INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***COVID-19 Prevention and Treatment Update***
-August 2023-

Background:

The Indian Health Service National Pharmacy and Therapeutics Committee (NPTC) provided an updated review of COVID-19 prevention and treatment agents. This topic was last reviewed by the NPTC in February 2022. While the United States' Public Health Emergency for the COVID-19 pandemic expired on May 11th, 2023, the virus continues to have a significant impact, especially in American Indian and Alaska Native communities where rates of morbidity and mortality exceeded those among other racial and ethnic groups.[1] Treatment continues to evolve in light of changing immunity rates and mutating variants. Currently, ACIP-recommended COVID-19 vaccines are listed on the National Core Formulary (NCF) for this condition. Following review and analysis, the NPTC voted to **ADD "nirmatrelvir/ritonavir (Paxlovid®)" to the NCF.**

Discussion:

The National Institutes of Health COVID-19 Treatment Guidelines provide comprehensive guidance for COVID-19 prevention and treatment. For prevention, vaccination continues to be the most effective strategy and it is recommended for all as soon as possible, when eligible. For inpatient treatment, there are 4 medications that are either FDA approved or used off-label under Emergency Use Authorizations (EUA). These medications include remdesivir, baricitinib, tocilizumab, and dexamethasone. Remdesivir is FDA approved for both inpatient and outpatient treatment. Within the inpatient guidelines, it is more strongly recommended for use in patients who are hospitalized and who require supplemental oxygen. It is also approved, albeit as a weaker recommendation, in both (1) patients who are hospitalized but are not requiring oxygen supplementation and (2) patients hospitalized requiring high flow nasal canula or non-invasive mechanical ventilation. It should be avoided in hospitalized patients who require mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Baricitinib and tocilizumab are also FDA approved for inpatient treatment of COVID-19. They are recommended for use in hospitalized patients that require oxygen, mechanical ventilation, or ECMO already on dexamethasone. Dexamethasone is recommended by the guidelines in all hospitalized patients who require oxygen, mechanical ventilation, or ECMO. For the treatment of non-hospitalized adults with mild to moderate COVID-19, nirmatrelvir/ritonavir, remdesivir, and molnupiravir are available options. They are only recommended in patients at a high-risk of progression to severe COVID-19, and preferred medications for use are recommended in the order above. Dexamethasone and other steroids are not recommended in non-hospitalized adults in the absence of another indication.[2]

Additional agents approved for inpatient use under EUAs are vilobelimab and anakinra. Vilobelimab is approved for COVID-19 treatment in hospitalized patients when initiated within 48 hours of receiving invasive mechanical ventilation or ECMO. Anakinra is approved for COVID-19 treatment in hospitalized patients with pneumonia requiring supplemental oxygen who are at risk of progressing to severe respiratory failure and likely to have an elevated suPAR.

Literature Evaluation: remdesivir

A Cochrane review from May 2022 looked at remdesivir use in adults with COVID-19 versus placebo. The study showed benefit in remdesivir use in both clinical improvement (95% CI: RR 1.11 [1.06 to 1.17]) and clinical worsening (95% CI: HR 0.67 [0.54 to 0.82]), suggesting a benefit for patients with mild to moderate COVID-19 in both the hospitalized and non-hospitalized setting.[3] A September 2022 meta-analysis evaluated remdesivir use in hospitalized adults with COVID-19 versus placebo. This analysis reported that remdesivir use reduced mortality for non-ventilated patients with COVID-19 requiring supplemental oxygen therapy (95% CI: RR 0.89 [0.79-0.99]). It did not demonstrate a significant mortality reduction for patients without oxygen or those on mechanical ventilation.[4]

Literature Evaluation: molnupiravir

A meta-analysis from March 2023 compared molnupiravir use versus placebo in hospitalized and non-hospitalized patients with COVID-19. Ultimately, there was a non-significant lowering of mortality in the molnupiravir group. When looking at subgroup analyses, it was discovered that benefits of molnupiravir on hospitalization and mortality were only evident in the unvaccinated outpatient population (95% CI; RR 0.12 [0.03-0.54]).[5] The PANORAMIC Trial from December 2022 evaluated molnupiravir in high-risk vaccinated patients with confirmed COVID-19. For this trial, molnupiravir did not reduce hospitalizations or death among high-risk vaccinated adults in the outpatient setting, but did lead to improvement across a number of secondary outcomes.[6]

Literature Evaluation: nirmatrelvir/ritonavir

A Cochrane review from July 2022 reviewed nirmatrelvir/ritonavir use versus placebo in unvaccinated high-risk outpatients without known previous COVID-19 infection and with symptom onset less than 5 days prior to randomization. The study found a low certainty of evidence that nirmatrelvir/ritonavir reduced risk of all-cause mortality (95% CI: RR 0.04 [0.00 to

