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Key Inforbits

- COVID-19
- Treatments for COVID-19
- COVID treatment evolution

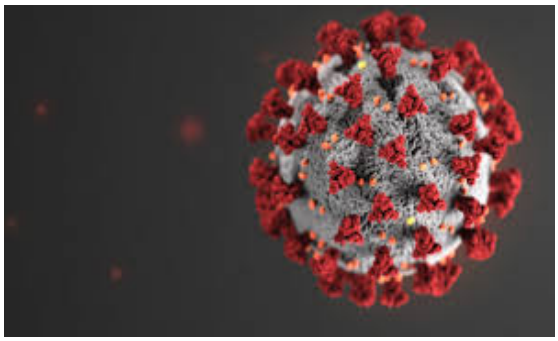

Photo by: Centers for Disease Control (CDC)

COVID-19

Corona virus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel coronavirus that originated from the Chinese city of Wuhan in late 2019. Since then, it has become a global pandemic that has shut down economies and killed a reported 371,000 people worldwide as of June 1st.[1] Previous coronaviruses have been shown to infect hosts by binding to ACE2 receptors, entering cells, and replicating.[2] COVID-19 is thought to infect its hosts in the same manner.[3]

Highly contagious, COVID-19 spreads primarily through airborne droplets that are expelled by an infected person breathing, coughing, sneezing, laughing, etc.[4] There is some possibility that it may spread through touch as well. It is more contagious than the flu. Once contracted, a typical 7 day incubation period begins and is followed by symptoms such as fever and/or chills, cough, shortness of breath, difficulty breathing, fatigue, body aches, headache, and loss of taste and/or smell. Some people may be asymptomatic and feel well, but still can spread the disease. The disease is hardest on elderly adults and people with underlying conditions and compromised immune systems.

Governments around the world have implemented strict measures to reduce spread of the virus, such as: restricted travel, restricted working conditions, mandatory distancing of six feet from those not in your household, and mandatory masks in public. Even though the virus has taken such a toll on the economy and global population, there remains few theoretically effective treatments. This *AU InforMed* investigates the top drug contenders for treating the virus and the evidence supporting or discouraging their use. It also offers a look at the progression of evidence for each medication as new studies are rapidly performed, potentially invalidating or strengthening previous studies.

Covid-19: Evolving Thoughts on Treatment

Then	Now
Hydroxychloroquine/chloroquine ● Early evidence and studies showed that these drugs killed COVID-19 *in vitro*, and that patients may experience faster clinical improvement when used. ● Studies have shown weak evidence that these drugs reduce viral load.	● The newest, largest study suggests that use of these drugs in the inpatient setting potentially increases cardiac arrhythmias, length of hospital stays, and death in patients with COVID-19. ● Food and Drug Administration (FDA) and National Institutes of Health (NIH) recommend *against* using it, for now, unless in the setting of a clinical trial. Studies are ongoing.
Azithromycin ● Azithromycin was initially thought to serve an anti-inflammatory purpose as a part of a regimen with hydroxychloroquine. ● It was also thought to lessen the body's overactive immune response to COVID-19 infection.	● Most recent studies suggest no benefit, and potential harm for Azithromycin and Hydroxychloroquine separately. ● In combination, these medications have potential for fatal arrhythmias. ● For these reasons, the National Institutes of Health (NIH) strongly recommends against this combination.
Remdesivir ● It is an antiviral drug that was originally made to combat the Ebola virus. The mechanism of action suggests remdesivir may fight COVID-19 as well. ● However, studies have had conflicting evidence of whether or not it truly helps.	● New data released on May 25th and June 1st suggest that remdesivir may reduce the time to recovery from COVID-19, allowing patients to be discharged faster and return home. ● Data is continuing to come in and the drug may benefit certain patients more than others.
ACE Inhibitors ● Data released on March 11, 2020 suggests that patients on angiotensin-converting enzyme (ACE) inhibitors are at an increased risk of severe COVID 19 infection.	● Data released on May 1, 2020 suggests that patients should continue taking their ACE-Inhibitors with or at risk of COVID 19 until further research is performed.
NSAIDs ● NSAIDs are anti-inflammatory medications. Inflammation is the body's defense against viral and bacterial pathogens. Because of this, the World Health Organization (WHO)recommended using Acetaminophen over NSAIDs for pain relief and fever reduction until more evidence was available.	● The WHO has downgraded their recommendation to suggest that use of Acetaminophen or NSAIDs is acceptable in COVID-19 cases. ● Many physicians are still cautious and recommend Tylenol over nonsteroidal anti-inflammatory drugs (NSAIDs) due to the initial recommendation.

