Residency Review

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COLLEGE of PHARMACY and HEALTH SCIENCES

COVID Pills: Light at the end of the tunnel?

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On March 11, 2020, the WHO declared COVID-19 a global pandemic.[1] The scramble to find treatment for the over 47 million people infected with SARS-CoV-2 resulted in the use of many different pharmacologic therapies and combinations, from hydroxychloroquine and azithromycin to remdesivir and dexamethasone.[2] While it was found that certain treatments, such as remdesivir, were beneficial, most recommended treatments were reserved for hospitalized patients.[3] After more than a year of working from home, canceled events, vaccinations, and uncertainty, there may now be a light at the end of the tunnel. In just over a month, two oral antiviral drugs have been reported to reduce COVID-19 hospitalizations and deaths in clinical trials of patients treated soon after their initial infection. Molnupiravir, developed by Merck, and Paxlovid™, developed by Pfizer, are making groundbreaking news as data from interim analyses are being reported.

MOVe-OUT trial

Molnupiravir (MK-4482/EIDD-2801) is an investigational, orally administered form of a potent ribonucleoside analog that inhibits the replication of SARS-CoV-2, the causative agent of COVID-19 (Figure 1). Molnupiravir was invented at Drug Innovations at Emory (DRIVE) LLC, a not-for-profit biotechnology company, and is being developed by Merck in collaboration with Ridgeback Biotherapeutics.

In October 2021, initial trial results reported by Merck and Ridgeback suggested that molnupiravir could halve hospitalizations and deaths from COVID-19, which led these companies to submit an emergency use authorization application to the U.S. Food and Drug Administration (FDA).[9] This submission was based on interim analysis of a phase 3 randomized, placebo-controlled trial, Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MOVe-OUT). This clinical trial is evaluating molnupiravir in non-hospitalized adult patients with mild to moderate COVID-19 who are at risk of progressing to severe COVID-19 and/or hospitalizations.[4] Molnupiravir was given to individuals within 5 days of symptom onset who had at least one characteristic or underlying medical condition associated with an increased risk for severe COVID-19. Common risk factors for poor disease outcome include obesity, older age (>60 years), diabetes mellitus, and heart disease. This interim analysis evaluated the data from 775 participants. The trial observed an approximate 50% reduction in risk of hospitalization or death in individuals with mild to moderate COVID-19 infections.[5] Sequencing data was available from approximately 40% of the participants and molnupiravir demonstrated consistent efficacy across the Gamma, Delta, and Mu viral variants. Currently, various strengths of molnupiravir (200mg to 800mg) are being evaluated versus placebo. Molnupiravir is administered orally every 12 hours for 5 days.

Based on the data, the incidence of any adverse event was comparable in the molnupiravir (35%) and placebo (40%) groups. The incidence of drug-related adverse events was also comparable at 12% for molnupiravir and 11% with placebo. It was also reported that fewer subjects discontinued study therapy due to an adverse event in the molnupiravir group (1.3%) than the placebo (3.4%) group.[5] Adverse events that occurred most frequently (in ≥2% of participants in either group) included: COVID-19 pneumonia (occurring in 6.3% of participants in the molnupiravir group versus 9.6% in the placebo group), diarrhea (2.3% versus 3.0%), and bacterial pneumonia (2.0% vs. 1.6%).[16] Worsening of COVID-19 infection was also reported as an adverse event, which occurred in 7.9% of molnupiravir participants and 9.8% of placebo participants.[16] Adverse events that were determined to be related to the trial regimen (occurring in ≥1% of participants in either group) were: diarrhea (1.7% vs. 2.1%), nausea (1.4% vs. 0.7%), and dizziness (1.0% vs. 0.7%).[16]

On November 26, Merck released an update on the results from the MOVe-OUT study. Data were made available from all of the enrolled participants (n=1433). An analysis of the entire study population described molnupiravir reduced the risk of hospitalization or death, which only occurred in 6.8% (48/709) in the molnupiravir group versus 9.7% (68/699) in the placebo group, with a relative risk reduction of 30% (relative risk 0.70; 95% confidence interval [CI]: 0.49-0.99) and an absolute risk reduction of 3.0% (95% CI: 0.1-5.9; p-value=0.0218).[10]

