Infectious Disease: SARS-CoV-2 (COVID-19) Treatments


- The Wuhan coronavirus is officially named SARS-CoV-2
- COVID-19 is the name of the disease caused by SARS-CoV-2
- As of 6/18/2020, WHO reported 8,375,368 confirmed cases of COVID-19 (coronavirus disease) and 449,530 deaths around the world (2,163,290 cases in US with 117,717 deaths, more than any other country)
- Death rate for COVID-19 averaging around 5.3% globally, but since denominator is underestimated, death rate is likely lower
- Death rate for other coronaviruses (SARS and MERS):
  - SARS: ~10% (777 deaths/8000 patients)
  - MERS: ~34% (858 deaths/2500 cases)
- Ebolavirus is not a corona virus, but has a much higher fatality ~50%
- Influenza virus (common flu) is common in US, infecting up to 45 million Americans each season, with a death rate of ~0.14%

Dexamethasone reduces risk of death by 35% in patients on a ventilator

- On June 16, 2020, top-line results from the RECOVERY trial led by the University of Oxford suggests that low-dose dexamethasone can reduce the risk of death by 35% in hospitalized patients with severe respiratory complications of COVID-19
  - 2,104 patients on 6mg of dexamethasone once a day (oral or IV) were randomly compared to 4,321 patients assigned to usual care alone
  - In patients who needed to be on a ventilator, dexamethasone reduced the death rate by 35%; need to treat 8 ventilated patients to prevent one death
  - In patients who needed oxygen but were not ventilated, the death rate was reduced 20%; need to treat 25 patients to prevent one death
  - Both results were statistically significant
- No benefit in patients who did not require any oxygen
- RECOVERY researchers stopped enrolling patients on dexamethasone on June 8 because they believed they had enough data to get a clear result
- Dexamethasone would be the first drug to show an improvement in survival benefit in patients who need oxygen
- RECOVERY has recruited over 11,500 patients who were randomized to one of multiple arms testing potential treatments for COVID-19:
  - Dexamethasone
  - Kaletra (lopinavir/ritonavir)
  - Actemra (tocilizumab)
  - Azithromycin
  - Convalescent plasma
  - Standard care
  - The hydroxychloroquine arm was stopped in early June after it was found to show no clinical benefit to hospitalized patients

FDA Revokes Emergency Use Approval for Hydroxychloroquine

- On June 15, 2020, the FDA said it has withdrawn EUA for hydroxychloroquine based on research over the past several weeks showing hydroxychloroquine was not effective at treating or preventing Covid-19
- The hydroxychloroquine arm of RECOVERY showed no benefit in hospitalized patients

FDA Issues Emergency Use Authorization (EUA) of Remdesivir on May 1, 2020

- Based on April 29, 2020, NIAID’s Adaptive COVID-19 Treatment Trial or ACTT, EUA issued as remdesivir accelerates recovery from advanced COVID-19
- Hospitalized patients with advanced COVID-19 and lung involvement who received remdesivir recovered faster than similar patients on placebo
- Randomized, controlled trial involving 1063 patients, which began on Feb 21, 2020
- Preliminary results:
  - Remdesivir patients had a 31% faster time to recovery than those who received placebo (p<0.001)
  - 11 days median time to recovery with remdesivir vs 15 days for placebo
- Results also suggest a survival benefit, with a mortality rate of 8.0% for remdesivir group vs 11.6% for the placebo group (p=0.059)

IDSA Guidelines Published April 11, 2020

- All drugs currently being used and studied to treat COVID-19 should be used only in the context of a clinical trial, that there is no data to support benefit outweighs risks at this point.
- This includes hydroxychloroquine +/- azithromycin, Kaletra, Actemra, corticosteroids, convalescent plasma

WHO to launch SOLIDARITY trial: multarm, multicountry clinical trial for potential coronavirus therapies

- Announced on March 18, 2020
- Numerous countries joined to test drugs to allow for larger numbers and better data to determine efficacy
- Multiple small trials with different methodologies make it difficult to obtain clear evidence needed to confirm efficacy
- Drugs to be studied include:
  - remdesivir
  - lopinavir + ritonavir (Kaletra)
  - lopinavir + ritonavir + interferon beta
  - chloroquine +/- azithromycin

FDA Issues Safety Alert for Use of Hydroxychloroquine/Chloroquine for COVID-19

- On April 24, 2020, the FDA warned against use of hydroxychloroquine and chloroquine for COVID-19 treatment to warn against its use outside of certain closely supervised settings due to risk of serious heart rhythm problems
Use of ACE Inhibitors/ARBs and Risk

ACE inhibitors/ARBs There have been reports regarding the use of some antihypertensive agents, known as ACE inhibitors or ARBs, causing a greater risk for the coronavirus. To dispel these reports, the Heart Failure Society of America (HFSA), the American College of Cardiology (ACC), and the American Heart Association (AHA) published a statement addressing these concerns on March 17, 2020.

