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EDITORIAL

Paxlovid Rebound: Proposed Strategy to Prevent Reinfection Following Treatment of COVID-19 Positive Nonhospitalized Patients

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Keywords: COVID-19; SARS-CoV-2; BA.5; BA.5; Omicron; Paxlovid; Malnupiravir; Bebtelovimab; EVUSHELD™; Malnupiravir; Remdesivir; CDC: Centers for Disease Control and Prevention; FDA: U.S. Food and Drug Administration; WHO: World Health Organization

B.1.1.529, the new lineage of SARS-CoV-2 variant was first detected in Botswana on November 11, 2021, and in South Africa on November 14, 2021. This new variant had many mutations in portions of the genome that increased its infectivity and transmissibility; conferred resistance to certain therapeutics; and reduced neutralization by monoclonal antibodies (1,2). Given these observations, On November 26, 2021, WHO classified B.1.1.529 as a variant of concern and named it Omicron (3). On November 30, 2021, the U.S. SARS-CoV-2 Interagency Group (SIG), which includes the Centers for Disease Control and Prevention (CDC), the National Institutes of Health, the Food and Drug Administration, the Biomedical Advanced Research and Development Authority, and the Departments of Defense, Agriculture, and Health and Human Services, classified the Omicron variant as a Variant of Concern.

Since its first identification, a total of six Omicron variants have been identified (Table 1). Many of the earlier variants were responsive to available experimental treatment including monoclonal antibodies such as Sotrovimab (4). However, both BA.4 and BA.5 were found less responsive to some for the existing therapies. BA.4 was first identified in the US in April 2022 but was soon replaced by BA.5 as the dominant variant that is currently responsible for majority of COVID-19 cases

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(Figure 1). BA.5 is probably the most transmissible variant of Omicron and has certain characteristic that are unique to this mutant:

- Infects those who have had previous natural infection from earlier variants of SARS-CoV2
- Escapes immunity due to COVID-19 vaccination
- Poor neutralization by previously existing experimental monoclonal antibodies

Given these characteristics, FDA revised its recommendation for the treatment of hospitalized and nonhospitalized patients infected with the BA.4 and BA.5 variants of Omicron (Table 2). Paxlovid, an oral antiviral medication, was recommended as the preferred option for the treatment of nonhospitalized mild-to-moderate SARS-CoV-2 infection in individuals 12 and older at high risk of progression to severe disease (Figure 3 and 4). Additionally, Bebtelovimab, a monoclonal antibody for the treatment of acute COVID-19 in the outpatient setting, is equally effective but in extremely short supply and it is recommended that it should be reserved for individuals with a contraindication to preferred therapies. More importantly, availability of Bebtelovimab after the third week of August is uncertain and as of August 01, 2022, patients would be required to pay to get treated with this monoclonal antibody. It is noteworthy that under an IRB-approved protocol, we at the DHR Health Institute for Research & Development have treated to date over 400 high risk COVID-19 positive patients with Bebtelovimab with very satisfactory outcomes.

While Paxlovid is the recommended drug of choice for treating mild-moderate nonhospitalized patients, it does have certain limitations (5). Despite its therapeutic effectiveness, Paxlovid is contraindicated in the following conditions which limits its utility (6):

- Patients requiring hospitalization
- For pre-exposure or post-exposure prophylaxis
- For use beyond recommended 5 consecutive days
- Patients with clinically significant hypersensitivity reactions (e.g., toxic epidermal necrolysis and Stevens-Johnson syndrome)
- Patients on drugs requiring CYP3A for clearance
- Patients on drugs that are potent induces of CYP3A

Of equal concern is the recent observation of high incidence of re-infection following treatment with Paxlovid (8). In a recent study involving 13,600 patients, it was reported that 7-day and 30-day COVID-19 rebound rates after Paxlovid treatment were 3.53% and 5.40% for SARS-CoV-2 infection, 2.31% and 5.87% for COVID-19 symptoms, and 0.44% and 0.77% for hospitalizations (8). While it requires further validation, there is however some recent evidence that the re-infection rate is probably as high as 20-40% in patients treated with Paxlovid (9). Rebound of SARS-CoV-2 infection in high profile cases following the recommended 5-day oral treatment with Paxlovid has further highlighted this concern (10 - 11). In one particular case, the patient resorted to taking a second course of Paxlovid after experiencing COVID-19 rebound which, at the present time is not recommended by the FDA (10).

