VOLUME 10 | ISSUE 1 | JUNE 2020

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A Crash Course on COVID-19: Information for Today's Practitioners

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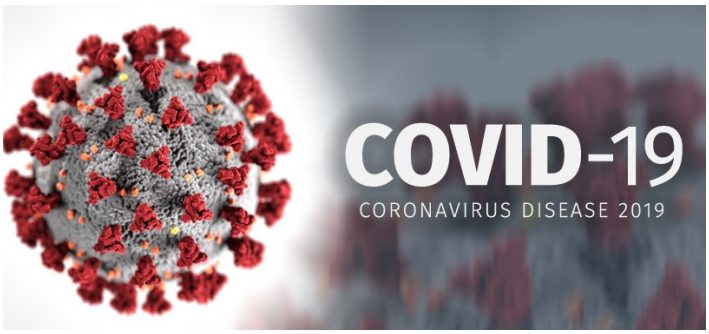
Nearly 7 months ago, the first cluster of a flu-like illness was reported in Wuhan, China. One week later, the virus was identified as coronavirus 2019-CoV. On January 30, 2020, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern. As more cases and deaths were reported around the world, WHO finally declared the new COVID-19 outbreak as a pandemic. The number of patients affected by the novel coronavirus continues to rise, and researchers are scrambling to find a cure. In the meantime, healthcare providers are seeking out any information they can to ensure they are managing patients with coronavirus effectively without placing other patients at risk.[1]

Patients often experience traditional flu-like symptoms at some point throughout their illness (cough with or without sputum production, shortness of breath, fever, fatigue, etc.).[2] Atypical symptoms include anosmia or ageusia prior to respiratory symptom onset, and some patients present with gastrointestinal complaints, such as diarrhea. Atypical presentations may complicate diagnosis, though – especially those who are asymptomatic. It is possible for asymptomatic patients to present with the bilateral, peripheral ground glass opacities in the lungs, a common manifestation of the novel coronavirus observed through imaging.[3]

While a chest CT may provide evidence of infection, it is not recommended for routine screening or diagnosis of COVID-19 due to a wide differential and non-specific results.[2] A stronger case for diagnosis may be built when imaging results are coupled with lab results. Patients infected with the novel virus may have various lab abnormalities, the most common of these being lymphopenia. The presence of neutrophilia, elevated liver enzymes (specifically ALT & AST), elevated lactated dehydrogenase, high C-reactive protein (CRP), and high ferritin may be indicators of worsening severity of illness.[3] Patients may have a higher risk of mortality if they have an elevated D-dimer or lymphopenia. Ferritin, C-reactive protein, and D-dimer are not standard of care, but they may be useful when considering prognosis. See Table 1 for more information.



As information is limited with regards to presentation, there are various classification schemata that may be used. Patients can be classified as asymptomatic/pre-symptomatic, mild, moderate, severe, or critical. Regardless of presentation, it is important that appropriate infection-control measures are put in place to decrease risk of transmission.[2,3] Institution wide policies may be put in place that limit visitors or delegate special COVID-19 units to mitigate risk of transmission from outside patients or from within an institution. Contact with patients infected with COVID-19 should be limited to medically necessary contact, when possible. It's also important that healthcare providers take appropriate measures in order to prevent transmission. All healthcare providers should practice good hand hygiene. Those dealing directly with patients infected with COVID-19 will require personal protective equipment (PPE).

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Providers should utilize a face shield or goggles, N95 or higher respirator (face mask as an alternative), non-sterile gloves, and an isolation gown when caring for those with COVID-19.[2]

In an outpatient setting, quarantine and isolation may be used to help prevent transmission. Patients who may have been exposed to an individual infected with COVID-19 should quarantine themselves in order to prevent possible transmission to others, even if they don't experience symptoms.[2] Quarantine should last at least fourteen days (provided the individual does not develop symptoms). Isolation is utilized when patients are infected with COVID-19. Patients may be able to end isolation once they have met the following criteria: afebrile for three days, improved symptoms, ten days since symptom onset. Asymptomatic patients with a positive test should also perform a ten day long isolation.

