Antimicrobial Stewardship News

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Outpatient COVID-19 Therapies:

Drugs in the Time of Omicron

Introduction

The Omicron variant of COVID-19 has swept across the United States over the past two months, with over 800,000 new cases of COVID-19 diagnosed daily at its peak in mid-January of 2022.[1] While Omicron's heightened infectivity has caused an enormous strain on the capacity of hospital systems nationwide, there is a notable disconnect between Omicron's daily case incidence and mortality as compared to prior waves of variants. With the decreased severity of Omicron and the significant impact of COVID-19 vaccination (and particularly boosting),[2] this difference might expand further with the recent increase in available effective therapies against COVID-19.

This month, we'd like to review the evolving evidence and indications for available outpatient COVID-19 medications, including pre-exposure prophylaxis. A summary table is provided at the end of this document for reference (Supplementary Figure 1).

Monoclonal Antibody Therapy

The COVID-19 monoclonal antibodies were specifically engineered to target the COVID-19 spike protein receptor-binding domain (RBD), as neutralizing antibodies from sera of recently infected or vaccinated individuals were found to predominantly target the RBD, in part to limit viral attachment to host cells.[3-5] However, given both COVID-19 infection and vaccination induce immunity that target this domain, the RBD is thought to be under significant evolutionary pressure with rapid mutation rates.[5] The Omicron variant harbors over 30 mutations in its RBD, which unfortunately allows viral escape from antibody neutralization with most of the available monoclonal antibodies *in vitro*.[6-7, 9]

Sotrovimab

In contrast, sotrovimab is a monoclonal antibody that targets an evolutionarily conserved epitope outside of the RBD. Available *in* vitro data suggests that sotrovimab is efficacious against Omicron, and prior studies have demonstrated its clinical activity against older variants, with a relative risk reduction of 79% against hospitalization or death in a randomized control trial of over 1,000 patients.[8-9] As such, for monoclonal antibody therapy of the Omicron variant, the NIH currently recommends use of sotrovimab and recommends against administration of bamlanivimab-etesevimab or casirivimab-imdevimab.

The FDA issued an emergency use authorization (EUA) for sotrovimab use among COVID-19 infected adults at high risk for disease progression (see Figure 1) within 10 days of symptom onset, though the above study used a 5-day cut-off for enrollment of note. The only listed contraindication is known anaphylaxis to sotrovimab.

Figure 1. Examples of risk factors for progression to severe COVID-19 disease. Available here from the CDC.

Age 65 or older	Neurodevelopmental conditions
Obesity	Cancer
Immunosuppressed state	Diabetes
Solid organ or stem cell transplant	Sickle cell disease
Chronic kidney disease	Pregnancy or recent pregnancy
Chronic lung diseases	Tobacco use
Chronic liver diseases	HIV or active tuberculosis
Heart conditions (heart failure, CAD, cardiomyopathy)	Mental health disorders

Tixagevimab-cilgavimab (Evushield): Pre-Exposure Prophylaxis for Highest-Risk Patients

On December 9th, 2021, the FDA issued an emergency use authorization (EUA) for tixagevimab-cilgavimab (Evushield) for pre-exposure prophylaxis of individuals at high risk for severe COVID-19 disease.[10-12] Currently, it is intended to provide additional protection against COVID-19 among the most immunocompromised individuals (see Figure 2) who may not mount an appropriate immune response to vaccination. It is also positioned to provide protection among those with serious adverse reactions to prior COVID-19 vaccination.

A double-blinded randomized control trial among adults 18 years of age or greater with certain comorbidities (including obesity, heart failure, pulmonary disease, chronic renal disease, and chronic liver disease in addition to the conditions in Figure 2) evaluated the role of Evushield as pre-exposure prophylaxis. Evushield recipients had a 77% reduction in incidence of COVID-19 positivity as compared to placebo at 3 months and 83% reduction at 6 months.[12] Notably, data from another randomized trial (STORM CHASER) found no significant difference in COVID-19 incidence between Evushield and placebo groups at 30 days when used as *post*-exposure prophylaxis.[12] At this time, Evushield is not approved as post-exposure prophylaxis nor as therapy.

