Treatment Drug Selection and Considerations for Adult Patients with Chronic Kidney Disease and COVID-19: A Post-Print Summary of Current Evidence

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Abstract

Chronic kidney disease (CKD) is characterized by abnormal urinalysis or progressive decline in renal function. Due to impaired renal function, long-term use of immunomodulatory medications, or multiple comorbidities, CKD patients are more susceptible to infection with the novel coronavirus (COVID-19) compared to the general population, and demonstrate higher rates of severe disease progression and mortality following infection. For the treatment of CKD patients with concurrent COVID-19 infection, rational pharmacotherapy is particularly crucial. To this end, this article integrates the latest research evidence on therapeutics for COVID-19, including antiviral agents, anti-inflammatory drugs, antithrombotic agents, convalescent plasma and neutralizing monoclonal antibodies, as well as commonly used symptomatic treatments for respiratory diseases (such as antipyretics, antitussives, expectorants, and antiallergic medications), with emphasis on dosage adjustment protocols across different levels of renal function, and summarizes key special considerations for the use of these medications in CKD patients, aiming to provide reference for clinical professionals, assist in clinical decision-making and rational drug use, and ensure therapeutic efficacy and safety.

Full Text

Selection and Consideration of Therapeutic Drugs for COVID-19 Infection in Adults with Chronic Kidney Disease—A Summary Based on Current Evidence

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Abstract Chronic kidney disease (CKD) is characterized by abnormal urinalysis or progressive decline in kidney function. Due to impaired renal function, long-term use of immunosuppressive agents, and multiple comorbidities, CKD patients are more susceptible to SARS-CoV-2 infection and have higher rates of severe disease progression and mortality compared to the general population. Rational drug use is therefore particularly critical for CKD patients with COVID-19. This article integrates current evidence on medications for COVID-19 treatment, including antiviral drugs, anti-inflammatory agents, antithrombotic drugs, convalescent plasma and neutralizing monoclonal antibodies, as well as commonly used symptomatic treatments for respiratory diseases (such as antipyretics, antitussives, expectorants, and antiallergic drugs). We highlight dose adjustment protocols for different levels of kidney function and summarize special considerations for medication use in CKD patients to provide clinical professionals with evidence-based guidance for decision-making and rational prescribing, ensuring both efficacy and safety.

[**Keywords**] Kidney diseases; Chronic kidney disease; Coronavirus disease 2019; Dialysis; Therapy; Medication; Guideline; Evidence-based medicine

Introduction

Chronic kidney disease (CKD) is characterized by abnormal urinalysis or progressive decline in kidney function. An estimated 850 million people worldwide suffer from various forms of CKD, accounting for 10% of the global population [1]. With its high prevalence, incidence, and disability rates, CKD has become one of the world' s top ten causes of death and a major global public health concern [2].

Research on SARS-CoV-2 infection has identified CKD as an independent risk factor for severe COVID-19. After excluding CKD populations, the global severe disease rate from COVID-19 infection would decrease from 22% to 17% [3-5]. Current treatments for COVID-19 include: (1) symptomatic treatments for respiratory diseases commonly used for fever reduction, cough suppression, and expectoration [6-9] (Table 1); (2) antiviral drugs that directly inhibit viral

replication [8,10-12] (Table 2); (3) anti-inflammatory agents that target the host immune system [8,10,13-14] (Table 3); (4) antithrombotic therapies that reduce secondary damage [15-23] (Table 4); and (5) convalescent plasma and recombinant neutralizing monoclonal antibodies that block viral entry into host cells [8,24] (Table 5). Some of these drugs require dose adjustment in CKD patients, and our research team has compiled medication dosing protocols for patients with different levels of kidney function.