Reports regarding the use of ACE inhibitors and ARBs surfaced after a scientific paper indicated that ACE 2 receptors have been shown to be entry points for SARS-CoV-2 (virus). The report also stated that in animal models, ACE inhibitors and ARBs have been shown to upregulate ACE2 expression in the heart. This has not been shown in human studies or in the setting of COVID-19, however, the potential upregulation of ACE2 by ACE inhibitors or ARBs has resulted in speculation of potential increased risk for COVID-19 infection in patients on these medications.

The statement published by the three organizations stated the following:

- ACE2, ACE, angiotensin II and other renin angiotensin aldosterone system (RAAS) system interactions are quite complex, and at times paradoxical.
- Tissue expression of ACE2 differs in heart, kidneys, and lungs of healthy patients, cardiovascular disease patients, and coronavirus-infected patients, and its role in the setting of COVID-19 infection in patients with cardiovascular disease is unclear.
- Furthermore, in experimental studies, both ACE inhibitors and ARBs have been shown to reduce severe lung injury in certain viral pneumonias, and it has been speculated that these agents could be beneficial in COVID-19.

The three organizations recommend continuation of these antihypertensive medications for those patients who are currently prescribed to treat indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease. The statement also mentions that there is not enough information about them and that in experimental studies, both ACE inhibitors and ARBs have been shown to reduce severe lung injury in certain viral pneumonias.

Use of NSAIDs in COVID-19 Patients

In addition to the antihypertensive speculation, there are also discrepancies as to whether nonsteroidal anti-inflammatory drugs (NSAIDs) are harmful in patients with the virus. French officials suggested that use of these agents should be avoided and that acetaminophen be used in their place. However, many physicians both inside and outside of France countered that there is insufficient evidence to state this. Physicians can recommend treatment with acetaminophen. Dr. Gregory Poland, a professor of medicine and infectious disease and director of the Vaccine Research Group at the Mayo Clinic in Rochester Minnesota said that without clarification of any new detailing effects, additional risks of NSAIDs related to COVID-19 are questionable.

Pandemic Influences on the Healthcare System

The pandemic could cause issues in many different sectors of the healthcare system. This includes:

- FDA medication reviews: Potential delays in FDA review of already submitted medications
- FDA Advisory Committee meetings: Potential for delays in FDA reviews due to postponement of FDA Ad Committees
- Clinical trials for non-COVID-19 studies: Potential delays in developing and starting medication studies, delays in physician and patient recruitment
- Postponement of New Drug Approvals and Launches: Pharmaceutical companies may delay launch of new medications
- Mergers: The merger between Mylan and Upjohn has been delayed to the second half of 2020

Clinical Snapshot

Coronaviruses and SARS-CoV-2 (COVID-19)

Coronavirus

- Common virus (crown-shaped) that mostly causes sinus infections and is spread the same way other cold-causing viruses, mostly by infected people coughing and sneezing or touching – most coronaviruses are not dangerous
- There are more virulent coronaviruses such as:
  - SARS (severe acute respiratory syndrome) – killed more than 800 people in 2002–2003 outbreak
  - MERS (Middle East respiratory syndrome)
- Coronaviruses are not as fatal as Ebolavirus (50% fatality rate)
- So far, COVID-19 has about 4.5% global fatality rate
- Symptoms are similar to flu
- Incubation time of 10 to 14 days, during which time the virus can be transmitted, patient does not have to be symptomatic to transmit coronavirus
- COVID-19 appears to be most life-threatening to the ill and elderly

Origin and Spread of SARS-CoV-2

- May have originated from an animal source, although WHO said they did not know specific source
- Coronaviruses are zoonotic, meaning they are transmitted between animals and humans
- 2002 SARS-CoV was transmitted from civet cats to humans and MERS-CoV was transmitted from dromedary camels to humans

How to Prevent Spread of SARS-CoV-2

- Practice respiratory hygiene: when coughing and sneezing, cover mouth and nose with tissue or flexed elbow and discard tissue immediately into a closed bin, and wash hands thoroughly with soap and water or alcohol-based hand rub
- Avoid touching eyes, nose, and mouth
- Wash hands often
- If fever, cough, and difficulty breathing are present, seek medical care early
- Observe travel bans
- Social distancing

Should Face Masks be Used?

about:blank
On April 2, 2020 CDC reversed its original recommendation and recommended that citizens should wear "non-medical, cloth masks" to help prevent the spread of coronavirus.

