Vol 6 | Issue 1 | Pages 84-90

Annals of Nephrology
ISSN: 2642-4827

Review Article

DOI: 10.36959/832/405

Review: Considerations in Current Treatment of COVID-19 in Patients with Chronic Kidney Disease

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Abstract

Background: Patients with CKD and particularly ESRD or transplantation are at a significantly high risk of mortality from COVID infection [1,2]. Given this high risk of poor outcomes, nephrologists and critical care physicians are more inclined to use available therapies in hospitalized patients without comprehensive insight into risks and safety in this population. Though the treatment recommendations continue to be updated regularly, the current approved treatment regimen in hospitalized patients with COVID-19 includes corticosteroids and the anti-viral drug Remdesivir and immune based therapies are also available for use in the outpatient population [3]. Majority of these approved medications pose risk of complications in the CKD population.

This review outlines the latest information about the safety of these and other current treatment regimens in patients with chronic kidney disease, and patients on dialysis and suggestions for treatment and monitoring in this patient population.

Key message

It is important to be able to effectively treat patients with COVID-19 who also have CKD as some of the current treatments being used in the treatment of COVID-19 must be modified in this patient population. And the use in less severe illness may need to be re-considered without clear evidence from the literature.

Introduction

It has been well documented that patients with a variety of co-morbid conditions have significantly increased risk of mortality from COVID 19 infection [4], including chronic kidney disease (CKD) [5]. This highlights the importance of understanding the nuances of treatment in patients with CKD in order to maximize appropriate care and management in this high-risk population. Also, in the acute setting, acute kidney injury (AKI) is common when COVID therapies are often used and pose the similar risks as patients with CKD and add to the complexity of treatment with changing GFR [6]. CKD is a spectrum of disease that is defined as having abnormalities of kidney function or structure present for more than 3 months and is classified based on estimated glomerular filtration rate (eGFR) and this review will focus on patients with CKD stage 4 (eGFR of 15-30 ml/min) and stage 5 (eGFR < 15 ml/min) [7]. In a hospital setting nephrologists and critical care physicians need to clearly understand and enforce these additional risks in treatment of hospitalized patients.

Remdesivir

Remdesivir is an anti-viral medication that works by inhibiting RNA-dependent RNA polymerase, preventing viral replication [8] and is the only drug that is FDA approved in the treatment of COVID-19 [9]. This treatment has been used widely in the treatment of COVID-19 in hospitalized patients with severe disease and has been shown to reduce recovery time, which in one study was defined as the time it took to be considered medically stable enough to be discharged from the hospital [10]. In that study, the median time to recovery for patients that received a 10-day course of Remdesivir was 11 days compared to 15 days in the placebo group [10]. The FDA has approved this medication for use in hospitalized children > 12-years-old and in adults with all ranges of disease severity [11]. Though due to lack of specific testing, Remde-

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Accepted: May 14, 2021

Published online: May 16, 2021

Citation: Dojcsak A, Hasni K, Sroya H (2021) Review: Considerations in Current Treatment of COVID-19 in Patients with Chronic Kidney Disease. Ann Nephrol 6(1):84-90

sivir is not recommended in patients with an eGFR < 30 ml/min [11]. The reason that this drug has been contraindicated in patients with a low eGFR is due to the renal elimination of its IV vehicle, sulfobutylether-β-cyclodextrin (SBECD), which is cleared by the kidneys and can therefore lead to accumulation in patients with impaired renal function [12,13]. Accumulation of this vehicle has been linked to liver necrosis and renal tubular obstruction, but this was found at much higher doses in animal studies [12].