Following China' s policy shift in COVID-19 management, clinical specialties face the challenge of managing COVID-19 infection in patients with underlying diseases, including CKD. This study systematically searched PubMed, Web of Science, Embase, CNKI, Wanfang Data, and VIP databases through January 2023 using search terms including "SARS-CoV-2," "chronic kidney disease," "COVID-19," and "Chronic kidney disease" as both subject headings and free text. We included domestic and international guidelines or expert consensus on COVID-19 treatment and relevant studies on commonly used COVID-19 medications in CKD patients. Our search prioritized top-tier medical journals such as *New England Journal of Medicine*, *Lancet*, *JAMA*, and *BMJ*, as well as leading nephrology journals including *Nature Reviews Nephrology*, *Kidney International*, *American Journal of Kidney Disease*, *Clinical Journal of the American Society of Nephrology*, and *Nephrology Dialysis Transplantation*. We also incorporated China' s 10th Edition Protocol for COVID-19 Diagnosis and Treatment, guidelines from the U.S. National Institutes of Health, UpToDate, Japan' s 8th Edition COVID-19 Treatment Manual, and Australia' s National Clinical Evidence Task Force (NCETF) guidelines. This article summarizes current evidence on commonly used COVID-19 treatments, with particular focus on adult CKD patients, to provide clinical professionals with reference information. As indications for COVID-19 treatments and related guidelines continue to evolve, clinical decisions should be made in consideration of patient preferences and clinical context.

Given that COVID-19 infection itself can cause acute kidney injury, unless otherwise specified, the CKD patients mentioned in this article primarily refer to adult CKD patients with pre-existing renal impairment not receiving renal replacement therapy. Maintenance dialysis or kidney transplant patients will be specifically noted when discussed.

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1. Overview of COVID-19 Treatment Medications

Currently available treatments for COVID-19 include symptomatic medications for respiratory diseases (antipyretics, antitussives, expectorants, and antiallergic drugs), antiviral agents, anti-inflammatory drugs, antithrombotic therapies, and convalescent plasma with neutralizing monoclonal antibodies. Dose adjustment considerations for these agents across different levels of kidney function are summarized below.

2. Symptomatic Treatment Drugs for COVID-19 Infection

Currently, mild COVID-19 cases in CKD patients often use symptomatic medications (antipyretics, antitussives, expectorants, antiallergic drugs) for symptom relief. Notably, ibuprofen, a commonly used NSAID for fever reduction, should be limited to $ $2 days of continuous use in CKD patients, as prolonged use may increase the risk of interstitial nephritis and acute kidney injury. For CKD stage 4-5 patients or those taking ACE inhibitors/ARBs, particular attention should be paid to the risk of hyperkalemia, and serum potassium should be monitored when using ibuprofen [6]. Acetaminophen requires extended dosing intervals as renal function declines [7]. Expectorants such as guaifenesin and ammonium chloride are contraindicated in CKD patients [7] (Table 1).

3. Antiviral Drugs

3.1 Remdesivir (Veklury®)

Mechanism of Action: Remdesivir is a nucleotide analog prodrug whose active metabolite inhibits RNA-dependent RNA polymerase, reducing viral genome replication.

Indications: Hospitalized COVID-19 patients requiring oxygen therapy [10]; or non-hospitalized mild-to-moderate COVID-19 patients with symptom onset within 7 days who are unvaccinated and have one or more risk factors for disease progression, or severe COVID-19 patients not requiring high-flow oxygen or non-invasive/invasive mechanical ventilation [25].

Dosage: 200 mg on day 1, followed by 100 mg daily on days 2-5, administered intravenously for 5 days (extended to 10 days if no clinical improvement or in patients receiving mechanical ventilation or ECMO) [10].

Special Considerations for CKD Patients: Remdesivir contains sulfobutylether-β-cyclodextrin sodium as a solubility enhancer, which carries a risk of renal tubular injury. It is not recommended for patients with eGFR $<30\ \mathrm{ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$ unless potential benefits outweigh risks. Limited efficacy data exist for dialysis patients, though it is generally considered well-tolerated. Hemodialysis can reduce the blood concentration of the intermediate metabolite GS-441524 by approximately 50% [26]. Cases of up to 6 days of use in dialysis patients have been reported [27].

Precautions: Concurrent use with hydroxychloroquine or chloroquine should be avoided due to potential drug interactions.