Treatment options for COVID-19

Photo by: YA Web Design

Plaquenil (Hydroxychloroquine): Hydroxychloroquine (HCQ) is best known for its antimalarial properties and effectiveness in certain conditions like and rheumatoid arthritis.[6] It modulates the immune response by inhibiting the locomotion of neutrophils and chemotaxis of eosinophils. It combats malaria by increasing pH and interfering with hemoglobin degradation by lysosomes. When combatting COVID-19, it may change the pH at the cell membrane specifically and interfere with viral fusion, cellular entry, and viral replication. Once inside, it can inhibit viral protein production and nucleic acid replication, and also assembly and release of new viruses. There has also been evidence for the use of chloroquine, which is structurally related to HCQ and is the drug from which HCQ is derived. However, HCQ is less toxic, more potent, and more readily available to prescribe if needed.[7]

The theoretical use of HCQ to inhibit COVID-19 was shown in mid-March when *in vitro* testing showed inhibition.[8] When used in COVID-19 patients at a dose of 800 mg/day, it also reduced viral load and length of hospitalization and viral detection. Following this, several small studies were conducted around the world with results that would appear beneficial. However, the results were compromised by lack of control groups, lack of clear clinical data, lack of study power to detect significant differences, and small sample sizes.[9,10,11]

On May 22nd, *The Lancet* published a narrative and practice-changing article claiming that the use of HCQ for treating COVID-19 amongst hospitalized patients was harmful.[12] Evidence from an analysis of 96,000 COVID-19 patients across 6 continents in the inpatient setting was completed and published on May 22nd, 2020. The data presented in this review indicated that use of HCQ or chloroquine in any demographic resulted in at least an average increase of 130% chance for the development of cardiac arrhythmias. The risk of death had at least an average increase of 33% amongst any demographic using hydroxychloroquine or chloroquine.

This study, although the largest and most recently completed so far, has come under fire by scientists and statisticians over concerns about how and from where the researchers acquired their data.[13] But evidence is still forthcoming, and questions about how different demographics of patients respond is being evaluated. The FDA now recommends against hydroxychloroquine or chloroquine unless in the setting of a clinical trial.[14]

Zithromax (Azithromycin): Azithromycin inhibits RNA-dependent protein synthesis by binding to the 50S subunit.[15] It's use in COVID-19 originated from its anti-inflammatory capabilities. It was intended to be an adjuvant therapy to hydroxychloroquine for its anti-inflammatory properties, and to dampen the body's overactive immune response to COVID-19; however, recent studies have shown no benefit, and potential harm to patients using hydroxychloroquine or azithromycin. In combination, these medications are particularly dangerous, potentially causing fatal arrhythmias. The FDA now formally recommends against

this combination and the NIH also strongly recommends against its use. The FDA has stated that it recommends against use of hydroxychloroquine and azithromycin unless in the setting of a hospital for the purpose of a clinical trial.[14]

Remdesivir: Remdesivir is an adenosine nucleotide prodrug that is metabolized to a nucleoside triphosphate metabolite after distribution into cells. COVID-19 viral RNA-dependent polymerase enzymes then incorporate the drug into the RNA chain that it is building.[16] The drug, once incorporated, prevents further additions to the chain, which in turn prevents replication and spread of the virus throughout the body. It is because of this MOA that researchers, physicians, scientists, pharmacists, and the biopharmaceutical industry holds high hopes for remdesivir treatment in diagnosed patients and for reduction of the duration of symptoms. Remdesivir is also an attractive treatment option because it is able to limit the reproduction and spread of the coronaviruses that caused severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), which are similar to the coronavirus responsible for COVID-19.[17]

In April, however, some cold water was thrown onto these hopes when a Chinese study found no statistical difference in discharge rates and symptom resolution between 158 patients taking remdesivir and 78 patients taking placebo when treatment began ten days after symptoms appeared. The study is one of the few randomized, double blind, placebo controlled standards that has been completed thus far, but the small study population resulted in the study only having a power of 58%, which is quite low.[18]

On May 25th, a new study was published with 1000 patients, a much larger sample size. This randomized, placebo controlled trial found that, after 10 days, remdesivir reduced symptom duration by 4 days to a statistically significant degree. Research is ongoing to determine if these effects are seen when treatment is initiated sooner rather than later, and if effects change between different demographics.[17]

Based on preliminary clinical trial data, the NIH COVID-19 treatment guideline panel recommends remdesivir for hospitalized COVID patients that have severe disease, defined as: SpO2 $\leq$94% requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. The guideline panel does not recommend remdesivir for treatment of mild or moderate COVID infection unless being used in a clinical trial.[19]

As an investigational drug, appropriate doses and side effects are still being evaluated. Notable side effects include elevated liver enzymes and potential hepatotoxicity, and infusion related reactions such as hypotension, nausea and vomiting, diaphoresis, and shivering. Drug-Drug interactions are not well defined, but remdesivir may be a minor substrate of CYP2C8, 2D6, and 3A4.[16]

Convalescent plasma: Convalescent plasma is plasma from a recovered COVID-19 patient. Convalescent plasma contains antibodies to SARS-CoV-2, which is the virus that causes COVID-19 infections. The antibodies found in this plasma are thought to help current COVID-19 patients fight the disease and reduce recovery time and severity of the disease. Although convalescent plasma has been used with varying success for similar diseases (2003 SARS-Cov-1 epidemic, measles, polio, 2009-2010 H1N1 pandemic, and 2012 MERS-Cov epidemic) in the past, its use in treatment of COVID-19 is considered investigational at this time. No clinical trial has been conducted for this treatment yet, so not much evidence is available to support convalescent plasma for treatment of COVID-19 in regards to safety and efficacy. On March 24, 2020, the FDA approved convalescent plasma use for patients with severe and life-threatening COVID infections.[14,20]