The suggested Remdesivir dose to be used in COVID-19 patients is 200 mg on day one followed by 100 mg daily for 5 days. Treatment can be extended up to 10 days if there is no clinical improvement and in more severe cases like patients requiring mechanical ventilation or extra-corporeal membrane oxygenation (ECMO) [3]. Each 100 mg dose of this drug contains about 3000-6000 milligrams of SBECD, meaning that with this treatment regimen the SBECD burden per day is, at most, 12000 milligrams on the first day and 6000 milligrams per subsequent day. The maximum recommended dose of SBECD is 250 mg/kg per day [12]. The average adult male weighs about 90 kg and the average adult female weighs about 77 kg [14]. This means that in an average male this equates to a maximum dosage of SBECD of around 22,500 mg/day and in an average female to a maximum dosage of 19,250 mg/day in patients with an eGFR > 30 ml/min. This means that the current Remdesivir dose contains at most 53% of the maximum recommended dose of SBECD in men and 62% in women.

These values afford some ability of clinicians to determine if patients with eGFRs < 30 ml/min should still undergo treatment with this drug as the duration of treatment is relatively short and the maximum dosages of the SBECD vehicle are well below threshold safety values. Further, it has been shown that a single 4 hours session of hemodialysis with standard blood flow and dialyzer size decreases plasma concentrations of this vehicle by 45-49% [15]. This indicates that people who are on hemodialysis will likely not have effects of accumulation. Additionally, it should be considered that this also means that there is a risk of under treatment of dialysis patients due to the fact that the drug is cleared with dialysis making the management quite complex.

Though the risk has not been studied extensively in this group, it appears that based on smaller studies in which Remdesivir was tolerated well in patients with kidney disease [16] and in one recent study on dialysis dependent patients that showed that administration of Remdesivir within 48 hours of hospital admission shortened the duration of their stay by a mean of 5.5 days [17]. This along with the dose calculation facts summarized above, support the fact that patients with an eGFR < 30 ml/min could still receive Remdesivir to improve their outcomes from COVID-19 infection with increased precaution to the balance between accumulation and clearance in this population.

Corticosteroids

Corticosteroids are widely known to cause potent anti-inflammatory effects and believed to be beneficial in COVID-19 induced systemic inflammation resulting in organ damage, including the lungs and kidneys [18]. Corticosteroids are currently recommended in treatment of COVID-19 in hospitalized patients who are either on supplemental oxygen therapy or on mechanical ventilation as they have been shown to increase mortality by 3.1% and 12.1% respectively [19]. Dexamethasone, a long-lasting glucocorticoid, is the recommended first line glucocorticoid to use at a suggested dose of 6 mg/day for a maximum of 10 days [20]. This is considered the upper limit of a moderate dose of dexamethasone meaning that doses higher than this are associated with side effects with use over 30 days [20]. Since the treatment course is relatively short (less than 30 days), side effects are therefore less likely to occur.

The dose of corticosteroids in patients with CKD stage 4 or 5 requires no dose adjustment and steroids are used in the treatment of a variety of inflammatory kidney diseases, so the safety issues regarding their use are generally well-described in the literature. It has also been found that the use of corticosteroids can also be useful in treating acute kidney injury (AKI) in settings of COVID-19 related sepsis. One study also found that physiologic doses of dexamethasone (0.12 mg/kg) were able to decrease sepsis induced AKI by decreasing levels of TNFα, IL1β and NFκB in the renal tubules and to a greater degree than a high dose of 12 mg/kg [21]. This physiologic dose equates to a dose of 10.76 mg in an average adult male and a dose of 9.28 mg in an average female which are both close to the 6 mg dose used in treatment of COVID-19. It has also been found that corticosteroids help to prevent proteinuria by stabilizing the actin cytoskeleton of podocytes [22,23]. Therefore, corticosteroids may actually play additional roles in acute protection of the kidney in the setting of sepsis or other systemic inflammatory reactions, such as acute respiratory distress syndrome (ARDS).