3.2 Nirmatrelvir/Ritonavir (Paxlovid®)

Mechanism of Action: Nirmatrelvir inhibits the main protease of SARS-CoV-2, thereby blocking viral replication. Ritonavir is co-administered to slow nirmatrelvir metabolism and maintain therapeutic concentrations.

Indications: Symptomatic mild-to-moderate outpatient COVID-19 patients at high risk for progression to severe disease (age >65 years, comorbidities, immunocompromised status) [14].

Dosage: Nirmatrelvir 300 mg plus ritonavir 100 mg co-administered orally twice daily for 5 days.

Special Considerations for CKD Patients: For moderate renal impairment (eGFR 30-59 $ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$), the dose should be reduced to nirmatrelvir 150 mg plus ritonavir 100 mg twice daily for 5 days. It is not recommended for severe renal impairment (eGFR <30 $ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$), though for patients with compelling need, a reported reduced-dose regimen is: Day 1: nirmatrelvir 300 mg + ritonavir 100 mg once daily; Days 2-5: nirmatrelvir 150 mg + ritonavir 100 mg once daily, with close renal function monitoring and administration after hemodialysis on dialysis days [11].

Precautions: Ritonavir affects drug-metabolizing enzyme CYP3A, influencing metabolism of both nirmatrelvir and other CYP3A-metabolized drugs, creating potential for drug interactions [40]. In CKD patients, concomitant use with certain drugs increases their plasma concentrations: for example, amlodipine concentrations double, enhancing hypotensive effects and requiring dose reduction or discontinuation; calcineurin inhibitors require dose reduction. Conversely, rifampin, carbamazepine, phenytoin, and St. John' s wort can enhance CYP3A activity, reducing nirmatrelvir/ritonavir concentrations [11,40]. Clinicians must evaluate CKD patients' medication regimens, adjusting, substituting, or holding drugs to ensure safety and efficacy. Additional interactions can be checked at https://www.covid19-druginteractions.org/checker.

3.3 Molnupiravir (Lagevrio®)

Mechanism of Action: Molnupiravir is a β-d-N4-hydroxycytidine (NHC) prodrug that acts on SARS-CoV-2 RNA-dependent RNA polymerase, inducing viral RNA mutations and inhibiting replication.

Indications: Symptomatic outpatient COVID-19 patients with mild-to-moderate disease within 5 days of onset who are at risk for progression to severe disease [8].

Dosage: 800 mg orally every 12 hours for 5 days in patients $ $18 years.

Special Considerations for CKD Patients: No dose adjustment is needed for hepatic or renal impairment.

Precautions: Molnupiravir has bone and cartilage toxicity and is contraindicated in patients <18 years. It is not recommended during pregnancy or lactation. Women should use reliable contraception during treatment and for 4 days after completion. Men should use reliable contraception during treatment and for at least 3 months after completion.

3.4 Azvudine

Mechanism of Action: Azvudine is a viral reverse transcriptase inhibitor originally developed for HIV treatment. On July 25, 2022, China' s State Food and Drug Administration (SFDA) approved its use for COVID-19.

Indications: Moderate COVID-19 patients [8].

Dosage: 5 mg once daily orally on an empty stomach for $ $14 days.

Special Considerations for CKD Patients: No clinical research data are available for patients with renal insufficiency or those undergoing dialysis or kidney transplantation. Azvudine is primarily excreted unchanged by the kidneys (>70% of total excretion) [44], theoretically requiring dose adjustment in CKD patients with reduced renal function, though no specific data are currently available.

Precautions: Not recommended during pregnancy or lactation; use with caution in patients with moderate-to-severe hepatic impairment.

3.5 VV116 (Deuremidevir Hydrobromide Tablets)

Mechanism of Action: VV116 targets and inhibits the activity of SARS-CoV-2 RNA replication enzyme RdRp.

Indications: Early treatment in adult COVID-19 patients at high risk for severe disease progression [12,28].

Dosage: 600 mg every 12 hours on day 1, then 300 mg every 12 hours on days 2-5, administered orally.