As we navigate this pandemic and all that comes with it, many people are left questioning what kind of world we may return to post-COVID-19. Scientists and researchers are spending countless hours studying available medications, developing new medications, and scrambling to develop a vaccine. The pandemic may be far from being over, but it's still fair to say that our lives have all been affected.

<Click for references>

Table 1: Initial Management of Patients with COVID-19[2,3]

	Mild	Moderate	Severe	Critical
Symptoms	Fever, cough, malaise Absence of dyspnea	Evidence of lower respiratory disease with SpO_2 >93% on room air	SpO_2 ≤93% on room air, RR >30, PaO_2/FiO_2 <300, or lung infiltrate >50%	ARDS, septic shock, cardiac dysfunction
Labs	Not indicated in otherwise healthy patients	Standard: CBC, CMP CRP, D-dimer, ferritin add prognostic value		
Imaging	Normal if taken	Chest x-ray, ultrasound, or CT may be considered	Pulmonary imaging and ECG if indicated	
Setting for Management	Telemedicine visits; outpatient	Inpatient for close monitoring as they may develop severe illness in second week	Inpatient	Intensive care

SpO_2: peripheral blood oxygen saturation; CBC: complete blood count; CMP: complete metabolic profile; CRP: C-reactive protein; CT: computerized tomography; RR: respiratory rate; PaO_2/FiO_2: arterial oxygen partial pressure/fractional inspired oxygen; ARDS: acute respiratory distress syndrome; ECG: echocardiogram

Potential Medication Options for COVID-19

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The COVID-19 pandemic has led to a surge in drug trials. Numerous pharmaceutical companies are working hard to find a cure or create a vaccination to prevent this deadly virus. Many potential treatment options have made the headlines including remdesivir, hydroxychloroquine, and the combination antiretroviral medication lopinavir/ritonavir.

One of the potential treatment options that may be the most promising so far is remdesivir.[1] It is a direct-acting antiretroviral that was granted emergency use authorization (EUA) on May 1, 2020 by the U.S. Food and Drug Administration (FDA).[1] This authorization allows adults and children to be treated with remdesivir if they are hospitalized with severe COVID-19 disease. Severe disease is defined as "SpO2 ≤94% on ambient air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation" per the National Institutes of Health (NIH).[2] Preliminary trials show that a 10-day course of remdesivir may lead to a shorter median time to recovery.[3] Trials are still in progress at this time. Dosing is provided in Table 1.

Another potential treatment option under investigation is hydroxychloroquine.[1] This anti-malarial agent has historically been used to treat malaria, systemic lupus erythematosus (SLE), and rheumatoid arthritis.

The FDA issued an EUA for hydroxychloroquine in April, allowing healthcare providers to request the medication from the Strategic National Stockpile for adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19.[1] These patients are either not able to participate in a clinical trial or there is not one that is available. The data for hydroxychloroquine use is variable and for that reason the NIH and the Infectious Diseases Society of America (IDSA) both recommend to only use hydroxychloroquine if it is in the setting of a clinical trial.[2,4] This recommendation also applies to the addition of azithromycin to hydroxychloroquine, stating that the risk for adverse effects with the combination, such as QT prolongation, outweighs the potential benefit.[2,4] Dosing is provided in Table 1.

Use of antiretroviral medications indicated for human immunodeficiency virus (HIV) have also been readily studied in clinical trials for COVID-19 treatment. The most common studied is the combination protease inhibitor, lopinavir/ritonavir.[1] Similar to hydroxychloroquine, the NIH and IDSA recommend against using any protease inhibitors, including lopinavir/ritonavir, unless the patient is in a clinical trial.[2,4] A study showed that time to clinical improvement was not shorter with lopinavir/ritonavir compared to standard care.[5] This medication class has adverse effects that were not tolerated well in trials including nausea, diarrhea, and abdominal discomfort.[4] Dosing is provided in Table 1.

