

Chinese expert consensus on the combined use of antiviral drugs for novel coronavirus infection

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SUMMARY: The persistent mutation of the novel coronavirus (SARS-CoV-2) not only remains a threat to human health but also continues to challenge existing antiviral therapeutic strategies. In current clinical practice, the resistance of novel coronavirus to antivirals, the rebound of viral load after treatment with drugs such as nirmatrelvir/ritonavir (NTV/r), and the urgent need for rapid clearance of the virus in the management of critically and emergently ill patients suggest that the existing single-drug regimens may have limitations and that the intensity of suppression may be insufficient in some cases. In clinical practice, we have observed that a combination of antivirals with different mechanisms of action can result in better efficacy and not significantly increase adverse drug reactions (ADRs). For some immunosuppressed, post-transplantation, or other special patients in particular, such as those in whom COVID-19 nucleic acids tended not to be negative after conventional treatment, when virus clearance is still the main goal, the combination of small-molecule antivirals can help to clear the virus as early as possible and attempt to improve the success rate of salvage. Based on evidence-based medicine and in light of the current situation of China, we assembled experts from disciplines such as infectious diseases, respiratory medicine, critical care medicine, and clinical pharmacy into a group to carry out a systematic literature search and identify key issues and to put forward relevant recommendations to reach an Expert Consensus on Combined Use of Oral Small-molecule Antivirals to Treat COVID-19, which is intended to serve as a reference for clinical practice.

Keywords: novel coronavirus infection, COVID-19, antiviral therapy, small molecule drugs, drug combination, expert consensus

1. Introduction

Despite significant progress in the global response to the COVID-19 pandemic, the continued mutation of SARS-CoV-2 not only makes it a continuing threat to human health but also continues to challenge existing antiviral therapeutic strategies. The World Health Organization (WHO) emphasizes the need for countries to continue to implement preventive and control measures, including monitoring virus mutation, enhancing vaccination of high-risk groups, and optimizing clinical capacity in order to consolidate the gains made in the prevention and control of the epidemic.

Sustained viral transmission, and especially in at-risk populations with weakened immunity such as elderly patients and patients with an underlying condition, makes effective antiviral treatment programs particularly critical. In current clinical practice, however, the resistance of novel coronavirus to antivirals, the rebound of viral load after treatment with drugs such as nirmatrelvir/ritonavir (NTV/r), and the urgent need for rapid clearance of the virus in the management of critically and emergently ill patients suggest that existing single-drug regimens may have limitations and that the intensity of suppression may be insufficient in some cases. Therefore, an important research direction is to explore the combination of oral small-molecule antivirals with different mechanisms of action in order to achieve better efficacy. The currently approved oral small-molecule antivirals for COVID-19 can be mainly divided into two categories: 3CL proteolytic enzyme inhibitors (exemplified by NTV/r) and RNA replicase inhibitors (exemplified by molnupiravir).

A retrospective analysis of data from nearly 10,000 patients who had been treated with oral small-molecule antivirals to analyze the changes in viral

load after treatment found that combining antivirals with different mechanisms of action resulted in better suppression of SARS-CoV-2 (1). According to the COVID-19 Diagnosis and Treatment Program (draft 10th edition) and related prescribing information issued by the National Health and Wellness Commission of China, the use of NTV/r for 5 days or azvudine for a maximum of 14 days is recommended for single-agent treatment (2). Previous case summaries have also shown that sequential or concomitant therapy with NTV/r and azvudine can increase the nucleic acid negative conversion rate and accelerate recovery without an increase in adverse drug reactions (ADRs), and all the ADRs observed were mild and low-grade. One study concluded that NTV/r and azvudine are safe and effective, whether administered sequentially or concomitantly, in patients with COVID-19 due to the Omicron variant (3).

The long-term symptoms associated with SARS-CoV-2 infection, which are referred to here as "long COVID (LC)" are also a conspicuous global public health concern (4). The variants of SARS-CoV-2 differ in their transmissibility and pathogenicity, with the Omicron variant having greater immune escape. One study even observed that despite the production of neutralizing antibodies in COVID-19 patients, they may still excrete infectious SARS-CoV-2 for more than 3 months (5). In addition, the rapid emergence of viral variants not only challenges vaccine efficacy and existing prevention and control strategies but may also affect the effectiveness of single-agent antiviral therapy and increase the risk of drug resistance, thus further highlighting the urgency of exploring more robust therapeutic strategies, such as drug combinations (6).

2. Methods

Based on the needs of clinical practice and according to evidence-based medicine and in light of the current situation in China, we assembled experts from disciplines such as infection diseases, respiratory internal medicine, critical care medicine, and clinical pharmacy to form a group to carry out a systematic literature search and identify key issues and to put forward relevant recommendations to reach an Expert Consensus on the Combined Use of Oral Small-molecule Antivirals to Treat COVID-19. It is intended for reference in clinical practice. The strength of the recommendations and the grades of evidence are shown in Tables 1 and 2 and are based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (7).