The FDA's Antimicrobial Drugs Advisory Committee (AMDAC) voted 13-10 in favor of the Emergency Use Authorization application based on the potential benefits of molnupiravir outweighing its known and potential risks for the treatment of mild to moderate COVID-19 infection in high-risk adult patients who are within five days of symptom onset.[11] While the committee's guidance is taken into consideration, the FDA was not bound by their advice. In anticipation of the published results from the MOVe-OUT trial and the potential Emergency Use Authorization, Merck stated that they were projected to produce 10 million courses by the end of 2021, and at least 20 million courses in 2022.[11]

On December 23, one day after the FDA issued an emergency use authorization (EUA) for Pfizer's Paxlovid™, the FDA issued an emergency use authorization (EUA) for Merck's molnupiravir.[15] It is authorized for the treatment of mild-to-moderate COVID-19 in adult patients with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.[15] Molnupiravir is not currently authorized for patients under the age of 18 because it may affect bone and cartilage growth. Furthermore, it is not recommended for use in pregnant patients because it was observed in animal studies to potentially cause fetal harm. The prescriber must deem that the benefits of initiating molnupiravir in the pregnant patient outweighs the potential risks for that individual patient.[15] Molnupiravir must be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.[15]

In a press release published by Merck on December 23, it states that they will be shipping molnupiravir "within days" through AmerisourceBergen, which is its sole distributor of molnupiravir.[17] Merck also entered into a procurement agreement with the U.S. government and agreed to supply approximately 3.1 million courses of molnupiravir to the U.S government.[17]

EPIC-HR trial

Soon after molnupiravir gained approval in the United Kingdom, Pfizer announced that its own antiviral drug, Paxlovid™ (nirmatrelvir, PF-07321332), cut hospitalizations due to COVID-19 by 89%. Paxlovid™ is an investigational SARS-CoV-2 protease inhibitor antiviral therapy. Like molnupiravir, it is designed to be administered orally at the first sign of infection, with the potential to avoid severe illness, hospitalization, and death.[8]

Paxlovid™ blocks the activity of the SARS-CoV-2-3CL protease, an enzyme that the coronavirus needs to replicate.[7] It inhibits viral replication at a stage known as proteolysis, which occurs before viral RNA replication (Figure 1). Co-administration with low dose ritonavir helps slow the metabolism of nirmatrelvir in order for it to remain active in the body for longer periods of time at higher concentrations to help combat the virus. Pfizer's interim analysis of their Phase 2/3 trial, Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR), a randomized, double-blind study of non-hospitalized adult patients with COVID-19, observed an 89% reduction in the risk of COVID-19 related hospitalization or death compared to placebo.[7]

In the interim analysis of the EPIC-HR study, Paxlovid™ or placebo was given to patients within three days of symptom onset. Following randomization, 0.8% of patients who received Paxlovid™ were hospitalized through day 28 (3/389 hospitalized and no deaths), compared to 7% of patients who received placebo and were hospitalized or died (27/385 hospitalized with 7 deaths).[7] Adverse effects were comparable between Paxlovid™ (19%) and placebo (21%), most of which were mild in intensity.[8] Currently, Paxlovid™ is being evaluated in combination with ritonavir at a dose of 300mg (two 150mg tablets) of Paxlovid™ with one 100mg tablet of ritonavir, both given twice daily for five days versus matched placebos.