Evushield retains some activity against Omicron, albeit less than its activity against prior variants.[9,11-12]

Figure 2. Examples of moderate/severe immunocompromising conditions as indications for Evushield per FDA EUA. Note these are the same suggested indications for additional COVID-19 vaccination.

- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Receipt of CAR T-cell therapy or hematopoietic cell transplant in prior 2 years
- Use of immunosuppressive therapy after solid-organ transplant
- Active treatment with other immunosuppressive or immune-modulatory drugs, including high-dose corticosteroids (>20mg/d of prednisone or equivalent) and TNF inhibitors

Oral Antiviral Medications

In December 2021, the FDA issued emergency use authorizations for nirmaltrelvir-ritonivir (Paxlovid) and molnupiravir within a 24-hour timespan for outpatient adults with mild-moderate COVID-19 disease at high risk for progression.[13-14]

Nirmatrelvir-ritonavir (Paxlovid)

As the active component of Paxlovid, nirmatrelvir inhibits the SARS-CoV-2 protease, which cleaves viral polyproteins into functional proteins after translation. With protease inhibition, SARS-CoV-2 polyproteins remain intact, which renders the virus incapable of replication. Due to rapid hepatic metabolism of nirmatrelvir by CYP3A4, nirmatrelvir is co-administered with ritonavir; similar to its use in HIV medication regimens, ritonavir is employed here to inhibit CYP3A4-mediated metabolism to boost serum levels of nirmatrelvir.[15]

Available clinical data for Paxlovid appears promising so far. In the EPIC-HR study, over 2,000 COVID-19 infected adults were randomized to receive either Paxlovid or placebo. These adults had at least one risk factor for severe disease plus symptom onset in the prior 5 days, while individuals with prior COVID-19 vaccination or infection were excluded. The study ultimately found an 88% relative risk reduction for hospitalization or all-cause 28-day mortality with Paxlovid.[16]

However, a major limitation of Paxlovid is the aforementioned interaction of ritonavir with the CYP3A4 enzyme, of which many commonly-used prescription medications are a substrate. Paxlovid is thus strictly contraindicated with many medications, including some anti-arrhythmics like amiodarone and anticoagulants like rivaroxaban. The Paxlovid EUA Fact Sheet[16] provides an extensive table of potential drug-drug interactions, and the University of Liverpool's COVID-19 Drug Interactions[17] website is a great resource to use in this setting for patients with complex medication list. Other contraindications to note include severe renal impairment (GFR ≤ 30 mL/min) and severe hepatic disease (Child-Pugh Class C).

Molnupiravir

Like remdesivir, molnupiravir is a nucleoside analogue that incorporates itself into SARS-CoV-2 RNA via the virus' RNA polymerase. However, their mechanisms of action differ. On one hand, remdesivir immediately terminates viral reproduction once incorporated into viral RNA. Molnupiravir, in contrast, allows ongoing viral replication, but it causes accumulation of errors in the viral genome that ultimately stops viral reproduction.

Overall, molnupiravir currently has less convincing data as compared to other therapy modalities. A randomized, double-blinded trial found that, among unvaccinated adults with one risk factor for disease progression, molnupiravir was associated with a 30% relative risk reduction of hospitalization and death due to COVID-19 when given within 5 days of symptom onset.[18-19]

Concerns of mutagenicity with molnupiravir have also been raised. Mice studies have either been equivocal or found no increase in mutagenicity, but molnupiravir is currently not recommended in pregnancy if other agents can be used.[19] The EUA further encourages strict contraception among women and men of reproductive potential, through the duration of treatment plus an additional 4 days for women and 3 months for men. Bone and cartilage toxicity was also observed in rat models, and thus molnupiravir is not approved for pediatric patients.

All-in-all, molnupiravir still remains a viable option for patients in the outpatient setting, but largely for those unable to take other treatments. NIH COVID-19 Treatment Guidelines (see Figure 3) currently rank molnupiravir 4th in preference behind nirmaltrelvir-ritonavir, sotrovomab and IV remdesivir.