Consensus Text

3. Theoretical basis for the combined use of antivirals

Although vaccination has significantly reduced the severe case rate and the mortality rate of COVID-19, viral mutations that allow the virus to break through the immune barrier and cause human infections, which are referred to as breakthrough infections, are still seen, and especially when new variants are prevalent or individuals with poor immune responses such as decreasing levels of antibodies over time or inadequate cellular immune responses; rapid and effective control of viral replication is essential to prevent disease progression (8). Cellular immunity plays an important role in combating SARS-CoV-2, which is synergistic with humoral immunity (9). Theoretically, the combined use of antivirals targeting different targets can gain the time for the host's immune system (including humoral immunity and cellular

immunity) to clear the virus through more potent or broad-spectrum viral suppression and may reduce the generation and selection pressure of immune escape variants by enhancing the intensity of viral suppression. This constitutes the theoretical basis for the combined use of antivirals.

Viral resistance has been associated with SARS-CoV-2 viral spiking protein mutations, and single antiviral therapy increases the emergence of drug-resistant mutations, some of which are found in strains that can disrupt antibody-binding sites and thus evade antibody neutralization (10). Some antivirals can induce resistance to SARS-CoV-2, which may lead to increased morbidity and mortality. Combined drug administration may improve efficiency and reduce the need for healthcare resources through the selection of drug combinations to maximize antiviral efficacy and reduce adverse drug interactions (11). Combination therapy can enhance the inhibitory effect on the virus, reduce the possibility of drug-resistant mutations, increase the virus clearance rate, and decrease the occurrence of virus rebound (12).

The presence of multiple SARS-CoV-2 antibody escape variants in patients with an immune deficiency may be one of the reasons why the nucleic acids of the novel coronavirus tend not to be negative in such patients. Similar corroboration is provided by a case reported in the United States, where a male COVID-19 patient in his 50s on long-term immunosuppressant therapy received convalescent plasma therapy, but the virus from samples on day 21 and 27 had developed new mutations (13). The use of strategies such as combinations of drugs that can more potently and durably inhibit viral replication can help to reduce the chances of viral mutation and immune escape.

Table 1. Recommended clinical classification

Strength of Recommendation	Grade	Grade Interpretation and Clinical Recommendations
A	Strong	Evidence is positive or good (Grade I - II); evidence is fair (Grade III - IV), but it is clearly recommended in domestic and international guidelines; it is able to improve health outcomes, and the benefits outweigh the disadvantages.
B	Medium	Evidence is fair (level III-IV), can improve health outcomes
C	Weak	Evidence is insufficient or contradictory. Its pros and cons cannot be identified, but it may improve health outcomes

Table 2. Level of evidence

Level of evidence	Grading Interpretation
I	Meta-analysis or systematic evaluation based on multiple randomized controlled trials; large randomized controlled trials
II	Based on at least 1 high-quality randomized controlled trial; observational or cross-sectional studies with standardized design and clear outcomes; prospective cohort studies
III	Based on well-designed non-randomized case-control studies; observational studies; non-prospective cohort studies
IV	Based on non-randomized retrospective studies; case reports; expert consensus

4. Pharmacologic basis for the combined use of antivirals

From a pharmacological point of view, similar to combination antiviral therapy for AIDS, a combination of antivirals with different mechanisms of action is a common strategy to improve efficacy and reduce the risk of drug resistance, and this theory is also applicable to the treatment of COVID-19. Currently, the main oral small-molecule antivirals used in clinical practice can be divided into two categories: 3CL protease inhibitors and RNA polymerase inhibitors, which work by inhibiting different aspects of viral replication. A 59-year-old female patient with follicular lymphoma, who had received anti-tumor treatment but had not been vaccinated against COVID-19, had persistent COVID-19 and her condition repeatedly worsened. After the initiation of combination antiviral therapy with NTV/r for 5 days and remdesivir for 10 days, the patient recovered (14). Another study of immunocompromised patients treated at the Infectious Diseases Clinic of the University of Turin, Italy between March 2022 and February 2023 noted good results in some patients who were treated with NTV/r in combination with either molnupiravir or remdesivir (15). Evidence from clinical practice is mounting daily in support of the combination of antivirals with different mechanisms of action as a promising treatment option, and especially when dealing with refractory or high-risk COVID-19 cases.