Immune Based Therapies

SARS-CoV-2 neutralizing monoclonal antibodies bamlanivimab or casirivimab plus imdevimab are available as emergency use authorizations (EUAs) and can only be used in outpatients who are at a clinically high risk of disease progression requiring hospitalization. Patients with CKD are at higher risk and are currently approved to receive this treatment [24]. These antibodies bind to the spike protein of the virus blocking its attachment to the ACE2 receptor. Bamlanivimab is given IV of 700 mg [24] and casirivimab plus imdevimab are administered IV together at a dose of 12,000 mg each [25]. Both of these infusions are given over at least 60 minutes with monitoring for at least one-hour post infusion for hypersensitivity reactions [24]. Though IV immunoglobulins are generally well tolerated, there are some reports of acute renal failure, particularly in those who are elderly and have diabetes and also if the preparations of the IV immunoglobulin contain high levels of sucrose [26]. These incidents are relatively rare, but serum creatine should be monitored for in patients receiving these therapies as these incidents have been reported between 1 to 10 days of infusion [27].

Other Immunomodulators

According to the current NIH recommendations, there is

insufficient data either for or against the use of other immunomodulators in the treatment of COVID-19 including IL-1 inhibitors and Interferon beta (the later only with potential use in early mild or moderate infections) [28]. IL-1 inhibitors have been shown to improve respiratory function and survival rate in patients with COVID-19, but these studies have had relatively small sample sizes and therefore must be evaluated further [29]. Levels of IL-1 and IL-1 receptor have been found to be increased in patients with CKD and treatment of such patients with IL-1 inhibitors has been shown to decrease cardiovascular disease incidence in this population [30]. This indicates that use of IL-1 inhibitors in the treatment of COVID-19 patients with CKD should be tolerated well.

Interferon beta exhibits anti-inflammatory effects and has been shown to inhibit viral replication of SARS-CoV-2 *in vitro* [31]. These trials have been small and this needs to be investigated further. It should be noted that there have been a few case reports of thrombotic microangiopathy with renal involvement as little as 2 weeks and up to 5 years of treatment with interferon beta-1a, though renal side effects were more common with interferon alpha therapy [32]. This means that though rare, kidney function should be continuously monitored in all patients, particularly in those with pre-existing CKD.

The same NIH recommendations also recommend against the use of other immunomodulators including IL-6 monoclonal antibodies, IL6 receptor monoclonal antibodies, interferon alpha or beta in critically ill patients, Bruton's tyrosine kinase inhibitors, or Janus kinase inhibitors [28].

Vitamins

Current NIH treatment guidelines indicate that there is not sufficient evidence for or against use of vitamins including vitamin C (ascorbic acid), vitamin D, and zinc in the treatment of patients with COVID-19 [28], though some practioners still use these vitamins in these patients and it is important to understand if there are any adjustments or special considerations when treating stage 4 and 5 CKD patients.

Vitamin C is an essential nutrient that has antioxidant effects, innate and adaptive immune system enhancing effects, is a required co-factor for hydroxylase enzymes (including dopamine beta hydroxylase which converts dopamine into norepinephrine), is essential for collagen production, and is essential for absorption of dietary iron [33]. In healthy individuals the daily recommended intake of vitamin C for men is 90 mg per day and 75 mg per day for women and it has been recommended to increase intake by 35 mg per day in smokers as they have a higher oxidant burden [34]. The recommended upper limit of intake daily in healthy individuals is 2000 mg per day. Higher doses have been associated with diarrhea, weakness and nausea [35]. High dose vitamin C has been shown to be safe without major side effects at a level of 1.5 g/kg body weight per day in patients receiving concurrent chemotherapy [35]. These high doses are likely tolerated well in these patients due to increased treatment induced oxidative stress in the body [35]. This may indicate a possible justification in using vitamin C treatment in patients with other inflammatory conditions such as COVID-19 induced ARDS. *In vitro* studies have shown that serum oxalate levels above 30 umol/L (normal range is 2-8 umol/L) can lead to precipitation of oxalate into tissues including the heart and retina resulting in tissue damage and also increases the risk of calcium oxalate stone formation [36]. Due to the risk of oxalate accumulation patients with a history of kidney stones are advised to avoid high dose vitamin C supplementation [37]. There have been case reports of patients with oxalate induced nephropathy post COVID-19 infection [38] and since oxalate is renally excreted, patients with CKD are at increased risk for this accumulation. Patients on dialysis are currently not recommended to take in more than 100 mg of vitamin C daily due to the risk of oxalate accumulation [39]. However, dialysis patients utilizing the most recent dialysis technologies are likely to not be at risk of oxalosis due to efficient removal by the dialysis machine [39]. This high dose vitamin C should be reconsidered in patients with stage 4 and 5 CKD but who are not on dialysis and oxalate level monitoring may be necessary.