Previously, the CDC had recommended that only those with COVID-19 symptoms wear masks.

The agency now recommends that those who aren’t feeling sick should still wear a mask, though compliance is voluntary.

This change in policy is based on new research that there are people who do not show symptoms and can still spread the virus as they move about in public.

The CDC specifically states "cloth face coverings fashioned from household items or made at home from common materials at low cost can be used as an additional, voluntary public health measure.

Sheltering in place is still the most effective way to protect oneself and those in the community, and the agency recommended maintaining 6-foot social distancing as the primary method of reducing exposure.

Are There Multiple Strains of SARS-CoV-2?

- WHO states there is no evidence that the virus is changing
- An analysis at the Peking University in Beijing studied the viral genome taken from 103 cases and identified 2 types of the virus based on differences in the genome at 2 regions: an "L-type" and "S-type"
- A larger, online database has collated sequencing results from 166 cases
- It is expected that more strains will emerge
- Epidemiologists generally agree that once a person is infected with SARS-CoV-2, they are unlikely to be infected again, unless the virus mutates, allowing it to overcome the specific antibodies created.

Acute Respiratory Distress Syndrome and COVID-19

Acute respiratory distress syndrome (ARDS) is an acute, life-threatening inflammatory lung injury characterized by hypoxia, and stiff lungs due to increased pulmonary vascular permeability, making breathing difficult or impossible. ARDS necessitates hospitalization and mechanical ventilation. Even with implementing standard of care, including mechanical ventilation, ARDS has an overall mortality rate of 41%.

One of the complications of COVID-19 is ARDS. Patients with severe cases of COVID-19 experience severe viral pneumonia that can progress to ARDS and death.

Mallinckrodt is evaluating the potential role for inhaled nitric oxide (iNOmax) for treating/preventing ARDS:
- Inhale nitric oxide (iNO) has demonstrated an inhibitory effect on the replication cycle of severe ARDS-related coronavirus
- In one study, investigators utilized iNO used to treat 5 patients infected with SARS-CoV-2 compared to controls:
  - Improvements found in blood oxygenation, reduction in supplemental oxygen, and reduction in amount of ventilator support

Potential Studies with tPA in Coronavirus-induced ARDS

- Scientists are considering developing a clinical trial for the use of tissue plasminogen activator (tPA)
- An article was published in the most recent edition of the Journal of Trauma and Acute Care Surgery (Yaffe, et al. 2020)

Other Ongoing and Potential Studies for Coronavirus-induced ARDS

- There are 14 ongoing clinical studies registered with the U.S. National Library of Medicine as of March 27, 2020, in coronavirus-induced ARDS. Some include:
  - IV aviptadil
  - gimsilumab
  - hydroxychloroquine
  - remdesivir
  - convalescent plasma
  - normal saline
  - losartan
  - streptokinase

Testing for SARS-CoV-2

Under the stimulus deal, manufacturers of the coronavirus tests will have to publish their 'cash prices.'

Rapid Test for SARS-CoV-2

On March 21, 2020, Cepheid's Xpert<sup>®</sup> Xpress SARS-CoV-2, a rapid molecular diagnostic test for qualitative detection of SARS-CoV-2, the virus causing COVID-19, was approved by the FDA via Emergency Use Authorization (EUA). The test will operate on any of Cepheid’s more than 23,000 automated GeneXpert<sup>®</sup> Systems worldwide, with a detection time of approximately 45 minutes.

With increased demand for hospital services, clinicians need a rapid, on-demand diagnostic test for real-time management of patients being evaluated for admission to hospitals. A test that provides lab-quality results in multiple settings where actionable treatment information is needed quickly can improve the process of triage and taking care of infected or non-infected patients efficiently.

Cepheid currently has nearly 5,000 GeneXpert<sup>®</sup> Systems in the US capable of point-of-care testing for use in hospitals and stated that test will begin shipping the week of March 31, 2020.