Intravenous antiviral therapy: Remdesivir

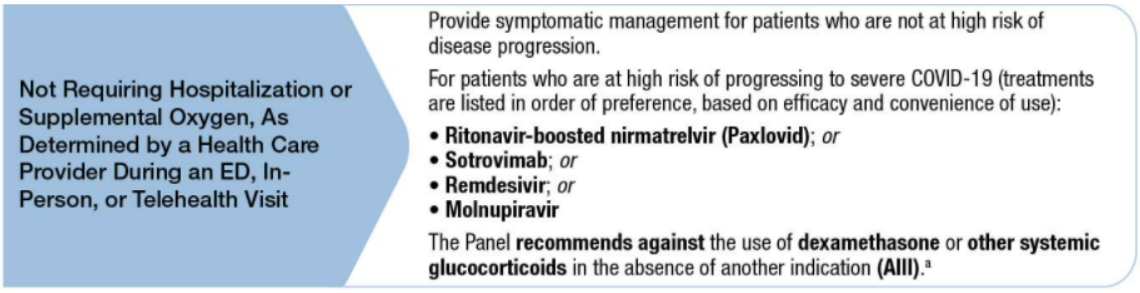
Some of the most convincing efficacy data for remdesivir has emerged from the PINE-TREE trial.[20] This randomized control trial enrolled COVID-positive, non-hospitalized, unvaccinated patients with at least one risk factor for disease progression. Symptom onset within 7 days and positive molecular testing within 4 days were required. The study groups were randomized to either receive 3 days of IV remdesivir (200mg on day 1, followed by 100mg on days 2 and 3) or placebo. While initially intended for around 1200 participants, the study was stopped early after enrollment of 500 patients, as a nearly 87% reduction in hospitalization or death was found in the remdesivir group.[20]

Based on these findings, the FDA recently expanded the approved indication for remdesivir last week.[21] Outpatient remdesivir therapy is perhaps best facilitated in nursing homes given it is administered intravenously. However, in centers that can facilitate remdesivir therapy through an infusion center, this option provides an effective alternative for COVID-19 therapy, particularly if oral medication supply is low.

Prioritization of therapies and Resource Allocation

Despite the expansion of available COVID-19 therapies, healthcare systems are faced with limited medication supply and significant demand with the Omicron wave. Fortunately, the NIH has provided a general framework for both application of the new therapeutics and resource allocation when medication supply is limited. Based on efficacy and ease of administration, the NIH recommends therapy with Paxlovid, sotrovimab, or remdesivir for high-risk patients with mild-moderate COVID-19, followed by molnupravir (Figure 3).[22]

Figure 3: NIH COVID-19 Treatment Guidelines for Non-hospitalized Adults with COVID-19.[22] Note the order of medications is in order of preference, based on both efficacy and convenience.



When resources are limited, the NIH has also issued guidance regarding patient priorization for outpatient COVID-19 therapy.[23] They suggest:

- Treatment of COVID-19 over post-exposure prophylaxis of SARS-CoV-2 infection.
- Treatment of COVID-19 in: 1) unvaccinated or incompletely vaccinated individuals with risk factors for severe illness; and 2) vaccinated patients who are not expected to mount an adequate immune response.
- Limiting tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis to severely immunocompromised individuals only.

The NIH additionally provides a prioritization table, (see Figure 4), if demand for medication exceeds supply. Clinical discretion will need to be applied as well, but overall this table at least provides a framework for identifying patients that would benefit most from COVID-19 therapy when resources are limited.

Conclusions

A number of new therapies are now available for treatment of mild-moderate COVID-19 disease in the outpatient setting. Selecting the most appropriate agent for each patient depends on a variety of factors, including patient co-morbidities, drug interactions, and medication supply. Fortunately, there are tools available to assist with decision-making, particularly as new information and therapies emerge.

Figure 4. NIH Tiers for Patient Prioritization for COVID-19 Treatment in Setting of Limited Medication Supply.[23] Listed in descending order of priority. Clinical discretion is required in addition to the above

Tier	Risk Group
1	- Immunocompromised individuals not expected to mount an effective immune response to COVID-19 vaccination or infection OR - Unvaccinated individuals at highest risk of severe disease (age ≥ 75 years or age ≥65 years with additional risk factors)
2	- Unvaccinated individuals at risk of severe disease not included in Tier 1
3	- Vaccinated individuals at highest risk of severe disease (age ≥ 75 years or age ≥65 years with additional risk factors) *Vaccinated but not boosted individuals should be prioritized
4	- Vaccinated individuals at risk of severe disease not included in Tier 1