Vitamin D is a fat-soluble vitamin that primarily functions to increase absorption of calcium from the gut as well as decreasing phosphate excretion [40]. Vitamin D deficiency is common in patients with CKD due to decreased dietary intake and functional deficiency from impaired hydroxylation to 1,25 Vitamin D [41]. The U.S. Recommended Dietary Allowance (RDA) of vitamin D for adults is 600 IU daily for adults under 70 years and 800 IU daily for adults over 70 [42]. The tolerable upper intake level for vitamin D is 4,000 IU daily though even levels of 50,000 IU daily for years have been shown to be safe in one study [43]. There are reports of vitamin C toxicity with doses as high as 60,000 IU daily for several months [44], though these cases are rare.

One meta-analysis on vitamin D supplementation in prevention of acute respiratory tract infections found that vitamin D supplementation in general was shown to decrease incidence of respiratory tract infections, primarily in patients who were previously deficient in the vitamin with levels of < 25 nmol/L [45]. This study also showed that daily or weekly dosing of vitamin D in these patients was more effective in prevention of respiratory infections than bolus dose [45]. KDIGO guidelines currently support the use of vitamin D supplementation in patients with any stage of CKD, including those on dialysis, due to the risks of secondary hyperparathyroidism and decreased bone mineral density [46] in this condition. This information suggests that the use of vitamin D supplementation may be well tolerated in all patients, even at high doses regardless of their kidney function, if they are found to have low vitamin D levels before time of infection and may help patients with COVID-19. Since patients with CKD are more likely to be vitamin D deficient, be sure to check levels prior to administration of supplementation and to monitor these levels regularly in hospitalized patients if they are receiving vitamin D supplementation long term. Further, since vitamin D toxicity can result in AKI through hypercalcemia [47], creatinine should also be monitored in patients receiving this therapy even though incidence of toxicity is relatively low. It is also important to remember that vitamin D may change other metabolic bone disease parameters in CKD (e.g.

phosphorus, intact PTH) and to address these appropriately.

One recent study has suggested that niacinamide (a vitamin B3 analog) has also been suggested to improve outcomes in patients with severe COVID-19 related AKI in patients with a GFR > 15 ml/min on or off dialysis [48]. This study looked at a group of 201 hospitalized patients with COVID related AKI and found that in the group treated with niacinamide, 38/90 (42%) either died or required renal replacement therapy (RRT) as compared to the placebo group in which 62/111 (56%) patients either died or required RRT [48]. This study shows the importance of monitoring kidney function and promptly and appropriately treating patients with AKI or CKD in the context of COVID-19 infection.

Zinc is an essential trace element that functions in immune function, cell division, and wound healing [49]. Though the NIH does not currently endorse or reject the use of zinc in treatment of COVID-19 in any patients, they do have specific recommendations to not exceed dietary daily doses of 8 mg for nonpregnant women and 11 mg for men due to the potential risk of copper deficiency resulting in hematologic and neurologic consequences [28]. Zinc has been shown to inhibit the RNA-dependent RNA polymerase used by the COVID-19 virus [50] and increased cellular uptake of zinc was seen when used in conjunction with hydroxychloroquine [51], but hydroxychloroquine is not recommended in the treatment of COVID-19 due to adverse effects including QTc prolongation [28]. Zinc supplementation has been linked to decreased incidence of infection, decreased inflammation, and decreased oxidative stress in elderly patients. This is most likely due to the fact that 30% of the elderly population in developed countries is zinc deficient [52]. Circulating zinc levels have been found to be lower in CKD patients [53]. Zinc levels or symptoms of zinc deficiency including anosmia, dysgeusia, decreased adult hair, and decreased wound healing [54] should be monitored in patients with CKD stage 4 and supplemented only as needed and within NIH daily dose recommendations.