The Accula™ SARS-CoV-2 Test from Mesa Biotech has been approved, which allows for an easy to use. It is a rapid molecular SARS-CoV-2 testing with diagnostic results in 30 minutes. The palm-sized system can be used at temporary screening facilities, physician offices, urgent cares, and long-term care facilities.

Abbott has also stated that they have received FDA approval for a fast acting molecular test, the Abbott ID NOW COVID-19, that can diagnose a positive viral test result within 5 minutes and a negative test result within 13 minutes. Again, this test is portable and can be used in hospital emergency rooms, urgent care centers, and physicians' offices. The company says it will start shipping out 50,000 tests a day by April 1st.

Serological Antibody Testing

- Current PCR testing is for viral load and relies on nasal or throat swabs.
- There are different companies working on serological tests to detect antibodies in patients who may not have shown symptoms could be available soon. These tests rely on blood samples.
Infectious Disease: SARS-CoV-2 (COVID-19) Treatments

6/30/2020

Cost, Utilization and Reimbursement

Impact on United States

Clinical Drug Trials and FDA

- Some clinical trials are reporting delays or suspension by the coronavirus issues
- Potential delays in new studies (just starting) or in development of studies

Healthcare System

- Increase in telemedicine and remote counseling
- Increase in mail order pharmacy use (There is speculation about whether this will be a lasting effect.)
- More health plans and insurers are overriding ‘refill too soon’ edits and are allowing for 90-day supplies even at retail pharmacies
- Increased use of retail clinics

Wholesale Companies

- Wholesale companies like to have a 30-day supply at hand, and a 10-day turn-over for expensive branded medication and specialty medication (if they dispense them)
- Wholesalers are worried about demand and are increasing their inventory levels
- People are requesting 30-90-day supplies of medications (health organizations are advising people to do so)

The Congressional Coronavirus Package includes:

- Guidance issued on April 11, 2020 clarifying coverage requirements for private payers
- Commercial health plans required to provide access to COVID-19 testing and visits for care related to the virus - both in-person and through telehealth - at doctor's offices, urgent care centers and emergency departments available at no cost
- CMS also said mandates will extend to antibody testing once it's made more readily available

Medication Pricing During Coronavirus Outbreak

One of the questions being bantered about regarding potential medications to treat the coronavirus is, if approved, what will they cost? There is potential for pharmaceutical companies to greatly profit by developing a medication for the virus. Recently, Rep. Jan Schakowsky and other House members wrote to the President and to Health and Human Services Secretary Alex Azar, asking to ensure that any treatment developed with taxpayer dollars be accessible, available, and affordable.

Many of the experimental medications for the coronavirus are conjointly developed by government bodies and the pharmaceutical industry. This means that there is taxpayer money being used to develop these drugs. Some examples include Regeneron and the federal Biomedical Advanced Research and Development Authority and Gilead’s remdesivir, which was developed by the University of Alabama and Antiviral Drug Discovery and Development Center (UAB was awarded a $37.5 million, five-year U19 grant from the National Institute of Allergy and Infectious Diseases Centers of Excellence for Translational Research to study and develop treatment for high-priority emerging infections).

Investigational Treatments with Approved Drugs

On April 14, 2020, the Infectious Diseases Society of America (IDSA) says there's not yet sufficient evidence to recommend any of them. The IDSA issued interim guidelines on medications for patients admitted to the hospital with COVID-19, most of which recommend their use only in the context of clinical trials, or not at all.

Many treatments, including antivirals already approved in the United States for other indications, are being used or studied around the world for coronavirus:

AbbVie's Kaletra was studied in the original SARS outbreak of 2002, but further studies were not completed because the outbreak ceased. For SARS-CoV-2, AbbVie donated Kaletra to be studied.

- Results of a randomized, controlled open-label clinical trial that evaluated oral lopinavir-ritonavir for treatment of hospitalized patients with severe COVID-19 infection conducted in China (Lopinavir Trial for Suppression of SARS-CoV-2 in China) were published in the March 18, 2020 edition of the New England Journal of Medicine.
- Trial conducted from 1/18/2020 through 2/03/2020 (the date of enrollment of the last patient), at Jin Yin-Tan Hospital, Wuhan, Hubei Province, China.
  - Eligible patients were randomly assigned in a 1:1 ratio to receive either oral lopinavir-ritonavir (400 mg and 100 mg) plus standard care, or standard care alone for 14 days
  - Standard care included supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation (ECMO) as necessary
  - Total of 199 adult patients enrolled in trial: 99 lopinavir-ritonavir; 100 standard care alone
  - Patients aged 49–68 years with a median age of 58 years
  - Median interval time between symptom onset and randomization was 13 days
  - Results for the primary endpoint (time to clinical improvement) were found not to be different between the two treatment groups (median of 16 days in each group)
  - Also, results showed no difference in the secondary outcome of 28-day mortality, which was 22.1% in this trial, reflecting the severity of illness in these patients
  - Authors suggested that based on results of sub-group analysis, there may be a possibility that patients may have better outcomes if treated earlier in the course of disease and may experience less severe symptoms when treated with lopinavir-ritonavir, but acknowledged that these observations can only be considered to be hypothesis-generating at this time.