Although the three medications discussed above are the most studied, there are many other potential treatment options that have been considered as well. Examples of antiviral medications studied are oseltamivir and baloxavir.[1] These potential treatment options were found to have no data to support their use in COVID-19 patients.[1] There are many other potential supportive treatment options available. An assessment of all studied treatments can be found at: https://www.ashp.org/COVID-19 <Click for references>

Table 1. Medication Dosing for Potential Treatment Options

Medication	Dosing
Remdesivir[6]	Adults and children ≥ 40 kg: 200 mg IV on day 1, then 100 mg IV on days 2-10 Children 3.5 kg to <40 kg: 5 mg/kg by IV infusion on day 1, followed by 2.5 mg/kg by IV infusion once daily on days 2-10
Hydroxychloroquine[7,8,9]	Various doses studied including: 400 mg twice daily on day 1, then 200 mg twice daily on days 2-5 800 mg on day 1, then 400 mg daily for 4-7 days 400 mg once or twice daily for 5-10 days Azithromycin dose, if added: 500 mg on day 1, then 250 mg once daily for 4 days
Lopinavir/ritonavir[3]	Lopinavir 400 mg/ ritonavir 100 mg orally twice daily for 10-14 days

Guidelines for Treatment of COVID-19

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There are currently no clinically proven treatments for COVID-19; medications used are based on limited observational studies and their *in vitro* antiviral activity or anti-inflammatory effects.[1] It is important for observational studies to occur during the epidemic to investigate treatment options; however, they often do not have concurrent controls, may have a significant risk of bias, and use surrogate outcomes like viral clearance rather than clinically important outcomes, such as patient improvement.[1] Therefore, medications that are thought to be beneficial *in vitro* and during observational studies may later show no benefit during clinical trials.[1]

The Infectious Diseases Society of America (IDSA) published guidelines on the treatment and management of patients with COVID-19 in April 2020. The IDSA recommends the use of hydroxychloroquine/chloroquine therapy for patients with COVID-19 that have been admitted to the hospital, only in the context of a clinical trial. The evidence failed to show or exclude a beneficial effect of hydroxychloroquine on clinical progression, represented by radiological findings, of COVID-19 or on viral clearance; however, a higher proportion of patients treated with hydroxychloroquine experienced clinical improvement. Outcomes, such as mortality, rate of progression to acute respiratory distress syndrome (ARDS), and need for mechanical ventilation were not available. Several studies evaluated the addition of azithromycin to hydroxychloroquine; however, this combination provided indirect comparisons of failure of virologic clearance to hospital controls. Treatment with hydroxychloroquine and azithromycin could lead to adverse effects, such as QT prolongation, and should be carefully considered when choosing therapy. Additional randomized controlled trials (RCTs) are needed to investigate the use of hydroxychloroquine alone or in combination with azithromycin for the treatment of COVID-19.

The IDSA recommends the combination of lopinavir/ritonavir for patients admitted to the hospital with COVID-19, only in the context of a clinical trial. Studies suggest that this combination does not have a measurable antiviral effect; additional clinical trials are needed.

The use of corticosteroids for patients admitted to the hospital with COVID-19 is not recommended unless the infection has progressed to ARDS. A small subset of patients may develop ARDS from COVID-19 and there is no clear benefit and possibly potential harm from corticosteroid use, such as acquiring serious secondary infections. RCTs are needed to determine the dose, route, timing, duration of corticosteroid treatment, and potential harms to better guide their place in therapy. The guidelines state that patients previously on a steroid should continue therapy.

The IDSA also recommends the use of tocilizumab for patients admitted to the hospital with COVID-19, only in the context of a clinical trial. Treatment with tocilizumab may increase patients' risk of serious secondary infections and hepatitis B reactivation. Other potential harms associated with tocilizumab use include anaphylaxis, severe allergic reaction, severe liver damage, hepatic failure, and intestinal perforation. Additional clinical trials are needed to determine the effectiveness of tocilizumab for COVID-19 treatment.

The guidelines conclude that the benefits of treatment with the proposed therapies is highly uncertain, and there are known harms associated with each agent; therefore, the outcome could potentially be negative with the use of these therapies. It has not been determined if the benefits outweigh the risks, so it would be ethical and practical to enroll patients with COVID-19 in clinical trials, rather than use clinically unproven therapies.[1] <Click for references>

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