With the data from Pfizer's interim analysis, the company submitted an application for Emergency Use Authorization for Paxlovid™ on November 16, 2021.[8] Two days later, Pfizer entered an agreement with the United States government to supply 10 million treatment courses of Paxlovid™.[12] On December 13, 2021, Pfizer announced the final results of the EPIC-HR study. The final data and analysis of all the high-risk patients enrolled in the study (n=2,246), confirmed prior results from the interim analysis.[14] The trial observed that Paxlovid™ reduced risk of hospitalization or death by 89% (within three days of symptom onset) and 88% (within five days of symptom onset) when compared to placebo. Of the patients who received Paxlovid™, 0.7% of patients were hospitalized through day 28 following randomization (5/697 hospitalized with no deaths). In comparison, 6.5% of patients who received the placebo were hospitalized or died (44/682 hospitalized with nine deaths).[14] Furthermore, a consistent safety profile for Paxlovid™ was observed between the interim data and the final results.[14]

Paxlovid™ reduced the risk of a secondary endpoint (hospitalization or death from any cause) by 88% in comparison to placebo in patients who were treated within five days of symptom onset. It was observed that 0.8% of patients who received Paxlovid™ were hospitalized 28 days following randomization (8/1039 hospitalized and no deaths), compared to 6.3% of patients who received placebo (66/1046 hospitalized and 12 deaths).[14] In an analysis of enrolled patients 65 years or older, the relative risk reduction of hospitalization and death was 94%. In this sub-group, 1.1% of patients who received Paxlovid™ were hospitalized through day 28 of randomization (1/94 hospitalizations and no deaths), compared to 16.3% who received placebo (16/98 hospitalizations and 6 deaths). Overall, there were no deaths reported in the Paxlovid™ group and 12 deaths (1.2%) reported in the placebo group.[14]

Another secondary endpoint, SARS-CoV-2 viral load, was evaluated at baseline and day 5 in 499 patients.[14] After factoring in baseline viral load, geographic region, and serology status, Paxlovid™ reduced viral load by about 10-fold when compared to placebo, indicating strong activity against SARS-CoV-2.[14] Moreover, recent in vitro data confirms that is a potent inhibitor of the Omicron 3CL protease. In addition to the data already available regarding in vitro antiviral and protease inhibition data from other variants, like Delta, indicates that Paxlovid™ will maintain its antiviral activity against the current variants of concern.[14]

Possible side effects of Paxlovid™ include impaired sense of taste (6% in the Paxlovid™ group versus <1% in the placebo group), diarrhea (3% versus 2%), high blood pressure (1% versus <1%), and muscle aches (1% versus <1%).[19] Another important consideration prior to initiation of Paxlovid™ is potential drug-drug interactions due to the component of ritonavir. Paxlovid™ is contraindicated with drugs that are highly dependent on CYP3A for clearance, such as amiodarone and clozapine.[19] In addition, Paxlovid™ is also contraindicated with drugs that are potent CYP 3A inducers, such as phenytoin and rifampin, as nirmatrelvir and ritonavir concentrations will be reduced.[19]

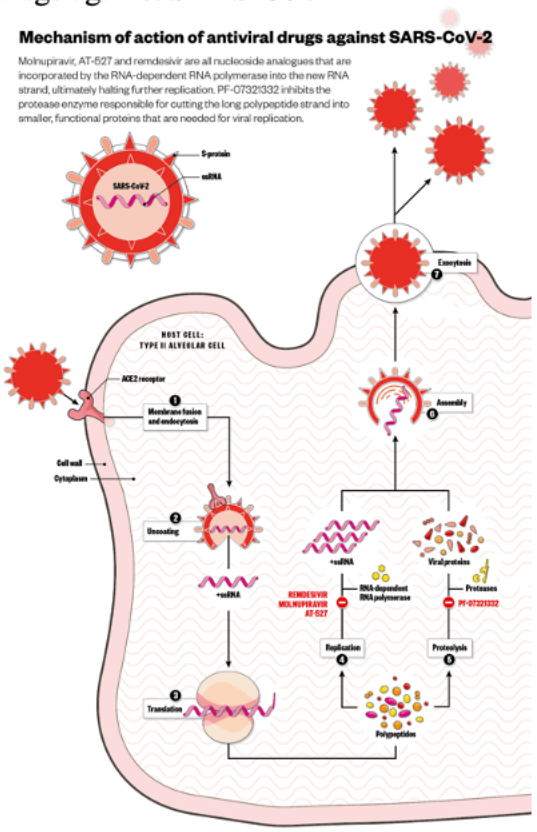
On December 22, the FDA issued an emergency use authorization (EUA) for Pfizer's Paxlovid™.[18] It is authorized for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age or older weighing at least 40 kilograms) and in adult patients. Patients must have a positive result from direct SARS-CoV-2 testing and be at high risk for progression to severe COVID-19, including hospitalization or death.[18] Similar to molnupiravir, Paxlovid™ must be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.[18] Paxlovid™ is to be administered at a dose of 300mg (two 150mg tablets) of nirmatrelvir with one 100 mg tablet of ritonavir, given by mouth twice-daily for five days. The container will contain five blister packs of Paxlovid™, as co-packaged nirmatrelvir tablets with ritonavir tablets, which will provide all required doses for a full five-day treatment course.[14]