Recommendations

Recommendation 1: Drug combination should strictly follow the principle of selecting drugs with different pharmacological mechanisms of action with a view to achieving synergistic efficacy and reducing the risk of drug resistance. [Evidence Level: III, Recommendation Grade: A]

Recommended combination regimen: A 3CL protease inhibitor should be selected for combination with an RNA polymerase (RdRp) inhibitor. Available 3CL protease inhibitors ("Drug I") include NTV/r, simnotrelvir/ritonavir, leritrelvir, and atilotelvir/ritonavir. Optional RNA polymerase (RdRp) inhibitors ("Drug II") include molnupiravir, azvudine, or mindeudesivir (VV116). Co-administration means selecting a drug from the "Drug I" category and combining it with one from the "Drug II" category. If ritonavir-containing drugs are selected, due consideration should be given to their interaction with other drugs used.

Unrecommended combination regimens: Two antivirals with the same mechanism of action should not be used in combination. In other words, use of the drugs listed in "Drug I" above in combination is not recommended, nor is use of the drugs listed in "Drug II" above in combination recommended.

Recommendation 2: During the process of combining medications, the patient's condition needs to be dynamically monitored. The cycle threshold value (Ct value) of nucleic acids for COVID-19, ADRs, adverse drug interactions, etc., need to be monitored and the drugs used need to be dynamically adjusted. If, for example, a ritonavir-containing 3CL protease inhibitor is currently in use, and if the condition requires the addition of a drug that may cause adverse interactions with ritonavir, the drug should be adjusted to a 3CL protease inhibitor without ritonavir, such as leritrelvir. After the combination, if the nucleic acid Ct value is greater than 30, or if clinical symptoms or imaging improve, or if an ADR is probably, very probably, or definitely associated, or if there is an adverse drug interaction, then consideration should be given to discontinuing the combination and, if necessary, to discontinuing all antivirals for SARS-CoV-2 altogether. [Evidence Level: III, Recommendation Grade: A]

Successful cases of salvage of refractory COVID-19 through use of small-molecule anti-SARS-CoV-2 drugs with different pharmacologic effects are reported in the literature. A 47-year-old male patient with non-Hodgkin's lymphoma and an immune deficiency whose condition was refractory to COVID-19 was successfully treated with NTV/r in combination with remdesivir (16). These cases offer potential remedies for refractory COVID-19. A 73-year-old lymphoma patient with COVID-19 who was treated with rituximab started early antiviral treatment with NTV/r (300/100 mg every 12 hours for 5 days) as a monotherapy while positive for SARS-CoV-2 nucleic acids (day 1), but the patient's symptoms recurred and the COVID-19 nucleic acids remained positive. On day 64 of the positive detection of SARS-CoV-2 nucleic acids, NTV/r (300/100 mg every 12 hours) combined with molnupiravir (800 mg every 12 hours) was administered for a total of 9 days and was successful, resulting in no ADRs (17).

A 64-year-old male patient with asthma and chronic lymphocytic leukemia (CLL) was initially treated with a conventional 5-day course of NTV/r, but his symptoms recurred, and he was subsequently treated with a combination of NTV/r and remdesivir (18). Three days afterwards, the patient's temperature returned to normal, and his physical pain, coughing, and breathing difficulties were significantly alleviated; after 9 days of treatment, his SARS-CoV-2 nucleic acid test was negative and he was discharged. The combination of medications was discontinued after 20 days of treatment and the patient's symptoms were completely relieved; chest CT showed significant alleviation of ground glass opacity. At follow-up two months later, the patient's symptoms completely disappeared, and the SARS-CoV-2 nucleic acid test was consistently negative. In a retrospective study in China, 3,647 patients were treated with NTV/r, 379 were treated with simnotrelvir/ritonavir, and 34 were treated with a combination of simnotrelvir/ritonavir and

mindeudesivir (VV116) (1). The combination therapy had significant superiority compared to single-agent use in patients with an initial Ct value of < 30. The patients in the combination therapy group had the fastest virus clearance rate, and no increase in liver or kidney toxicity related to the increase in medication was observed.

An *in vitro* experimental study reported that drug combinations similar to nirmatrelvir and molnupiravir, as well as the combination of camostat and molnupiravir, have inhibitory effects on SARS-CoV-2 variants (beta and delta), further enhancing their antiviral efficacy (19). That study provides strong evidence for the development of combined drug regimens against SARS-CoV-2, suggesting that combinations of drugs are more effective than single drugs, and they are expected to provide more options in controlling SARS-CoV-2 infections and preventing serious diseases. In animal experiments, NTV/r combined with molnupiravir administration was found to reduce the viral mutation-inducing effects of molnupiravir (20). In a macaque model of COVID-19, use of molnupiravir and nirmatrelvir in combination improved the individual inhibitory effect of both drugs, resulting in milder disease progression, greater reduction of virus shedding from mucosal tissues of the upper respiratory tract, greater reduction of viral replication in the lower respiratory tract, and reduced lung pathology; these findings indicate the superiority of molnupiravir and nirmatrelvir in the combined treatment of SARS-CoV-2 infections (21). These experimental results support the combination of drugs.