Blood Derived Products/Passive Antibody Therapy

According to the current NIH recommendations, there is not sufficient data either for or against the use of blood derived products in the treatment of COVID-19 including the use of convalescent plasma or SARS-CoV-2 immunoglobulins [28]. In the past, these therapies have been shown to be safe and have improved survival in previous viral epidemics and pandemics in the treatment of Spanish Flu, MERS, SARS, and Ebola [55]. In most viral illnesses, viremia reaches peak levels during the first week of infection [56] suggesting that use of convalescent plasma or immunoglobulins during this time period may be the most effective. These treatments should therefore be used primarily earlier in hospitalized COVID-19 patients [57], particularly those that are considered high risk including those with kidney disease, COPD, cardiovascular disease, obesity, diabetes, and immunocompromised patients [58]. There is no current evidence that passive antibody therapy is contraindicated in patients with CKD stage 4. It should also be noted that due to their large molecular size, these antibodies are not dialysable [59], so patients with CKD or those undergoing dialysis can receive these treatments.

Vaccines

According to the CDC, it is critical to give those with chronic kidney disease appropriate vaccines [60] including the current approved COVID-19 vaccines. Patients with chronic kidney disease are at increased risk of serious systemic infections largely due to decreased renal clearance of toxins from the blood [61] and due to impaired T cell proliferation and B cell lymphopenia that are secondary to ESRD [62]. Sepsis accounts for about 20% of deaths seen in patients with end stage renal disease (ESRD) and in these patients, both innate and adaptive immunity are compromised due to uremia, inflammation, and often concurrent immunocompromising medications [62].

COVID-19 vaccinations are a relatively new development and there is much more research needed in the area of how protective these vaccines are in the context of CKD with or without dialysis, though based on the study of other vaccines it is possible that vaccine schedule adjustments could be beneficial in the future. Many vaccines including hepatitis A, annual influenza, *Haemophilus influenza*, and polio have all been shown to be effective in creating a comparable immune response in patients with CKD when compared to normal controls [63]. Though study of other vaccines have shown improved protection in CKD patients with modifications to the standard vaccine schedules including varicella (an additional booster dose may be necessary in children with ESRD), MMR (assessment of seroconversion after administration should be done in patients with kidney disease), tetanus and diptheria toxoids (assessment of seroconversion after administration should be done in patients with kidney disease), pneumococcal (decreased protection seen over time so patients with CKD should be revaccinated again within 3 to 5 years of initial vaccination), and hepatitis B (a better response is seen in protection prior to starting dialysis when possible) [63].

There are currently 3 vaccines that are authorized and recommended by the CDC to prevent COVID-19. These approved vaccines include 2 mRNA based vaccines (Pfizer-BioNTech and Moderna) that create a host immune response against the spike protein of the virus [64] and with the 2 dose series of either of these vaccines, they provide 94.1%-95% efficacy [64]. Another positive of the mRNA based vaccines is that there is decreased processing time and no required addition of toxic chemicals or cell cultures that could be contaminated which is particularly important in patients who are immunocompromised [65]. The most recently approved vaccine is an adenovirus vector based vaccine (Johnson and Johnson's Janssen) that produce the spike protein which triggers an immune response [64]. This vaccine only requires 1 dose, but the efficacy is lower than the mRNA based vaccines at 66.3% [64]. Other vaccines that are still in clinical trials and that are not approved in the US include adenovirus vector vaccines (Astrazeneca, CanSino Biologics, Gamaleya Institute), a recombinant protein nanoparticle vaccine with a trimeric spike protein and a matrix M1 adjuvant (Novavax), and inactivated vaccines with aluminum hydroxide adjuvants (Sinopharm, Sinovac) [66].