In a press release published by Pfizer on December 22, it states that Pfizer is ready to start delivery in the U.S. "immediately" under the agreement to supply the U.S. government with 10 million treatment courses between 2021 and 2022.[19] At the end of December, an initial 65,000 courses of Paxlovid™ were shipped to dispensing sites throughout the states and U.S. territories. First week allocations ranged from 40 treatment courses to the Northern Mariana Islands to 6,180 courses to California.[20]

Looking ahead

Both the MOVe-OUT and EPIC-HR studies are still in progress, and the full study data is not expected to be published until late 2021 to early 2022. Both companies submitted their data to the FDA, and both gained authorization for emergency use within days of each other. While the current data available for both drugs are promising, the full trial data has yet to be published. Prescribers must take into consideration the patient population that each medication is currently authorized for use in. Molnupiravir is only authorized for adult patients, whereas Paxlovid™ is approved for patients 12 years of age and older. Drug-drug interactions may also influence the medication that may be chosen. There is still limited information regarding the full side effect profile of each drug and administration of these medications may be a challenge in some areas of the world.

Figure 1. Mechanism of action of antiviral drugs against SARS-CoV-2[14]



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Monoclonal Antibodies: Coming Soon to a Clinic Near You

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SARS-CoV-2, more commonly referred to as COVID-19 has been a global presence since its first case in December 2019. Since its spread to the United States in January 2020, over 60 million people in the United States have contracted the virus, with over 836,000 succumbing to it.[1] To help curb the spread of COVID-19,[3] vaccines have been released by Pfizer®, Moderna®, and Janssen®, all of which are recommended by the FDA and CDC to promote immunity. To date, 73.1% of the total US population has received at least one dose of vaccine.[1] With the recent recommendation of a booster dose for all individuals 12 years of age and older in the case of Pfizer®, and 18 years and older for Moderna® and Janssen®, the world is starting to find hope that this pandemic will end. Despite the increasing vaccination numbers, there are still tens of thousands of cases reported of COVID-19 every day in the United States.[1] Just as important as the prevention of the disease, is how we treat those actively infected.

Treating an Active Case

One of the longest used treatment modalities for COVID-19 has been the use of monoclonal antibodies (mAbs). Monoclonal antibodies are similar to those that naturally exist as a product of the human immune system. When the body is exposed to a foreign substance, their immune cells will produce antibodies to help fight off infection. Monoclonal antibodies on the other hand, are developed in a laboratory setting and are designed to target a specific protein.[2] This has allowed mAbs to be used in a variety of disease states ranging from autoimmune diseases to various types of cancer. In the case of COVID-19, there are four major structural proteins that have been considered for the design of monoclonal antibodies. These are the spike, envelope, membrane, and nucleocapsid proteins as shown in Figure 1.[3] The main focus of mAb therapies have targeted the spike protein. The spike protein has two subunits that mediate attachment and invasion of host cells. The S1 subunit is the receptor binding domain which attaches to angiotensin-converting enzyme 2 to allow for infiltration into the host cell and is the primary target of mAb therapy.[4]