Chloroquine phosphate, an old malaria drug: Scientists at the Wuhan Institute of Virology’s State Key Laboratory of Virology write that both chloroquine and the antiviral remdesivir were, individually, "highly effective" at inhibiting replication of the novel coronavirus in cell culture. Their drug screen evaluated five other drugs that were not effective.

- Mechanism of action:
  - Broad-spectrum antiviral activity by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV-2
Infectious Disease: SARS-CoV-2 (COVID-19) Treatments

Management Opportunities and Strategies

Drug Shortages

The FDA website lists drugs currently in shortage; however, the ASHP website may be more up to date.

- https://www.accessdata.fda.gov/scripts/drugshortages/
- https://www.ashp.org/Drug-Shortages/Current-Shortages

As of March 24, 2020, ASHP lists both hydroxychloroquine and albuterol MDIs in shortage, while the FDA website does not.

Due to the potential for stockpiling, the FDA is not informing which drugs are in short supply specifically due to coronavirus. Italy is the world’s third largest producer of active pharmaceutical ingredients behind India and China. We will continue to monitor for potential shortages.

The US may be impacted by the possibility of shortage of raw ingredients or drugs, as most often they come from China or India. China provides the raw material used in 13% of US drugs. SARS-CoV-19 is shutting down factories in China and preventing FDA from ensuring the plants meet US manufacturing standards, which could impact US supply if this disruption is sustained over several months.

There could be more reasons for drug shortages than the supplier issues. The CDC and other healthcare agencies are telling patients to stock up on their chronic medications. This has left many insurers and health plans to allow for 90-day supplies at retail pharmacies, not just mail order. In addition, they have lifted the 'refill too soon' edit, which allows patients to pick up as many refills as they deem. Wholesalers have traditionally allowed for a 30-day supply in their stocks, with a 2-3 weeks supply of expensive branded products. Wholesalers may be increasing their stock supply which could in turn cause supply issues.

Another issue that could potentially cause shortages is relaxing of patents. It was announced that AbbVie would relax its patent on Kaletra, a medication being tested for treatment of Covid-19. Once this happened, more generic manufacturers stated they would be producing the product which could cause a shortage of the active ingredient.

Metered Dose Inhalers instead of Nebulizers

Is there a nebulizer that can decrease the risk of aerosolizing the coronavirus?

- There does not seem to be a nebulizer that can decrease the risk of aerosolizing the coronavirus.
- Pulmonologists are trying to refrain from use of nebulizers altogether if they can.
- In the hospital setting they are trying to avoid the use of nebulizers as well as high flow oxygen and non-invasive ventilation among patients with known or suspected coronavirus who are in the hospital, due to risk of aerosolization of virus and increasing the risk of spread.
- For patients in their home who need to use a nebulizer and who are also sick, it is suggested that they consider using a designated room or closet while using nebulizers to decrease the risk of contaminating others at home.
- The situation in a nursing home or other group living situation is obviously much more difficult to control.
  - Some patients with COPD are unable to generate sufficient inspiratory force to use/activate many of the inhaler devices and therefore need nebulized therapy.
  - For them, switching to an alternative could be problematic for controlling the underlying condition.