Recommendation 3: For critical COVID-19 according to the COVID-19 Diagnosis and Treatment Program (draft 10th edition) issued by the National Health Commission of China are met, that is, any of the following conditions are met: 1. Respiratory failure and need for mechanical ventilation; 2. Shock; and 3. The presence of other organ failure requiring ICU supervision and treatment. Regardless of previous antiviral use, as long as the disease duration is within 5 days or the viral nucleic acid test is positive and the Ct value is less than 30, combining medication with oral small-molecule drugs against COVID-19 is recommended (refer to *Recommendation 1* for drug selection), as long as there are no contraindications to the use of those drugs. For patients with combined hepatic and renal insufficiency, however, *Recommendations 11* and *12* need to be referred to, hepatic and renal function need to be fully determined, and caution should be exercised when combining drugs if conditions permit. [Evidence Level: III, Recommendation Grade: A]

Most of the patients with critical COVID-19 have an impaired immune system and prolonged detoxification of SARS-CoV-2, and that prolonged detoxification may induce the emergence of mutant strains or induce vaccine immune escape, potentially increasing the difficulty of treatment (22). *In vitro* characterization

and sequencing revealed mutations in SARS-CoV-2, suggesting that chronic infection with SARS-CoV-2 leads to viral evolution and reduces susceptibility to neutralizing antibodies in immunosuppressed individuals treated with plasma during convalescence (23). Several animal studies have confirmed that molnupiravir has a synergistic effect with nirmatrelvir, which more effectively inhibits SARS-CoV-2 virus replication and reduces morbidity and mortality in animals infected with COVID-19 (24,25), and extended antiviral regimens or combinations of antivirals with different pharmacological mechanisms may be considered in critically ill patients with prolonged viral retention.

The general view is that SARS-CoV-2 is the initiating factor of COVID-19, and virus clearance is fundamental. The Third People's Hospital of Shenzhen used combined NTV/r and azvudine treatment in 12 cases of critical patients with COVID-19 and achieved better results (3). Sequential or concomitant therapy with NTV/r and azvudine may increase the nucleic acid negative conversion (NANC) rate and accelerate recovery without an increase in ADRs. All of the ADRs observed in that study were mild and low-grade. It concluded that NTV/r and azvudine are safe and effective in patients with COVID-19 caused by the Omicron variant, whether administered sequentially or concomitantly. As an example, a critical patient with COVID-19 and asthma and acute lymphoblastic leukocytes responded poorly to a routine course of NTV/r and was then switched to molnupiravir combined with NTV/r, which resulted in a better outcome (18).

Fifteen critical patients were studied, of whom 11 suffered from blood disorders and 4 were diagnosed with HIV/AIDS; of the 15 critical patients, 6 received a single antiviral regimen, 4 received antivirals and monoclonal antibodies sequentially, 2 received three antivirals (remdesivir, NTV/r, or molnupiravir) or two drugs, and 3 were given two antivirals or one antiviral plus a monoclonal antibody (15). Results indicated that the COVID-19 nucleic acid test was negative within 16 days after the end of treatment, and the median time to viral conversion was 2.5 days, confirming that the combination regimen displayed better efficacy and safety in immunosuppressed high-risk populations in that study.

Recommendation 4: For severe COVID-19 according to the COVID-19 Diagnosis and Treatment Program (draft 10th edition) issued by the National Health and Health Commission of China, if the antiviral has been used for one course of treatment but the COVID-19 nucleic acid test is still positive with a Ct value of less than 30, and there are no contraindications to the use of medication, a combination of oral small-molecule antivirals should be used, and the antiviral can continue to be used as previously, along with another antiviral with different pharmacologic effects, or a switch can be made to a new group of antivirals in line with the

provisions of *Recommendation 1*. [Evidence Level: III, Recommendation Grade: A]

Recommendation 5: For severe COVID-19 according to the COVID-19 Diagnosis and Treatment Program (draft 10th edition) issued by the National Health and Health Commission of China, if antivirals have previously been used but for less than one full course of treatment, the COVID-19 nucleic acid test is still positive with a Ct value of less than 30, disease tends to progress or worsen, such as the persistence of a fever, and lung imaging shows that the infection has not improved or has progressed, then as long as there are no contraindications to the use of these drugs, a combination of oral small-molecule antivirals should be used, and the antiviral can continue to be used as previously, along with another antiviral with different pharmacologic effects in line with the provisions of *Recommendation 1*. [Evidence Level: III, Recommendation Grade: A]