There are currently three mAb treatment options for patients with active cases of COVID-19 which the FDA granted emergency use authorization (EUA). The treatment criteria include a positive test for COVID-19, symptom onset within 10 days, and mild or moderate severity of disease likely to progress to hospitalization. Some risk factors associated with such progression include being age 65 or older, being overweight or obese (BMI>25), having a chronic health condition, or being immunocompromised or immunosuppressed. The emergency use authorizations for all mAb therapies specify that other patients with factors not directly stated in the EUA may also be eligible based on the prescriber's clinical decision making.[5,6] The first mAb combination authorized by the FDA was casirivimab/imdevimab (casi/imdev), also known by the brand name REGEN-COV from Regeneron.[5] Originally authorized on November 21, 2020, this combination has received the most attention and has the largest clinical trial with 736 patients receiving active therapy and 748 patients receiving placebo. The study is ongoing and examines COVID-19 related hospitalizations and all-cause deaths through 29-days post treatment. The active arm had seven (1%) deaths compared with twenty four (3.2%) in the placebo arm, showing a relative risk reduction of 70% for COVID-19 related hospitalization and all-cause deaths. Casi/imdev is authorized as either an intravenous infusion or a consecutive 4-injection subcutaneous series. This combination has managed to stay relevant in the fight against COVID-19 even in the wake of the new variants, as the combination of both casi/imdev has shown activity against all the major variants including alpha, beta, gamma, and delta. When used alone however, casirivimab has shown reduced efficacy against both the beta and gamma variants in vitro. While data remains limited and studies are ongoing, casi/imdev is predicted to have reduced effectiveness against the omicron variant.[4]

The second monoclonal antibody regimen in use is manufactured by Eli Lily. The combination of bamlanivimab 700mg and etesevimab 1,400mg (bam/etes) is available as an IV infusion only. The trial for this combination, while smaller in participation than for casi/imdev, observed similar improvements in patient outcomes. As of December 16, 2021 this combination has been authorized for pediatric patients as young as neonates.[7] Out of 769 participants, 511 received active therapy compared with 258 patients who received placebo.[6] The placebo arm saw fifteen (6%) COVID-19 related hospitalizations or all-cause deaths by day 29 compared to four (0.8%) in the active arm. This shows a relative risk difference of 87%, which is comparable to REGEN-COV. The trial of bam/etes has not been published in a peer reviewed journal as of yet. Thus far, this combination may have less of an effect on certain COVID-19 variants. Both the beta and gamma variants have shown reduced susceptibility to bam/etes, leading to a temporary revocation of the emergency use authorization in April 2021.[8] The EUA for this combination was re-instated with the caveat that its use is restricted in any states, territories and US jurisdictions in which the combined frequency of resistant variants exceeds 5%. Currently, bam/etes is authorized for use in all 50 states and the District of Columbia.[6] While data remains limited and studies are ongoing, bam/etes is predicted to have reduced effectiveness against the Omicron variant.[4]

The third monoclonal antibody regimen was created by GSK and was originally identified in 2003 for the SARS-CoV-1 virus. The receptor binding domain of the SARS-CoV-1 spike protein was conserved in SARS-CoV-2 allowing for antiviral activity to remain[4]. Sotrovimab has shown similar improvements in patient outcomes compared with the above regimens. In its study, out of 1057 participants, 528 received active therapy of sotrovimab 500mg IV infusion while 529 received placebo one hour infusions.[9] The primary endpoint of this study was the proportion of participants hospitalized for more than 24 hours or who died from any cause by day 29. Six (1%) of the sotrovimab arm experienced this endpoint compared with thirty (6%) in the placebo arm. Sotrovimab was found to have a 79% adjusted relative risk reduction compared with placebo.[9] Despite all the new mutations from the base COVID-19 virus, sotrovimab has retained activity against all variants including delta and omicron.[4]