Potential for Patients to Stockpile Inhalers

- Although payers are loosening refill-too-soon policies to remove this barrier for access to medications, it might be prudent to keep some in place for inhalers (specifically bronchodilators) and keep some quantity controls in place.
- Because inhalers expire, it would be prudent to encourage those patients with extra inhalers "hanging around" to suspend early refills until they draw down their supply.
### Pipeline

<table>
<thead>
<tr>
<th>Antivirals</th>
<th>Immunomodulators</th>
<th>Immune globulins</th>
<th>Other</th>
</tr>
</thead>
</table>

---
Infectious Disease: SARS-CoV-2 (COVID-19) Treatments

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
<th>Status</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-5734 Remdesivir</td>
<td>Gilead</td>
<td>Intravenous</td>
<td>Antiviral</td>
<td>Phase III</td>
<td>Ebola virus disease (EVD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Coronavirus disease 2019 (COVID-19)</td>
</tr>
</tbody>
</table>

- Multiple clinical trials worldwide
- Safety information already available from Ebola trials (failed efficacy against Ebola)
- Many small, compassionate use studies or non-controlled trials published
- No definitive conclusions can be made from these studies
- Gilead continues to increase the number of patients in 2 x Phase 3 clinical trials in US:
  - Randomized, open-label, multi-center studies in nearly 7600 patients (6000 patients with severe symptoms - up from original 400, and 1600 patients with moderate symptoms, up from 500):
    - Dose: 200mg IV on day one, followed by 100mg once daily for 5-10 days
    - Primary endpoints:
      - Odds of Ratio for Improvement on 7-point Ordinal Scale on Day 14 (1 = death, 7 = not hospitalized)
      - Data from the large open-label Phase 3 trial in severe patients expected end of April
      - Skepticism still exists that no conclusions can be made until placebo-controlled study reads out in late May
- On April 13, 2020, Gilead announced its large trials in China have been terminated or suspended because of a lack of patients to enroll - both patients with severe disease and milder forms of COVID-19. Some critics are commenting that if remdesivir had overwhelming efficacy, trials may have enrolled.

FDA Issues Emergency Use Authorization (EUA) of Remdesivir on May 1, 2020 Allowing Immediate Use in Hospitals

- Based on April 29, 2020, NIAID's Adaptive COVID-19 Treatment Trial or ACTT (NCT04280705), EUA issued as remdesivir accelerates recovery from advanced COVID-19
- Hospitalized patients with advanced COVID-19 and lung involvement who received remdesivir recovered faster than similar patients on placebo
- Randomized, controlled trial involving 1063 patients, which began on Feb 21, 2020
- Preliminary results:
  - Remdesivir patients had a 31% faster time to recovery than those who received placebo (<0.001)
  - 11 days median time to recovery with remdesivir vs 15 days for placebo
  - Results also suggest a survival benefit, with a mortality rate of 8.0% for remdesivir group vs 11.6% for the placebo group (p=0.059)
- Gilead also announced top-line results for one of its Phase 3 SIMPLE trials (NCT04292899), an international study that compared a 5-day to a 10-day course of remdesivir to determine whether a shorter duration of therapy may have the same efficacy and safety as the longer duration.
  - No control placebo control group
  - Found no significant difference in clinical improvement between the 5-day and the 10-day group on day 14 in hospitalized, but not ventilator-dependent COVID-19 patients
  - More than half the patients in both groups were discharged from the hospital by day 14
  - By day 14, 65% of the 5-day group and 54% of the 10-day group achieved clinical recovery.
  - Improved outcome was seen for patients receiving remdesivir within 10 days of symptom onset compared with those who started treatment later

<table>
<thead>
<tr>
<th>Plaquenil Hydroxychloroquine Sulfate</th>
<th>Concordia</th>
<th>Oral</th>
<th>Antimalarials</th>
<th>Phase III</th>
<th>Coronavirus disease 2019 (COVID-19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- On June 15, 2020, the FDA said it has withdrawn EUA for hydroxychloroquine based on research over the past several weeks showing hydroxychloroquine was not effective at treating or preventing Covid-19
- The hydroxychloroquine arm of RECOVERY showed no benefit in hospitalized patients
  - A total of 1542 patients were randomised to hydroxychloroquine and compared with 3132 patients randomized to usual care alone
  - There was no significant difference in the primary endpoint of 28-day mortality (25.7% with hydroxychloroquine vs. 23.5% for usual care)
  - There was also no evidence of beneficial effects on hospital stay duration or other outcomes
- On June 4, 2020, both Lancet and NEJM retract COVID-19 studies, including one that specifically raised safety concerns about hydroxychloroquine
- Both studies relied on data from a company that could not validate its primary data sources
- On May 7, 2020 NEJM published an analysis of hydroxychloroquine that showed minimal benefit
  - The observational study examined the association between hydroxychloroquine and outcomes in a large NYC medical center
  - 1376 patients evaluated for 22.5 days:
    - 59% received hydroxychloroquine 600mg BID on day 1, then 400mg QD x 5 days
    - 46% were treated within 24 hours after presentation to ED, and 86% within 48 hours
  - Hydroxychloroquine patients were more severely ill at baseline
    - 346 patients (25.1%) had a primary endpoint event
    - 180 patients were intubated, of whom 66 subsequently died
    - 166 died without intubation
  - No significant association between hydroxychloroquine use and intubation or death (HR 1.04, 95% CI, 0.82 to 1.32)
  - Results similar in multiple sensitivity analyses
  - Conclusion: Hydroxychloroquine was not associated with either a greatly lowered or an increased risk of the composite endpoint of intubation or death