Medications that may pose a problem:

ACE Inhibitors: ACE Inhibitors (lisinopril, captopril, enalapril, etc.) are a class of antihypertensive medications that work by blocking the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Angiotensin II enzyme works in the RAAS system by countering RAAS activation, SARS-CoV-2's functional receptor. Speculation was posed to RAAS inhibitors affecting and altering the angiotensin II enzyme would lead to increased disease virulence of COVID 19[3,21]; however, new reports illustrate that there has been no connection between ACE inhibitors and any deleterious events associated with the COVID 19 pandemic.[3]

NSAIDs: NSAIDs, like ibuprofen, reversibly inhibit COX 1 and 2 enzymes, which leads to a reduction in prostaglandin precursors.[22] It is believed that COX-2 has a role in upregulation of human B lymphocytes and plays a role in antibody synthesis.[23] In early studies, a theory existed that taking ibuprofen could lead COVID-19 patients to develop severe illness, like pneumonia.[14] Recently, the World Health Organization announced that there is no evidence of severe adverse events or other negative health outcomes on COVID-19 infection directly associated with NSAIDS.[24] NIH COVID-19 guidelines state no difference in safety outcomes between acetaminophen and ibuprofen; however, many physicians remain wary of NSAIDs and continue to give acetaminophen because of early recommendations.[19]

In Summary:

COVID-19 is a developing situation. Recommendations are constantly changing as more studies are conducted, and the most effective treatment regimen is still not known. The treatment options listed here have received the most focus, but others like anti-retroviral HIV treatments, monoclonal antibodies, and interleukin-6 antagonists use is under investigation.[7] There are 120 candidate vaccines are also being rapidly developed, but there is still no recommended or commercially available vaccine at this time.[1]

Photo by: Psychiatric Times

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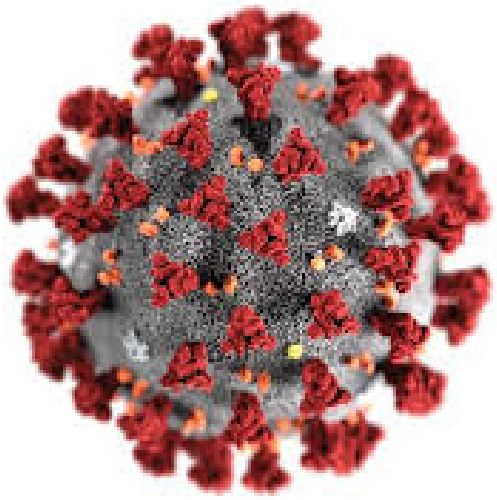

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The last "dose" …

"You can't go back and change the beginning, but you can start where you are and change the ending."

- C.S. Lewis (British writer and lay theologian; 1898 – 1963)

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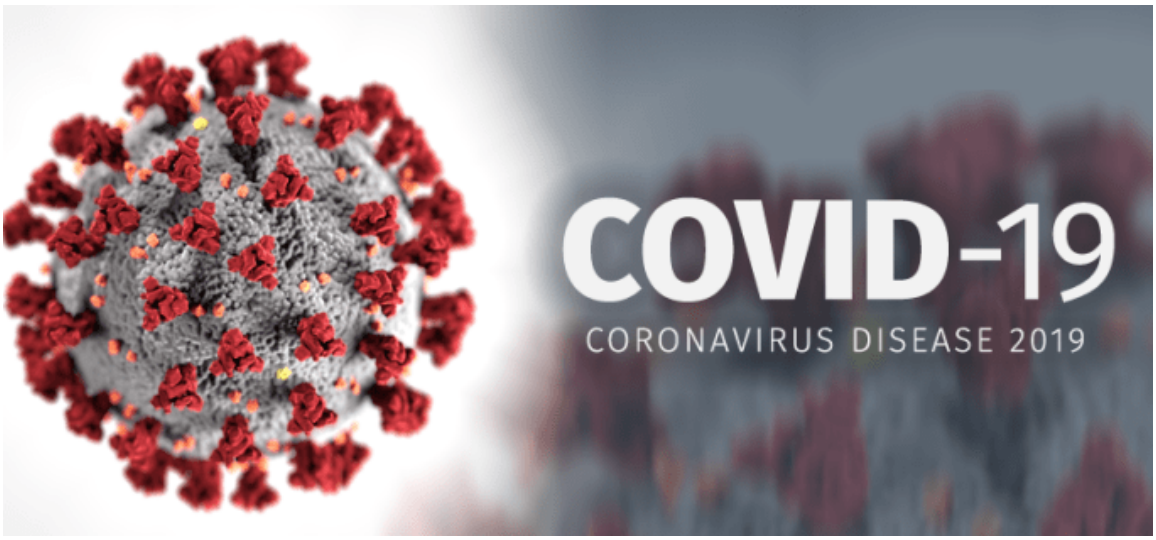

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