Post-Exposure Prophylaxis

Post-exposure prophylaxis (PEP) is the act of administering a medication following a potential exposure to a harmful agent. This is used in an attempt to block or reduce the risk of infection and is commonly associated with HIV and AIDS.[10] PEP should not be considered an alternative to immunization against COVID-19 but rather an additional resource used to supplement the protection granted by the vaccines. As of December 16, 2021 the FDA has authorized the use of bam/etes and casi/imdev in adults and pediatrics 12 years and older and at least 40kg for PEP.[7] Sotrovimab is not authorized for PEP at this time. Post-exposure prophylaxis should be considered in anyone at high risk of progression to severe COVID-19, including hospitalization or death, including those not fully vaccinated or immunocompromised who have been exposed to an infected individual or at high risk of exposure. Post-exposure prophylaxis doses are the same as treating active cases.[7]

Crush COVID

The Crush COVID campaign was started in November 2020 as a crowdfunded effort to meet the needs caused by the pandemic. It is currently headed by the federal Department of Health and Human Services acting as an information center for COVID-19 treatment centers.[11] Through their efforts, mobile clinics have been organized across the nation to improve patient access to these potentially life-saving treatments. The Department of Health and Human Services also provides information regarding infusion sites which have recently received shipments of monoclonal antibody therapy. All three regimens are available at these clinics.[11] There are currently six fully operating mobile units in Massachusetts that are providing monoclonal antibody therapy to patients with COVID-19. The referral process for treating an active COVID-19 case and post-exposure prophylaxis are the same. The Massachusetts Department of Public Health has published a checklist providers can follow in determining eligilibity of patients to receive mAb therapy as shown in Figure 2.[12]

In Massachusetts, the first organized unit originated with UMass Memorial Medical Center, located on the Hahnemann Campus at 281 Lincoln Street in Worcester. This clinic operates Monday to Saturday from 8:30 a.m.–4:30 p.m.[13] The second clinic available is associated with Cape Cod Hospital at 27 Park Street in Hyannis. This clinic runs Monday to Saturday from 1:00 p.m.–6:00 p.m.[14] The newest location was launched in association with Baystate Health. The clinic can be found at Baystate Noble Infection Control Treatment Unit at 115 West Silver Street in Westfield.[15] The Department of Public Health has recently contracted with Gothams to open three new clinics for patients based in Holyoke, Everett, and Fall River. Providers may refer patients to one of these sites by calling 508-974-3431. There are plans for more clinics currently being developed at other health institutions. All clinics are able to provide either mAb regimen to patients, depending on which is shipped to that location. Eligibility for treatment includes a positive test for COVID-10 within the past 10 days, not fully vaccinated, or immunocompromised after being exposed to the virus.[11] Currently, all mAb therapies are covered by the federal government. The only cost that a patient may incur is the administration fee associated with the infusions. Not all insurance plans cover this fee, so patients should contact their insurance company to discover what the out-of-pocket expense may be.[11] Patients should be encouraged to discuss eligibility with providers regarding receiving mAb for treatment or as post-exposure prophylaxis. Should the provider deem the patient eligible to receive therapy, providers can contact the nearest infusion site to schedule an infusion appointment. To schedule with Cape Cod Hospital, providers should fax their request to 508-568-1650, after which a member of the scheduling team will contact the provider to schedule the appointment.[12] To schedule with UMass Memorial, providers should call 855-UMASS-MD to book an appointment.[13] To schedule with any of the three Gothams clinics, providers can fill out the form available on their website at www.baystatehealth.org/locations/noble-hospital which can then be emailed to the appropriate location.[15] For additional information about mAb therapy locations, please see **www.mass.gov/info-details/information-for-providers-about-monoclonal-antibody-mab-therapy-treatment-for-covid-19#monoclonal-antibody-therapy-locator**.

