered, open-label randomized controlled trial (JAMA. 2020 Jun 3. doi: 10.1001/jama.2020.10044) comparing convalescent plasma in addition to standard treatment (n=52) to the control of standard treatment alone (n=51) found no statistically significant difference in time to clinical improvement at 28 days, the primary endpoint: 51.9% in the convalescent plasma group vs 43.1% in the control group (difference, 8.8% [95% CI, -10.4% to 28.0%]. For those with severe disease the primary outcome occurred in 91.3% (21/23) of the convalescent plasma group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; P = 0.03) of those with severe disease and in 20.7% (6/29) of the convalescent plasma group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; P = 0.83) of those with lifer-threatening disease. 28-day mortality was not statistically significantly different (15.7% vs 24.0%; P = 0.30). Convalescent plasma treatment vs. control was associated with conversion of viral PCR to negative at 72 hours: 87.2% vs 37.5% (P < 0.001).
  - A case series (J Clin Invest. 2020 Jun 1;130(6):2757-2765) of more than 5,000 patients with COVID-19 who received convalescent plasma found the incidence of serious adverse events in the first 4 hours of transfusion to be <1%.

- **IL-6 receptor antagonists**
  - **Efficacy unproven.**
  - **Sarilumab:** Regeneron Pharmaceuticals and Sanofi announced in a press release that the U.S. Phase 3 randomized controlled trial of sarilumab added to best supportive care compared to best supportive care alone (placebo) failed to meet its primary and secondary endpoints.
  - **Tocilizumab:** Roche announced in a press release of that its phase III tocilizumab failed to meet its primary endpoint in hospitalized adult patients with severe COVID-19 associated pneumonia. The primary endpoint was clinical status, which was measured by a 7-category ordinal scale based on need for supplemental oxygen requirements, and intensive care and/or ventilator use.
- **Chloroquine or Hydroxychloroquine ± Azithromycin**
  - **Not recommended in any setting due to lack of efficacy and risk of serious, potentially fatal cardiac arrhythmia.**
  - FDA Emergency Use Authorization (EUA) revoked on June 15, 2020.
  - **Outpatient, mild disease; post-exposure prophylaxis**:
    - Double-blind randomized placebo controlled trial (NCT04308668) of 491symptomatic, non-hospitalized patients with confirmed (58%) or probable COVID-19 and high risk exposure within 4 days of symptom onset: hydroxychloroquine for 5 days **did not significantly reduce symptom severity** (Ann Intern Med online 16 Jul 2020).
    - Double-blind randomized placebo controlled trial of hydroxychloroquine (N Engl J Med.2020 Jun 3. doi: 10.1056/NEJMoa2016638): **lack of efficacy** of hydroxychloroquine **as post-exposure prophylaxis.**
  - **Hospitalized, mild-to-moderate disease:**
    - Multicenter, randomized, open label trial (N Engl J Med . 2020 Jul 23. doi: 10.1056/NEJMoa2019014) of hospitalized patients with suspected or confirmed Covid-19 who were receiving either no supplemental oxygen or a maximum of 4 liters per minute of supplemental oxygen. Hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as assessed with a seven-level ordinal scale as compared with standard care. QTc prolongation and elevation of liver-enzyme levels were more frequent in patients receiving hydroxychloroquine, alone or with azithromycin.
  - **Hospitalized, severe disease:**
    - **Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial** (NCT04381936): hydroxychloroquine arm terminated with 1,542 patients randomized to hydroxychloroquine and 3,132 patients randomized to usual care alone due to **lack of clinical benefit** in hospitalized patients with COVID-19: no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10); no beneficial effects on hospital stay duration or other outcomes.
    - Study from Brazil (JAMA Netw Open. 2020 Apr 24;3(4.23):e208857) comparing 2 dosage regimens of chloroquine diphosphate terminated early due to **toxicity:** ventricular tachycardia in 2 patients (both in the higher dose arm), 15% with QTc prolongation > 500 msec (11% in the lower dose group, 18% in the higher dose group).
- **Cytidine nucleoside analogs**
  - EIDD-1931: Broad spectrum antiviral activity against SARS-CoV-2, MERS-CoV, SARS-CoV, and group 2b or 2c Bat-CoVs. Increased potency against CV bearing resistance mutations to remdesivir. Now entering Phase I studies in patients with COVID-19.
  - EIDD-2801: Similar compound as EIDD-1931 except it has an isopropyl ester at the 5' position. In mice models infected with SARS-CoV and MERS Co-V, this drug reduced virus titers and body weight loss, while improving pulmonary function. Sci. Transl. Med. 12: 541, Apr 2020

- **HIV protease inhibitors:**
  - **Clinical benefit not demonstrated.**
  - **Lopinavir/ritonavir**
    - RCT showed no benefit and no antiviral effect vs. standard care (N Engl J Med doi: 10.1056/NEJMoa2001282)(03/18/20). High risk of adverse drug-drug interactions (see University of Liverpool compilation: https://www.covid19-druginteractions.org/).
    - Open label, phase 2 randomized controlled trial of a 14-day triple drug combination of lopinavir/ritonavir 400 mg/100 mg + ribavirin 400 mg every 12 h + up to 3 doses of 8 million international units of interferon beta-1b on alternate days (86 subjects) versus 14 days of lopinavir/ritonavir 400 mg/100 mg every 12 h alone (41 subjects) for mild to moderate COVID-19 found that the combination reduced viral load to undetectable more rapidly (7 days vs. 12 days) and shortened time to clinical improvement (4 days vs. 8 days). There were no deaths in either group.
  - **Darunavir**: no in vitro activity, no evidence of any effect - do not use (https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hv-treatments-for-coronavirus)
- **Interferon-beta**
  - **Efficacy unknown.**
  - Press release on July 20 from Synairgen announced positive results of a phase II placebo controlled trial of inhaled interferon-beta.
- **Clinical trials of interest:**
  - **ACTT-2** (NCT04401579) will evaluate the combination of baricitinib (a Janus kinase inhibitor) and remdesivir compared to remdesivir alone in hospitalized patients with COVID-19
  - **ACTT-3** (NCT04492475) will evaluate the combination of interferon beta-1a and remdesivir compared to remdesivir alone for hospitalized patients with COVID-19.
  - **BLAZE-1** (NCT04427501) will evaluate a single dose of intravenously administered LY3819253 (LY-CoV555, a neutralizing IgG1 monoclonal antibody directed against the spike protein of SARS-CoV-2) compared to placebo in out-patients with Mild to Moderate COVID-19
  - Updates on COVID-19 research here.
- Other therapeutic options under evaluation:
  - See CDC Guidance on therapeutic options: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. See Summary table of on-going trials compiled by the American Society of Health-Systems Pharmacists. Review of treatment options being explored: April 13, 2020 AMA Network
  - See ClinicalTrials.gov (search term = COVID-19) for current status of trials.