Rebound of COVID-19 symptoms following the use of Paxlovid treatment is likely due to insufficient drug exposure: not enough of the drug was getting to infected cells to stop all viral replication. This could be due to the drug being

metabolized more quickly in some individuals or that the drug needs to be delivered over a longer treatment duration. ***It is therefore our recommendation that has also been voiced by others (12) that both Pfizer (the manufactures of Paxlovid) and FDA review the data and either increase the duration of treatment (from 5 days to 7-10 days) and/or allow the use of another 3–5-day course of Paxlovid for patients suffering from rebound. Alternatively combined use of Bebtelovimab and Paxlovid could be considered for contemporaneous reduction of both the circulating viral load and prevention of viral replication in infected cells.***

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Conflict of Interest:

The authors have reported no conflict of interest

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TABLE 1: VARIOUS VARIANTS OF OMICRON SINCE ITS FIRST IDENTIFICATION IN NOVEMBER 11, 2022 AND THE FREQUENCY OF PATIENTS INFECTED IN THE UNITED STATES AS OF JULY 23, 2022

OMICRON Lineage	Percentage Of Patients Infected
BA.1.1	0.0%
BA.1.1.529	0.0%
BA.2	0.3%
BA.2.12.1	5.0%
BA.4	12.9%
BA.5	81.9%

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FIGURE 1: TIMELINE OF VARIOUS OMICRON LINEAGES CAUSING SARS-COV-2 INFECTION IN THE UNITED STATES (Adopted From CDC Website): https://covid.cdc.gov/covid-data-tracker/#variant-proportions)

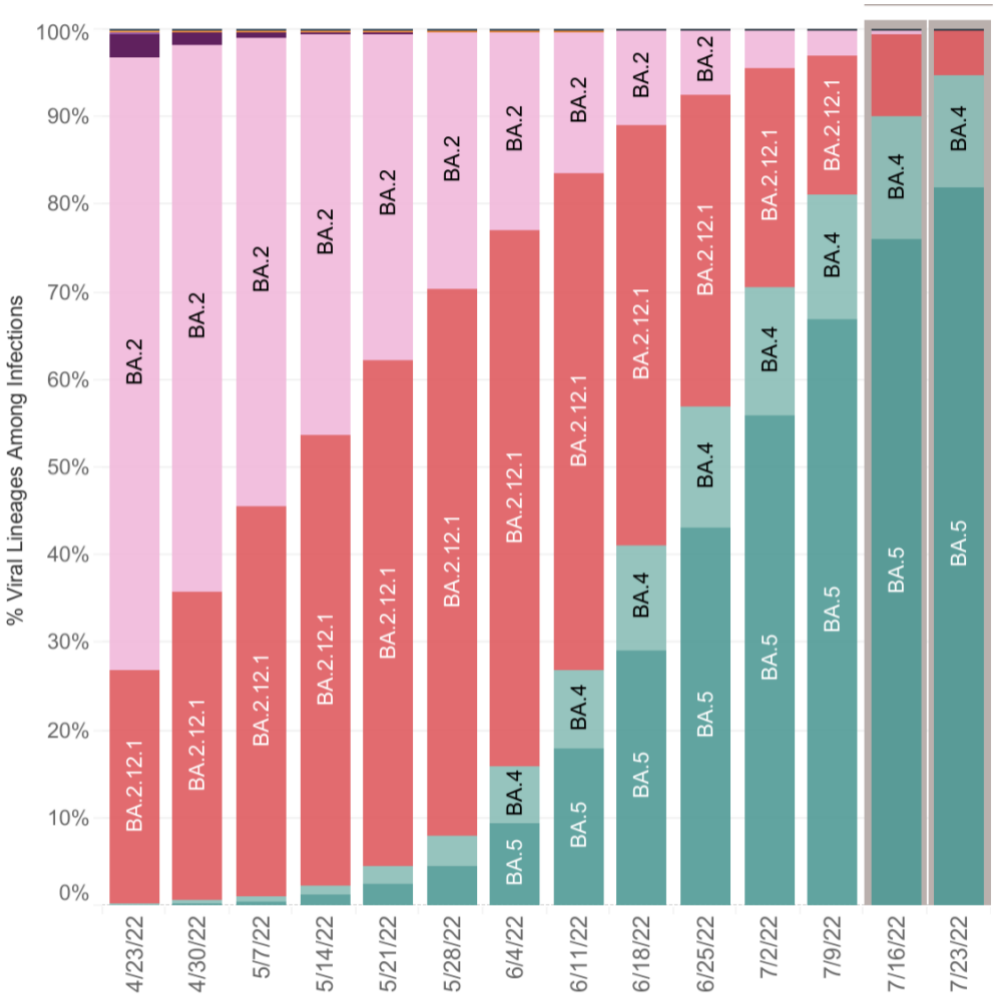

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TABLE 2: HOSPITALIZED AND OUTPATIENT TREATMENT OF PATIENTS INFECTED WITH THE BA.4 AND BA.5 VARIANTS OF OMICRON