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Name	Indications	Contraindications and Considerations	Dosing	Adverse Reactions
Monoclonal Antibodies				
Tixagevimab-cilgavimab *Pre-exposure Prophylaxis*	- Age ≥ 12 years and weight ≥ 40kg One of the following: - Moderate-severe immunocompromise* - Prior serious adverse reaction to COVID-19 vaccination	- Hypersensitivity to Evushield or its components - Active COVID-19 infection	Intramuscular (IM) injection: - Tixagevimab 150 mg/1.5mL (single-dose vial) - Cilgavimab 150 mg/1.5 mL (single-dose vial) Monitor patient for 1 hour after receipt.	- Hypersensitivity reactions - Headache, fatigue, cough
Sotrovimab	- Age ≥ 12 years and weight ≥ 40kg - Mild-moderate COVID-19 with high risk for disease progression - Within 10 days of symptom onset (ideally <5 days)	- Hypersensitivity to sotromivab or its components	Intravenous (IV) infusion over 30 minutes: - Sotromivab 500mg once Monitor patient for 1 hour after receipt.	- Hypersensitivity reactions - Diarrhea, rash
Antiviral Medications				
Nirmatrelvir-ritonavir (Paxlovid) Protease inhibitor	- Age ≥ 12 years and weight ≥ 40kg - Mild-moderate COVID-19 with high risk for disease progression - Within 5 days of symptom onset	- Hypersensitivity to Paxlovid components - Co-administration with CYP3A4 substrates or inducers that would result in serious adverse events due to toxicities, loss of virologic response, or development of virologic resistance - Not recommended with: 1) Severe renal impairment: eGFR <30 mL/min 2) Severe hepatic impairment: Child-Pugh Class C	Oral tablets: - Nirmatrelvir 300mg (two 150mg tablets) - Ritonavir 100mg (one 100mg tablet) Taken together twice daily for 5 days. Dosing for eGFR ≥30 to <60 mL/min: - Nirmatrelvir 150mg (one 150mg tablet) - Ritonavir 100mg (one 100mg tablet) Taken together twice daily for 5 days.	- Drug interactions via CYP3A4 - Hepatotoxicity - HIV drug resistance in people with undiagnosed or uncontrolled HIV - Dysgeusia, diarrhea, hypertension, myalgias
Remdesivir Nucleoside analogue	- Age ≥ 12 years and weight ≥ 40kg - Mild-moderate COVID-19 with high risk for disease progression - Within 7 days of symptom onset	- Hypersensitivity to remdesivir or its components - ALT>5x upper limit of normal - Assess risk/benefit in renal impairment	Intravenous (IV) infusion: - Remdesivir 200mg on day 1 - Remdesivir 100mg daily on days 2-3	-Hypersensitivity reaction -Increased AST/ALT -Nausea -Rash
Molnupravir Nucleoside analogue	- Age ≥ 18 years - Mild-moderate COVID-19 with high risk for disease progression - Within 5 days of symptom onset - In patients for whom alternative FDA-authorized COVID-19 treatment options are not accessible or clinically appropriate	- Avoid in pregnancy due to risk of embryo-fetal toxicity. However, if no other options available, risk-benefit discussion may be pursued - Avoid if <18 years of age due to risk of bone/cartilage damage - Adults of reproductive potential should use reliable contraception during treatment and an additional: 1) Females: 4 days after completion 2) Males: 3 months after completion	Oral tablets: - Molnupiravir 800mg (four 200mg tablets) Taken together twice daily for 5 days. If administering to lactating individual, avoid feeding an infant breast milk during molnupiravir treatment and for 4 days after the final dose	-Diarrhea, nausea, dizziness

*Defined per FDA as moderate or severe primary immunodeficiency; advanced or untreated HIV infection; CAR T-cell or hematopoietic cell transplant in prior 2 years, use of immunosuppressive therapy after solid-organ transplant, active treatment with other immunosuppressive or immune-modulatory drugs, including high-dose corticosteroids (>20mg/d of prednisone or equivalent)

***Supplemental Figure 1*: Overview of Available Outpatient COVID-19 Therapies as of 1/25/2022**