Special Considerations for CKD Patients: Although 38 patients with eGFR 30-60 $\mathrm{ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$ participated in the phase III non-inferiority trial without adverse events, the updated protocol excluded these participants [12]. The drug received conditional approval in China on January 29, 2023, and its potential in COVID-19 treatment warrants further investigation.

3.6 Evidence Summary of Commonly Used Antiviral Drugs for COVID-19 in CKD Populations

Randomized controlled trials of remdesivir excluded patients with eGFR $<30\ \mathrm{ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$ [29-31]. Remdesivir contains sulfobutylether-β-cyclodextrin as a solubility enhancer, which is renally excreted and can cause renal tubular injury in rats at high doses [32]. However, the safety risk of

short-course remdesivir remains unclear, with several reports of its use in patients with severe renal impairment [27,33-36]. Current Australian guidelines do not recommend remdesivir for eGFR <30 $ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ [25], though a phase III trial in this population is ongoing [37].

The EPIC-HR trial of nirmatrelvir/ritonavir excluded patients with eGFR <45 $ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ [38], though the U.S. FDA allows reduced-dose use for eGFR 30-59 $ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ [39]. The MOVe-OUT trial of molnupiravir excluded eGFR <30 $ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ patients, with only 5.9% CKD participants [41]. However, since molnupiravir' s active metabolite NHC is metabolized through the endogenous pyrimidine pathway, the European Medicines Agency does not restrict its use in severe renal impairment or dialysis patients, and no dose adjustment is required.

Azvudine' s published COVID-19 literature includes two clinical studies [42-43]. One randomized, open-label trial of 20 mild-to-moderate COVID-19 patients showed shorter time to viral negativity in the azvudine group compared to national guideline-recommended antivirals [$(2.60\$\pm0.97)days vs.(5.60\pm3.06)days, P = 0.008]. However, the study excluded patients with eGFR < 60 $ml \cdot min^{\{-1\} \cdot (1.73m}\{2\})\hat{}\{-1\}\$$, and no direct evidence exists for CKD patients.

VV116 has a mechanism similar to remdesivir but is orally administered. A phase III non-inferiority trial showed median time to clinical symptom resolution of 4 days in the VV116 group versus 5 days with nirmatrelvir/ritonavir [HR=1.17, 95%CI (1.02, 1.36)]. Although 38 patients with eGFR 30-60 $ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ participated without adverse events, they were later excluded from the updated protocol [12].

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4. Anti-inflammatory Drugs Targeting Inflammatory Pathways in COVID-19

Severe COVID-19 is characterized by a hyperinflammatory state [45-46]. Compared to healthy adults, hospitalized COVID-19 patients show elevated acute-phase proteins (e.g., ferritin [45]) and pro-inflammatory cytokines such as interleukin-6 (IL-6) [47], with these elevated inflammatory markers correlating with increased mortality risk [47-48]. Based on these findings, clinical trials have investigated anti-inflammatory agents, generating evidence for treating critically ill COVID-19 patients.

4.1 Dexamethasone [13]

Mechanism of Action: Dexamethasone has anti-inflammatory effects that reduce and prevent tissue inflammatory responses, inhibit inflammatory cell accumulation (including macrophages and leukocytes) at inflammatory sites, and suppress phagocytosis, lysosomal enzyme release, and synthesis/release of inflammatory mediators.

Indications: Severe and critically ill cases with progressive oxygenation deterioration, rapid radiographic progression, and excessive inflammatory response [8]; or critically ill COVID-19 patients requiring oxygen or mechanical ventilation support [10].

Dosage: Dexamethasone 5 mg [8] or 6 mg [13] once daily for up to 10 days (oral/nasogastric tube/intravenous), whichever is shorter. If dexamethasone is unavailable, equivalent doses of other glucocorticoids may be used (e.g., hydrocortisone 150 mg/d, methylprednisolone 40 mg/d, or prednisone 40 mg/d).

Special Considerations for CKD Patients: No dose adjustment is needed.