Recommendation 6: For severe or moderate COVID-19 according to the COVID-19 Diagnosis Treatment Program (draft 10th edition) issued by the National Health and Wellness Commission of China, if antivirals have previously been used but not for a full course of treatment, the viral nucleic acid test is still positive, the patient's condition tends to improve, and patients are non-critical and not in high-risk groups, then they can be closely observed, and antivirals need not be combined for the time being. [Evidence Level: III, Recommendation Grade: A]

Recommendation 7: For moderate COVID-19 according to the COVID-19 Diagnosis and Treatment Protocol (draft 10th edition) issued by the National Health and Wellness Commission of China, if a course of antiviral medication has been used, the COVID-19 nucleic acid test is still positive, and the Ct value is less than 30, then as long as there are no contraindications to the use of these drugs, oral small-molecule antivirals should be used, and the antiviral can continue to be used as previously, along with another antiviral with different pharmacologic effects, or a switch can be made to a new group of antivirals in line with the provisions of *Recommendation 1*. [Evidence Level: III, Recommendation Grade: A]

Case-cohort studies have shown that prolonged use of antivirals leads to better results. In an American cohort study, a mathematical model was developed to analyze the viral load dynamics of 51 patients infected with SARS-CoV-2 who were treated with a regular 5-day course of NTV/r, 20 of whom experienced a viral rebound (26). Dividing the population into a group that experienced viral rebound (20 individuals) and a group that did not experience viral rebound (31 individuals) showed that there were significant differences between the two groups in terms of target cell protection parameters and

mortality of infected cells and that these differences resulted in better maintenance of target cells in the group that did not experience viral rebound. Extending the NTV/r regimen to 10 days significantly reduced the risk of viral rebound. There was an average delay of 1.23 days in the initiation of the adaptive immune response in the NTV/r-treated group compared to the untreated group. Target cell preservation and incomplete viral clearance were the main causes of viral rebound after NTV/r treatment. Extending the NTV/r treatment regimen to 10 days can significantly reduce the risk of viral rebound. The Third People's Hospital of Shenzhen used a combination of NTV/r and azvudine treatment for 8 critical patients with COVID-19 and achieved better results; the drug combination did not increase the risk of safety and significantly improved the nucleic acid conversion rate, especially for patients in whom a single drug was ineffective (3).

Another study reported that 67 patients treated with a combination of at least two direct antivirals (protease inhibitor + polymerase inhibitor) had a viral clearance rate of 79% and a relapse rate of 16% (27). In immunocompromised patients with persistent SARS-CoV-2 infection, combination therapy is beneficial in achieving SARS-CoV-2 clearance and reducing the risk of relapse. In clinical trials, combination regimens have been found to enhance antiviral efficacy, reduce the emergence of drug-resistant variants, and lower the dose of each component of combination therapy while targeting viral invasion and viral replication, providing opportunities for synergistic drug combinations (19).

In refractory cases with recurrent symptoms, the combination of 3CL protease inhibitors and RNA polymerase inhibitors has been successful. A patient first tested positive for SARS-CoV-2 in October 2022 and was subsequently treated with NTV/r but had recurrent symptoms (17). The patient received a combination of molnupiravir and NTV/r on day 64, which resulted in a negative antigen test and rapid symptomatic relief 5 days later (day 69). *In vitro* studies have shown that molnupiravir exhibits enhanced antiviral activity when combined with other antivirals (17).

Nine patients with hematologic malignancies in a hospital in central Italy who had received unsuccessful SARS-CoV-2 therapy were treated with a combination of antivirals for persistent infection (28). The combination therapy consisted of NTV/r plus molnupiravir ($n = 4$), NTV/r plus remdesivir ($n = 4$), or remdesivir plus molnupiravir ($n = 1$) over a 10-day course of treatment, with 8 of them having clinical and virologic success confirmed by radiologic follow-up, and all the patients receiving the combination tolerated the drug well.

Recommendation 8: In patients > 65 years of age and with underlying conditions such as cardiovascular disease (including hypertension), chronic lung disease, diabetes, chronic liver, renal disease, and neoplasms,

as well as in patients on maintenance dialysis, the presence of early warning indicators of severe/critical illness, including 1. Progressive exacerbation of hypoxemia or respiratory distress; 2. Deterioration of tissue oxygenation indices (e.g., pulse oximetry or the oxygenation index) or progressive elevation of lactate; 3. Progressive decrease according to the peripheral blood lymphocyte count or a progressive increase in inflammatory factors such as interleukin 6 (IL-6), C-reactive protein (CRP), and ferritin; 4. Significantly elevated coagulation-related markers, such as D-dimer; and 5. Significantly progressive lung lesions on chest imaging. Regardless of the previous use of antivirals, as long as the COVID-19 nucleic acid test is positive and the Ct value is less than 30 and there are no contraindications to the use of drugs, a combination of oral small-molecule antivirals is recommended (for drug selection, refer to the provisions of *Recommendation 1*). For patients with combined hepatic or renal insufficiency, however, *Recommendations 11* and *12* need to be referred to, hepatic and renal function need to be fully determined, and caution needs to be exercised when combining drugs if conditions permit. [Evidence Level: III, Recommendation Grade: A]

Elderly patients and some patients with COVID-19 and underlying conditions have a higher mortality rate. In a retrospective cohort study at Rasoul Akram Hospital, Tehran, Iran, results indicated that mortality was higher in patients who were male, older than 55 years of age, and who suffered from comorbidities such as renal disease, cancer, and Alzheimer's disease (29).