Figure 1: Schematic Representation of SARS-CoV-2 Structure[3]

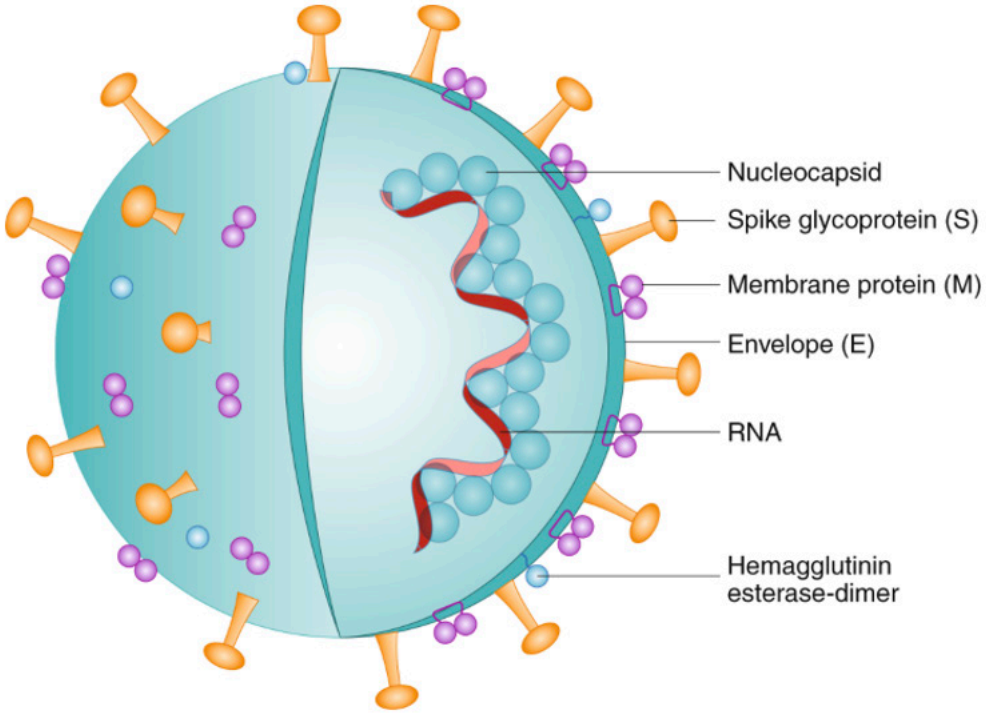

Figure 2: Massachusetts Department of Public Health COVID-19 Monoclonal Antibody (mAb) Therapy Checklist for Providers[12]

mAb is a critical treatment for patients with COVID-19 who meet certain inclusion criteria. mAb administration has shown to decrease severe disease and reduce the likelihood of hospitalization.

A patient being referred for mAb should meet the following criteria:

- ❑ Mild-to-moderate, symptomatic, COVID-19 with at least one symptom, including but not limited to: Fever, chills, aching, new loss of taste or smell, nausea, vomiting, cough, sore throat, nasal congestion, runny nose, diarrhea, shortness of breath, headache, etc.
- ❑ Symptoms began within the past 10 days and received a positive COVID-19 test within the past 10 days (antigen or molecular)
- ❑ Has at least one risk factor for progression to severe disease or death from COVID-19, including but not limited to:
  - ❑ Age greater than or equal to 65 years old
  - ❑ Pregnancy
  - ❑ Chronic Kidney Disease
  - ❑ Diabetes
  - ❑ Immunosuppressive Disease
  - ❑ Immunosuppressive Treatment
  - ❑ Cardiovascular Disease
  - ❑ Hypertension
  - ❑ Chronic Lung Disease
  - ❑ Sick Cell Disease
  - ❑ Neurodevelopmental Disorder
  - ❑ Medical-Related Technological Dependence (i.e. on ventilator)
  - ❑ Obesity/Overweight (BMI > 25 or above 85th percentile for age/gender)
  - ❑ Other medical conditions or factors that place me at high-risk for severe disease
- ❑ Has not had an allergic reaction (hives, facial swelling, difficulty breathing, anaphylaxis, etc.) after receiving a monoclonal antibody therapy
- ❑ If using home oxygen therapy, has not required increased oxygen dose since symptoms began/tested positive for COVID-19

If the patient meets the above criteria, you may refer them by calling
(508) 974-3431 or access a publicly available mAb site:
https://mdphgis.maps.arcgis.com/apps/instant/nearby/index.html?appid=82983fa9f6d44e2aaf1d5bd420aa57ff

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