0.68]) and hospital admission or death (95% CI: RR 0.13 [0.07 to 0.27]) in this unvaccinated population.[7] A population-based cohort study from May of 2023 reviewed adult outpatients with confirmed positive COVID-19 using nirmatrelvir/ritonavir versus usual care. The study showed a significant reduction in hospitalizations and deaths (OR 0.56, [95% CI: 0.47-0.67, p<0.001]) in the nirmatrelvir/ritonavir group, and results overall were similar in the stratified analysis by age, vaccine status, comorbidities, drug-drug interactions, and risk stratus. However, the study also showed a possible decrease in effectiveness over time during a subgroup analysis. When stratified for time, the April-June 2022 group had an OR of 0.43 (95% CI: 0.33-0.57), NNT 48 whereas the July-August 2022 group had an OR of 0.67 (95% CI: 0.52-0.86), NNT 83.[8]

Finally, a literature search was conducted for any comparative studies for antiviral agents. A meta-analysis from April 2023 directly compared nirmatrelvir/ritonavir against other antiviral drugs for treatment of COVID-19. Finding from this analysis showed that nirmatrelvir/ritonavir was superior in decreasing long-tern hospitalizations (OR 0.65, 95% CI: 0.44-0.97, p=0.03) and mortality (OR 0.29, 95% CI: 0.13-0.66, p=0.003). It also suggested, based off secondary outcomes pertinent to the condition, that nirmatrelvir/ritonavir was more effective in alleviating long-term symptoms of COVID-19.[9] The Veterans Affairs conducted a study to evaluate if there was an association of treatment with nirmatrelvir/ritonavir and the risk of post-COVID conditions, or “long COVID.” High-risk outpatients with confirmed-positive COVID-19 who received nirmatrelvir/ritonavir were compared to those who did not receive an antiviral or antibody treatment. The study suggested that treatment with nirmatrelvir/ritonavir during the acute phase of COVID-19 may reduce the risk of post-acute adverse health outcomes. This benefit was seen across all vaccination and previous infection statuses.[10]

Findings:

There are currently 6 medications that are FDA approved or authorized under an EUA for the inpatient management of patients with COVID-19. These medications include remdesivir, baricitinib, tocilizumab, dexamethasone, vilobelimab, and anakinra. There are currently 3 medications that are FDA approved or authorized under an EUA for the outpatient management of patients with COVID-19. These medications include nirmatrelvir/ritonavir, remdesivir, and molnupiravir. Most recent guidelines and evidence recommend a preference for nirmatrelvir/ritonavir in treating outpatients at high-risk for progression to severe COVID-19, followed by remdesivir. Molnupiravir should be reserved for those who cannot tolerate one of the other two options. All therapeutic options need to continue to be monitored for real world effectiveness as immunity and vaccination levels change and new variants emerge. For long COVID or post-COVID conditions, there have been positive data emerge with nirmatrelvir/ritonavir use and a corresponding decrease in these conditions, but more research is needed to confirm these findings. Current evidence from published literature and guidelines support the addition of nirmatrelvir/ritonavir to the NCF.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

1. Arrazola J, Masiello MM, Joshi S, et al. COVID-19 Mortality Among American Indian and Alaska Native Persons—14 States, January-June 2020. MMWR Morb Mortal Wkly Rep 2020; 69:1853-56.
2. National Institutes of Health, Coronavirus Disease 2019 (COVID-19) Treatment Guidelines
3. Grundeis F, Ansems K, Dahms K, et al. Remdesivir for the treatment of COVID-19. Available at: https://pubmed.ncbi.nlm.nih.gov/36695483/. Cochrane Database Syst Rev 2023, no. 1 (January 25, 2023).
4. Lee TC, Murthy S, Del Corp O, et al. Remdesivir for the Treatment of COVID-19: A Systematic Review and Meta-Analysis. Clin Microbiol Infecti 2022; 28(9):1203-10.
5. Huang PY, Ting-Hui L, Jheng-Yan W, et al. Clinical Efficacy and Safety of Molnupiravir for Nonhospitalized and Hospitalized Patients with COVID-19: A Systematic Review and Meta-analysis of Randomized Control Trials. J Med Virol. 2023; 95(3):e28621.
6. Butler CC, Hobbs FD, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Available at: https://www.thelancet.com/action/showPdf?pii=S0140-6736%2822%2902597-1 Lancet. 2023; 401(10373):281–93.
7. Reis S, Metzendorf MI, Kuehn R, et al. Nirmatrelvir Combined with Ritonavir for Preventing and Treating Covid-19. Cochrane Infectious Diseases Group, ed. Cochrane Database Syst Rev. Published April 11, 2022.
8. Schwartz KL, Wang J, Tadrou M, et al. Population-Based Evaluation of the Effectiveness of Nirmatrelvir–Ritonavir for Reducing Hospital Admissions and Mortality from COVID-19. CMAJ. 2023; 195(6):E220–26.
9. Tian F, Zhaoyan C, Qiyi F. Nirmatrelvir–Ritonavir Compared with Other Antiviral Drugs for the Treatment of COVID-19 Patients: A Systematic Review and Meta-analysis. J Med Virol. 2023; 95(4):e28732.
10. Xie Y, Taeyoung C, Ziyad AA. Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition. JAMA Intern Med. 2023; 183(6): 554-64.