One study proposed a comprehensive predictive model based on multiple factors. Being older, being male, and being of a certain race were associated with a higher risk of serious illness and death. Fever, shortness of breath, dyspnea, and gastrointestinal symptoms are early warning signs of exacerbation. Conditions such as hypertension, diabetes, obesity, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), chronic liver disease (CLD), chronic kidney disease (CKD), and cancer significantly increase the risk of serious illness. Immunodeficiencies (e.g., HIV infection or congenital immunodeficiencies) may increase the risk of serious illness, and especially those associated with type I interferon (IFN-I). Acute kidney injury (AKI), coagulation disorders, and thromboembolism (such as pulmonary embolism) are hallmarks of deterioration. Administration of an anticoagulant may reduce mortality. Leukocytosis, lymphocytopenia, eosinophilia, elevated D-dimer, and elevated indicators such as lactate dehydrogenase (LDH), CRP, procalcitonin (PCT), IL-6, IL-1, and ferritin are associated with the severity of the disease. Impaired interferon type I (IFN-I) activity or autoantibodies may lead to severe disease. The extent of pneumonic lesions on chest CT correlates with disease severity. Vitamins C and D, a high-fiber diet, a Mediterranean

diet, intermittent fasting, and a ketogenic diet may be beneficial in improving prognosis. Smoking significantly increases the risk of severe disease. Healthcare workers have a high risk of exposure (30). An active combination of oral small-molecule antivirals is recommended for this particular group of patients, similar to critically and severely ill patients.

Recommendation 9: In patients with an immunodeficiency (e.g., patients with AIDS and those using corticosteroids or other immunosuppressive drugs for a prolonged period leading to compromised immunity) or patients using immunosuppressants for a prolonged period for organ transplantation who present with early warning signs as described in *Recommendation 8*, regardless of previous antiviral use, then as long as COVID-19 nucleic acid testing is positive with a Ct value of less than 30 and there are no contraindications to the use of drugs, the use of a combination of oral small-molecule antivirals is recommended (for drug selection, refer to the provisions of *Recommendation 1*). [Evidence Level: IV, Recommendation Grade: A]

Recommendation 10: For patients with COVID-19 who are undergoing organ transplantation or who have a blood disease or tumor, selection of a ritonavir-free drug is recommended when selecting a 3CL protease inhibitor, such as leritrelvir due to the adverse interactions between ritonavir and commonly used immunosuppressants such as tacrolimus, methylprednisolone, and cyclosporine, the blood concentration of which can be increased by ritonavir. [Evidence Level: IV, Recommendation Grade: A]

The literature points to the generation of SARS-CoV-2 variants in immunosuppressed patients and its public health implications and calls for comprehensive measures to reduce the risk of variants and to protect this high-risk group and public health. Immunosuppressed patients (e.g., cancer patients, organ transplant recipients, or HIV-infected individuals) may experience prolonged SARS-CoV-2 infections due to compromised immunity. This persistent infection provides an environment for the SARS-CoV-2 to evolve rapidly, leading to the emergence of multiple mutations and variations, which are related to globally concerned variants such as Alpha, Beta, Gamma, Delta and Omicron. Viral evolution is characterized by (i) Adaptive evolution: viruses gain transmission or immune escape advantages through mutation, (ii) Convergent evolution: different viral lineages independently produce the same key mutations, or (iii) Jump evolution: rapid accumulation of multiple mutations may occur in immunosuppressed patients, resulting in highly mutated viral variants. Immunosuppressed patients may become a source of new mutations, and enhanced protective measures need to be taken to reduce the spread of COVID-19. Vaccination should be given priority to this group of people, and their immune responses

should be monitored. Household contacts should also be vaccinated to break the chain of community transmission. Monoclonal antibodies and antivirals such as molnupiravir can be used for prophylaxis or treatment, but the potential for mutation-induced drug resistance needs to be borne in mind. A new generation of vaccines against variants needs to be developed. Further studies on the relationship between specific immunosuppressive conditions and viral variants need to be conducted in the future, and targeted prevention and control guidelines need to be developed (22).