<table>
<thead>
<tr>
<th>Resochin Chloroquine Phosphate</th>
<th>Bayer</th>
<th>Oral</th>
<th>Antimalarials</th>
<th>Developing</th>
<th>Coronavirus disease 2019 (COVID-19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- In vitro activity against various viruses, including coronaviruses
  - Study protocol from one trial in China: http://rs.yiigle.com/yufabiao/1182323.htm
  - Dose of chloroquine phosphate used in above trial:
    - 500mg twice daily for 10 days
    - If severe GI side effects occur, reduce dose to 500mg once daily or discontinue if necessary
    - Minimum course of treatment should be 5 days
  - Efficacy for treatment or prevention of Covid-19 has not been established.

<table>
<thead>
<tr>
<th>Kaletra Lopinavir; Ritonavir</th>
<th>AbbVie</th>
<th>Oral</th>
<th>Protease inhibitor</th>
<th>Developing</th>
<th>Coronavirus disease 2019 (COVID-19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Study results on the use of Kaletra in very ill patients with COVID-19 showed no benefit.
- Study examined 199 patients in China (99 patients received LP/RTV 400mg/100mg twice daily for 14 days) versus 100 patients who received standard of care - published in the New England Journal of Medicine
  - Kaletra did not lower mortality rate, nor did it significantly shorten time to clinical improvement
  - Time to clinical improvement in both arms of the study, Kaletra + standard of care(SOC) versus SOC alone, was 16 days
  - Should be noted that if the patients received Kaletra within 12 days after the onset of symptoms, there was a shorter time to clinical improvement
  - Duration from randomization to hospital discharge was 12 days in the SOC/Kaletra group and 14 days in the SOC alone group.
  - No significant differences in duration of oxygen therapy, duration of hospitalization and time to death.
  - More studies needed to determine whether earlier treatment could be beneficial

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Skepticism still exists that if remdesivir had overwhelming efficacy, trials may have enrolled.
On April 9, 2020, BoCryst Pharmaceuticals began enrollment into a randomized, double-blind, placebo-controlled clinical trial to assess the safety, clinical impact and antiviral effects of galidesivir in patients with COVID-19. The trial (NCT03891420) is being funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health. Galidesivir is a broad-spectrum antiviral drug that was safe and well tolerated in previously reported Phase 1 trials in healthy subjects. Galidesivir is an adenosine nucleoside analog that acts to block viral RNA polymerase. Galidesivir has demonstrated broad-spectrum activity in vitro against more than 20 RNA viruses in nine different families, including the coronaviruses that cause MERS and SARS.

In the COVID-19 trial, efficacy measures include time to clinical improvement, time to hospital discharge, time to undetectable levels as measured by PCR in respiratory specimen of SARS-CoV-2, and all-cause mortality.

Galidesivir COVID-19 Trial Design
- Part 1 of the trial will enroll 24 hospitalized adults diagnosed with moderate to severe COVID-19 confirmed by PCR.
- Three cohorts of eight patients will be randomized to receive intravenous (IV) galidesivir (n=6) or placebo (n=2) every 12 hours for 7 days.
- Upon completion of part 1 of the trial, an optimized dosing regimen of galidesivir will be selected for part 2 of the trial, based on part 1 results including safety, viral load reduction in respiratory tract secretions, improvement in COVID-19 signs and symptoms and clinical manifestations, and mortality.
- In part 2 of the trial, up to 42 hospitalized patients with COVID-19 will be randomized 2:1 to receive IV galidesivir or placebo.
- After treatment, the patients will remain hospitalized until resolution of COVID-19 symptoms allows release. All patients will be followed for mortality through Day 56.

The galidesivir development program is substantially funded with federal funds from NIAID and by the Biomedical Advanced Research and Development Authority (BARDA).