Experimental Drug	Inpatient Vs. Outpatient	Severity Of Disease	Reference
Bebtelovimab Monoclonal Antibody	Outpatient	Mild to Moderate	https://www.fda.gov/media/156152/download
Remdesivir (Velkury)	Outpatient	Mild to Moderate	https://www.fda.gov/news-events/press-announcements/fda-takes-actions-expand-use-treatment-outpatients-mild-moderate-covid-19
Remdesivir + Baricitinib (Olumiant)	Inpatient	Severe	https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-combination-treatment-covid-19
Ritonavir-boosted Nirmatrelvir (Paxlovid)	Outpatient	Mild-Moderate	https://www.paxlovid.com/?source=bing&HBX_PK=s_paxlovid&skwid=43700068281647229&gclid=c926586053d315737f663a86b3210308&gclsrc=3p.ds
Malnupiravir (Lagevrio)	Outpatient	Mild-Moderate	https://www.nejm.org/doi/full/10.1056/NEJMoa2116044
EVUSHELD™ (Tixagevimab and Cilgavimab)	Outpatient	Pre-Exposure Prophylaxis in High-Risk Patients	https://www.evusheld.com/en/patient https://www.fda.gov/drugs/drug-safety-and-availability/fda-authorizes-revisions-evusheld-dosing

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FIGURE 2: COVID-19 OUTPATIENT THERAPEUTICS CLINICAL DECISION AID FOR AGES 12+ YEARS ADULT OR PEDIATRIC PATIENT (AGES 12 AND OLDER WEIGHING AT LEAST 40 KG) WITH MILD TO MODERATE COVID-19 AND AT HIGH RISK FOR PROGRESSION TO SEVERE DISEASE

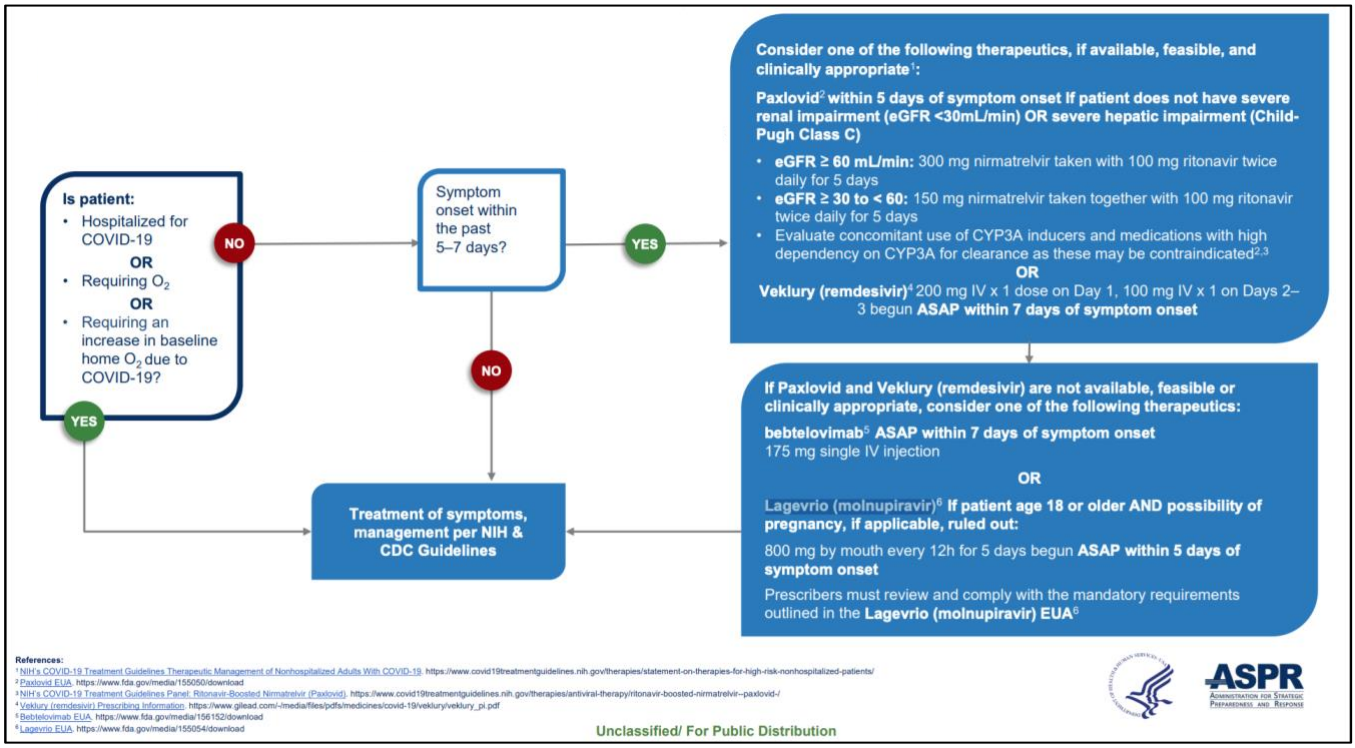

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FIGURE 3: COVID-19 OUTPATIENT THERAPEUTICS 18 JULY 2022 CLINICAL DECISION AID FOR AGES 28 DAYS TO LESS THAN 12 YEARS PEDIATRIC PATIENT (28 DAYS OF AGE TO LESS THAN 12 YEARS, WEIGHING AT LEAST 3 KG TO LESS THAN 40 KG) WITH MILD TO MODERATE COVID-19 AND AT HIGH RISK FOR PROGRESSION TO SEVERE DISEASE