In a retrospective cohort study, for 11 immunocompromised patients (7 in the early stage of COVID-19 and 4 in the late stage), treatment lasted 10 days, with intravenous remdesivir plus 5 days of oral NTV/r for all patients. Patients in the early treatment group had 100% virologic clearance 30 days after the end of treatment and all survived at follow-up: 50% and 75% in the late treatment group, respectively (31). The results of that study provide new combination therapy options and support the early treatment of COVID-19 in immunocompromised patients, suggesting that early combination therapy may be helpful in achieving complete and durable viral clearance and preventing the development of severe disease.

A hospital in New Jersey in the US studied a man in his 50s who was hospitalized for COVID - 19, had received a kidney transplant, and was on long-term immunosuppressive therapy (13). The study analyzed the viral genome by sequencing nasopharyngeal swabs and tracheal aspirate samples collected on multiple occasions. In immunosuppressed patients receiving convalescent plasma therapy, there is a risk of their becoming immune to escape mutant strains that may possess greater antibody resistance. The study's results indicated the risk of viral evolution that may be triggered by convalescent plasma therapy in immunosuppressed hosts, and the possible impact of the patient's immune status on viral evolution needs to be considered when formulating antiviral treatment strategies, which may benefit from combining antivirals.

Due to the use of immunosuppressants, the risk of SARS-CoV-2 infection increases in solid organ transplant recipients (SOTRs), and the hospitalization rate, severe case rate, ICU hospitalization rate, and mortality rate are all higher than those for non-organ transplant patients (32). Being older, being male, and having multiple underlying conditions are associated with a higher risk of death in SOTRs. The cited study emphasized the high risk of COVID-19 in SOTRs, and targeted measures need to be taken to improve their prognosis. Another study has suggested that SOTRs infected with SARS-CoV-2 have a higher risk of AKI than non-transplant patients.(33). Age, multi-organ failure and mechanical ventilation are the main predictors of mortality in organ transplant recipients. Studies have highlighted the need for individualized management strategies for SOTRs. Another study has found that patients who

have undergone solid organ transplantation (SOT) face a higher hospitalization rate and risk of adverse renal events after being infected with the SARS-CoV-2, highlighting the importance of enhanced protection and early intervention (34).

Recommendation 11: In patients with renal insufficiency, and especially severe renal insufficiency, combined medications are not recommended. For severe renal insufficiency, molnupiravir can be used in regular doses; for patients with mild or moderate renal impairment, NTV/r can be used and the dose used can be adjusted according to the glomerular filtration rate (eGFR); for mild renal impairment, azvudine can also be used. Relevant trials and studies on VV116 and leritrelvir have not been conducted, so there are no clinical data on patients with renal impairment and there are no reliable references. Thus, those drugs are not recommended for patients with renal insufficiency. Regardless of whether a patient has mild or moderate renal insufficiency, a combination of drugs should be used with extreme caution, fully weighing the pros and cons. [Evidence Level: IV, Recommendation Grade: A]

Recommendation 12: Combining medications is not recommended in patients with hepatic insufficiency, and especially in patients with severe hepatic impairment. For patients with severe hepatic impairment, molnupiravir at regular doses may be used; for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, NTV/r, simnotrelvir/ritonavir, leritrelvir, azvudine, and VV116 may be used with caution. In patients with either mild or moderate hepatic insufficiency, a combination of drugs should be used with extreme caution, fully weighing the pros and cons. [Evidence Level: IV, Recommendation Grade: A]

Molnupiravir does not require dose adjustment in patients with renal impairment. NTV/r does not require dose adjustment in patients with mild renal impairment ($60 \leq \text{eGFR} < 90$). In patients with moderate renal impairment ($30 \leq \text{eGFR} < 60$), the dose of NTV/r should be reduced to 150 mg/100 mg once/12 h for 5 d. NTV/r should not be used in patients with severe renal impairment ($\text{eGFR} < 30$), including those with end-stage renal disease on hemodialysis. An important point worth noting that the concepts of the eGFR and creatinine clearance (CrCl) differ, and CrCl should not be used as a substitute for the eGFR. When the CrCl is very low, the eGFR may still be >30 . The relevant formula for calculating the eGFR, which can be found at <https://www.23bei.com/tool/603.html>, is used for reference.