4.2 Baricitinib [49-53]

Mechanism of Action: Baricitinib is a Janus kinase (JAK) inhibitor that may also exert antiviral effects by interfering with viral entry.

Indications: Patients requiring high-flow oxygen or non-invasive ventilation, and those receiving low-flow oxygen who progress despite dexamethasone therapy to require higher-level respiratory support [10].

Dosage: Baricitinib 4 mg once daily for up to 14 days (oral).

Special Considerations for CKD Patients: For moderate renal impairment (eGFR 30-59 $\mathrm{ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$): 2 mg once daily; for severe renal impairment ($15 \leq$ eGFR $<30\ \mathrm{ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$): 2 mg once every 48 hours (maximum 7 doses) [14]; contraindicated for eGFR $<15\ \mathrm{ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}}$.

Contraindications: Absolute neutrophil count $<0.5\$\times 10^{\{9\}/Lorlymphocytecount < 0.2\times 10}\{9\}\$/\mathrm{L}$.

4.3 Tocilizumab [54-57]

Mechanism of Action: Tocilizumab is a humanized IL-6 receptor antagonist.

Indications: Severe and critically ill patients with significantly elevated IL-6 levels [8]; patients requiring high-flow oxygen or stronger respiratory support within 24-48 hours of ICU admission. For patients receiving low-flow oxygen, tocilizumab is recommended if clinical deterioration occurs after starting dexamethasone with significantly elevated inflammatory markers (e.g., C-reactive protein $ $75 mg/L) [10].

Dosage: 8 mg/kg intravenous infusion, generally as a single dose, only in combination with dexamethasone (or another glucocorticoid). Baricitinib and tocilizumab should not be used simultaneously.

Special Considerations for CKD Patients: No dose adjustment is needed for renal impairment according to prescribing information and clinical trials [24].

Contraindications: Tocilizumab allergy, uncontrolled serious infections other than COVID-19, neutrophil count $<0.5\$\times 10^{\{9\}/L, plateletcount < 50\times 10}\{9\}/L, ALT >$

5×$ upper limit of normal, and increased risk of gastrointestinal perforation.

4.4 Evidence Summary of Anti-inflammatory Drugs for COVID-19 in CKD Populations

Randomized controlled trials evaluating dexamethasone [13] and tocilizumab [58] in COVID-19 included CKD patients, requiring no dosage adjustment for renal impairment. However, baricitinib requires dose adjustment when eGFR $<60\ \text{ml} \cdot \text{min}^{-1} \cdot (1.73\ \text{m}^2)^{-1}$, though consensus on dosing for severe renal impairment ($15 \leq \text{eGFR} <30\ \text{ml} \cdot \text{min}^{-1} \cdot (1.73\ \text{m}^2)^{-1}$) has not been established. Whether these drugs show differential efficacy in treating COVID-19 across different renal function levels requires further investigation.

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5. Antithrombotic Therapy for COVID-19 in CKD Populations

Thromboembolism, particularly venous thromboembolism (VTE), is a common complication in COVID-19 patients. Early in the 2020 pandemic, hospitalized COVID-19 patients had high VTE risk, with ICU patients experiencing incidence rates of 22-39% [59-61]. Although VTE risk has decreased with improved disease understanding, better healthcare systems, and vaccination, antithrombotic therapy remains key to preventing adverse outcomes.

COVID-19-associated thrombosis results from multiple interacting factors, including immune response-induced endothelial injury, blood stasis from immobilization, and hypercoagulable states. Therefore, all hospitalized COVID-19 patients should receive pharmacologic thromboprophylaxis after excluding contraindications, rather than relying solely on mechanical measures like compression stockings [62]. In non-critically ill hospitalized patients with high thrombotic risk (e.g., elevated D-dimer $ 2×$ upper limit of normal), therapeutic-dose anticoagulation often improves survival [20,63-64]. Generally, therapeutic anticoagulation is indicated for confirmed VTE, patients already on therapeutic anticoagulation (e.g., atrial fibrillation), or hospitalized COVID-19 patients with high thrombotic risk and low bleeding risk. For ICU patients without confirmed VTE, prophylactic-dose anticoagulation is preferred [63-64]. Additionally, high-risk, low-bleeding-risk patients may receive post-discharge rivaroxaban for thromboprophylaxis [23]. Regarding antiplatelet therapy, while the RECOVERY study suggested potential benefits [18-19,22], other studies found increased bleeding risk [15,20-21]. Therefore, further research is needed before adding antiplatelet therapy. Table 4 summarizes dose adjustments for commonly used antithrombotic drugs across different renal function levels.