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company</th>
<th>Route</th>
<th>Mechanism</th>
<th>Status</th>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favipiravir</td>
<td>Fujifilm Toyama Chemical</td>
<td>Oral</td>
<td>Antiviral</td>
<td>Developing</td>
<td>Galidesivir COVID-19 Trial Design</td>
</tr>
<tr>
<td>Avigan</td>
<td>Toyama Chemical</td>
<td>Oral</td>
<td>Antiviral</td>
<td>Developing</td>
<td>Focus on efficacy measures including time to clinical improvement, time to hospital discharge, time to undetectable levels as measured by PCR in respiratory specimen of SARS-CoV-2, and all-cause mortality.</td>
</tr>
<tr>
<td>Glenmark</td>
<td>Toyama Chemical</td>
<td>Oral</td>
<td>Antiviral</td>
<td>Developing</td>
<td>Based on premise that galectin-1 is implicated in COVID-19</td>
</tr>
<tr>
<td>BXT-10</td>
<td>BioXyTran</td>
<td>TBD</td>
<td>Galectin inhibitor</td>
<td>Developing</td>
<td>Based on premise that galectin-1 is implicated in COVID-19</td>
</tr>
<tr>
<td>Stromectol</td>
<td>Merck &amp; Co</td>
<td>Oral</td>
<td>Antiparasitic agent</td>
<td>Developing</td>
<td>Old anti-parasitic drug used to treat head lice.</td>
</tr>
<tr>
<td>RVX-208</td>
<td>Resverlogix</td>
<td>Oral</td>
<td>Bromodomain and extraterminal (BET) inhibitor</td>
<td>Phase III Phase II</td>
<td>Reduce risk of myocardial infarction, stroke* Chronic kidney disease</td>
</tr>
<tr>
<td>COVID-19 Antibody</td>
<td>Formycon</td>
<td>TBD</td>
<td>Antiviral antibodies</td>
<td>Developing</td>
<td>Apabetalones shown to inhibit proteins called bromodomain and extraterminal domain (BET) proteins from interacting with a SARS-CoV-2 viral protein, with potential for disrupting viral reproduction while also limiting entry of the virus into human cells.</td>
</tr>
</tbody>
</table>

Note that these outcomes may only apply for those patients with no symptoms or mild symptoms.

Japanese health ministry suggests that favipiravir is not as effective in patients with more severe symptoms.

One study showed that favipiravir shortened the time to viral clearance in patients who took medication.

91% of patients who took favipiravir had lung improvement versus 62% of patients who did not get the medication.

Note that these outcomes may only apply for those patients with no symptoms or mild symptoms.

Glenmark announcement May 26, 2020:
- Glenmark studying favipiravir in Phase 3 clinical trials in India.
- Glenmark also starting FAITH trial to enroll 158 hospitalized patients with moderate COVID-19 to receive combination of 2 antiviral drugs: favipiravir and umifenovir.

Glenmark studying favipiravir in Phase 3 clinical trials in India

Glenmark also starting FAITH trial to enroll 158 hospitalized patients with moderate COVID-19 to receive combination of 2 antiviral drugs: favipiravir and umifenovir.

Glenmark also starting FAITH trial to enroll 158 hospitalized patients with moderate COVID-19 to receive combination of 2 antiviral drugs: favipiravir and umifenovir.

Based on premise that galectin-1 is implicated in COVID-19

Old anti-parasitic drug used to treat head lice.

In April 2020, researchers at Melbourne's Monash University Biomedicine Discovery Institute found ivermectin inhibited activity of COVID-19 in vitro, causing about a 5000-fold reduction in viral RNA after 48 hours.

Small observational study from University of Utah found that "critically ill patients with lung injury requiring mechanical ventilation may benefit from administration of ivermectin".

Phase 1 study recruiting 50 patients to compare ivermectin plus hydroxychloroquine in COVID-19 patients with pneumonia to hydroxychloroquine alone - recruitment starts April 8, 2020.

Ivermectin 0.2mg/kg (single dose at once = 2 tablets of 6mg weekly) plus hydroxychloroquine 400mg daily

Expected study completion date Aug 1, 2020.

Apabetalones shown to inhibit proteins called bromodomain and extraterminal domain (BET) proteins from interacting with a SARS-CoV-2 viral protein, with potential for disrupting viral reproduction while also limiting entry of the virus into human cells.

Resverlogix looking for collaboration with other company testing drugs for COVID-19 (per press release March 23, 2020).