Recommendation 13: According to the COVID-19 Diagnosis and Treatment Program (draft 10th edition) issued by the National Health and Wellness Commission of China, the combination of drugs is not recommended

for patients diagnosed with mild COVID-19, in order to avoid unnecessary drug exposure and potential adverse effects and in light of the self-limiting course of the disease. [Evidence Level: III, Recommendation Grade: A]

Co-administration is not recommended when not necessary, taking into account the adverse effects of the drugs. Although the ADRs to NTV/r are generally considered to not be serious, a total of 8,098 reports of ADRs to it were identified from January-June 2022, with the most common symptoms being dysphagia, diarrhea, cough, fatigue, and headaches; serious cases were also reported, with cardiac arrest, tremor, sedation, and death reported in 1, 3, 67, and 5 cases, respectively (35). ADRs have also been reported in relation to molnupiravir, with the most commonly reported being related to gastrointestinal disorders and skin and subcutaneous tissue disorders. In addition, individuals 65 years of age and older are at higher risk for heart disease, hepatobiliary disease, renal and urinary tract disease, and vascular disease. In patients younger than 65 years of age, molnupiravir demonstrated a lower risk of serious ADRs compared to other RNA antivirals such as remdesivir. However, its safety still needs to be closely monitored in elderly patients 65 years of age and older. As the use of molnupiravir increases, and especially in high-risk populations, further studies need to be conducted to continuously assess its safety (36). Therefore, in patients with mild COVID-19, monotherapy is recommended as the mainstay, and combinations are not recommended for non-essential use.

Recommendation 14: For pediatric patients, drug combinations are not recommended. For COVID-19 in children (<18 years of age), oral small-molecule antivirals should not be used unless necessary, as indicated by the current Chinese Drug Formulary and the COVID-19 Diagnosis and Treatment Program (draft 10th edition). For adolescent patients ages 12-17 years with a body mass ≥ 40 kg, high-risk factors (as defined in the National Diagnosis and Treatment Program (10th edition)), and a SARS-CoV-2 infection, off-label medication should be considered when necessary, and NTV/r should be given at the adult dosage. [Evidence Level: III, Recommendation Grade: A]

NTV/r is not recommended for use in children under 12 years of age or those weighing less than 40 kg because its safety and effectiveness have not been demonstrated in pediatric patients. Monoravir is not recommended for use in persons under 18 years of age, and animal studies have shown that it can cause impaired conversion of cartilage into new bone (37). When using NTV/r, an important point to note is that ritonavir is a potent CYP3A4 inhibitor, which may significantly increase the risk of ADRs in children when combined with other drugs metabolized by CYP3A4 (e.g., immunosuppressants and anticoagulants) (38).

Recommendation 15: In pregnant women, drug combinations are not recommended. NTV/r may be used with caution at routine doses with the patient's informed consent when the potential benefit to the mother outweighs the potential risk to the fetus, as assessed for the specific combination. [Evidence Level: III, Recommendation Grade: A]

The higher odds of a cesarean delivery, low birth weight, and preterm delivery in pregnant women with COVID-19 suggests a possible association between development of COVID-19 and pregnancy complications. Although the risk of vertical transmission is low, SARS-CoV-2 can be detected in the placenta.

The Chinese package inserts for simnotrelvir/ritonavir, leritrelvir, atilotelvir/ritonavir, molnupiravir, azvudine, and VV116 state that all of these drugs are contraindicated for use in pregnant women, are not recommended for use, or have been shown to be toxic to the fetus in animal studies. When choosing oral small-molecule antivirals, these factors need to be taken into account and the safety of the drugs should be weighed for both the mother and the fetus (39). According to the current Chinese package inserts, in addition to considering NTV/r in pregnant women with COVID-19, leritrelvir and atilotelvir/ritonavir may be used with caution when the benefits outweigh the risks, with the informed consent of the patient. In principle, drug combinations are not recommended for pregnant woman.

Booster vaccination is advocated for pregnant women, due to the higher risk of severe disease after COVID-19 infection in pregnant women and the significantly increased risk of severe disease and adverse pregnancy outcomes after infection in unvaccinated individuals. Priority needs to be given to increasing vaccination rates in pregnant women (and especially those in younger and low-income groups) to protect the health of mothers and infants (40). The literature suggests that the benefits of using NTV/r in pregnant women with COVID-19 may outweigh the associated risks. However, data from animal studies have indicated that molnupiravir may pose a risk of fetal harm when administered during pregnancy (37). A single-arm meta-analysis of 427 pregnant patients receiving NTV/r was performed to comprehensively assess outcomes in the maternal, delivery, and neonatal phases, and results indicated that it was safe and effective in pregnant women with mild or moderate COVID-19, with low rates of hospitalization and low adverse maternal outcomes (41). Subsequent dosing for pregnant women with COVID-19 requires relevant dosing adjustments based on additional clinical studies and updated package inserts.

5. Conclusion

A point worth noting is that in clinical practice, the conventional use of a single drug for the treatment

of COVID-19 should be considered first. Our suggestion is that in special cases, such as critically ill, immunosuppressed, post-transplant, or other special patients, or patients in whom COVID-19 nucleic acids tend not to be negative after conventional treatment, when virus clearance is still the main goal the combined use of small-molecule antivirals, after full consideration and discussion, can help clear the virus as soon as possible and improve the success rate of rescue.

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