When using anticoagulants in CKD patients, several considerations apply: First, unlike unfractionated heparin which is cleared by reticuloendothelial cells, low-molecular-weight heparin (LMWH) is primarily renally excreted, often caus-

ing accumulation and increased bleeding risk in CKD patients [65]. Although LMWH is more convenient and carries lower risk of heparin-induced thrombocytopenia [66], doses must be adjusted based on eGFR in hospitalized COVID-19 CKD patients, or unfractionated heparin used to reduce renal metabolic burden. Second, CKD increases risks of both VTE and platelet dysfunction [67-68]. For hemodialysis patients with recurrent circuit clotting, therapeutic-dose anticoagulation may be appropriate, with small studies suggesting direct thrombin inhibitor argatroban may be useful [70-71]. For multi-organ failure patients with acquired antithrombin deficiency causing heparin resistance, antithrombin supplementation or direct thrombin inhibitors may be considered [72].

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6. Convalescent Plasma and Neutralizing Monoclonal Antibodies in CKD Populations

China' s current guidelines (10th edition) [8] suggest that convalescent plasma may be considered in early-stage patients with high risk factors for progression to severe disease, high viral load, and rapid disease progression. Since CKD patients have higher risk of severe disease or death from COVID-19, they may benefit from convalescent plasma. Observational studies have reported its use in kidney transplant patients [73-74], though efficacy in CKD patients requires further clinical trial validation.

Small observational studies suggest that dialysis or kidney transplant patients with moderate COVID-19 may benefit from early use of recombinant monoclonal neutralizing antibodies [75-76]. As monoclonal antibodies are metabolized through target-mediated clearance, no dose adjustment is theoretically needed for CKD patients with renal impairment [24]. However, efficacy in CKD populations requires further clinical validation, and most currently available neutralizing antibodies were developed before the Omicron variant and may not neutralize Omicron subvariants [77-79].

Summary

This article summarizes COVID-19 treatment drugs, including respiratory symptomatic medications (antipyretics, antitussives, expectorants, antiallergic drugs), antiviral agents, anti-inflammatory drugs, antithrombotic therapies, and convalescent plasma with neutralizing monoclonal antibodies, along with dose adjustment protocols based on renal function. Among anti-inflammatory drugs, dexamethasone and tocilizumab require no renal adjustment. Among antivirals, remdesivir is only used in CKD stage 4 or higher, nirmatrelvir/ritonavir requires renal dose adjustment but has numerous drug interactions, while molnupiravir has slightly lower efficacy but needs no renal adjustment. For antithrombotic therapy, LMWH requires renal dose adjustment, while antiplatelet agents lack

sufficient evidence of benefit. Convalescent plasma and neutralizing monoclonal antibodies require no renal adjustment but have limited data in CKD patients. Chinese COVID-19 guidelines recommend several Chinese patent medicines, but direct evidence in CKD patients is lacking. In clinical practice, individualized traditional Chinese medicine decoctions (without aristolochic acid) under experienced practitioners may be effective for CKD patients with COVID-19, though interactions between St. John' s wort and nirmatrelvir/ritonavir should be noted. Due to space limitations, this study could not further address important clinical issues such as COVID-19 vaccination in CKD patients, adjustment of baseline CKD medications (e.g., immunosuppressants) during COVID-19 infection, and potential drug interactions with COVID-19 therapies. As many drugs still lack direct clinical trial evidence for CKD patients, further research is needed to guide clinical practice.

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