Included in the first phase of patients (1C) to be recommended to get a COVID-19 vaccine were those ages 16 to 64 with high-risk conditions including CKD using the standard vaccine dose and 2 dose administration [66]. With this in mind, in the future more research should be done on the efficiency of the immune response created in patients with CKD and other immunocompromising conditions after getting a COVID-19 vaccine, but for now standard dosage and scheduling is appropriate.

Antimalarials, Protease Inhibitors, Antiparasitics, Mesenchymal Stem Cells, and Anti-coagulants

Treatments that the NIH currently does NOT recommend in the treatment of COVID-19 include chloroquine or hydroxychloroquine with or without azithromycin, lopinavir or ritonavir (or any other HIV protease inhibitors), ivermectin, or mesenchymal stem cells [28].

The NIH also recommends usage of anti-coagulants in all hospitalized patients being treated for COVID-19 to the same standard as any other hospitalized patients [28]. Many medical centers are using systemic anti-coagulation in COVID-19 based on proprietary algorithms along with the increased risk of thrombosis with COVID-19. Patients with CKD stages 1-3 should be given direct oral anticoagulants (which are renally excreted) including the direct thrombin inhibitor Dabigatran and the direct factor Xa inhibitor rivaroxaban, or heparin which do not require any dose adjustments [67]. In patients with CKD stage 4, the dosages of these direct oral anticoagulants need to be adjusted and in CKD stage 5 or patient on dialysis, warfarin is the preferred anticoagulant [67].

Note: The NIH also currently recommends that the following medications be continued in patients already taking them prior to the initiation of treatment for COVID-19: ACEi/ARBs, chronic inhaled or oral steroids (with stress doses used as needed), statins, chronic anti-coagulant or anti-platelet therapy, and NSAIDs [29]. Note that NSAIDs should not be used in patients with CKD. In patients with normal kidney function, there was no difference found in the antipyretic effects of NSAIDs versus acetaminophen [28].

Conclusion

In conclusion, the treatments that are currently most widely being used in the treatment of COVID-19 including Remdesivir, corticosteroids, and immune based therapies, are relatively safe, even in patients with advanced chronic kidney disease and a GFR < 30 ml/min. This susceptible population is generally not included in trials and for this reason, these patients are often deprived of the benefits of interventions that may improve survival. Though many of the considerations are outlined here, a nephrologist should be contacted to help to monitor these patients during treatment, but treatment should still be considered quickly in these patients in order to improve mortality in both inpatient and outpatient settings as well as to decrease length of stay in hospitalized patients. It is also important to stay up to date with current recommendations and research in regards to treatment of COVID-19 and special considerations for different patient populations must always be kept in mind (Table 1).

Table 1: Summary of current COVID-19 therapies, benefits, and considerations in patients with CKD stage 4-5 and patients on dialysis.

Therapy	Benefit	Considerations in CKD
Remdesivir	Decreased hospital stays	Fairly likely tolerated with increased monitoring for accumulation or undertreatment
Corticosteroids	Decreased systemic organ damage and inflammation	No adjustments needed or special considerations
Immune based therapies	Decreased disease progression requiring hospitalization	Rare AKI reported; increase monitoring of creatinine
Vitamin C	Anti-oxidant effects	Renally cleared; patients with CKD stage 4-5 and patients not on dialysis are currently not recommended to take in more than 100 mg of vitamin C daily due to the risk of oxalate accumulation and potential resultant nephropathy
Vitamin D	Increased calcium absorption in the gut and decreased infection rates	Well tolerated; check vitamin D level before initiating therapy
Niacinamide	Improved outcomes in COVID-induced AKI	No adjustments needed or special considerations
Zinc	Potential to decrease incidence of infection, decrease inflammation, and decreased oxidative stress in elderly patients	Circulating zinc levels are commonly lower in CKD patients; check levels and only supplement if levels are low in all patients
Blood derived products/passive antibody therapy	Improved survival post-infection.	There is no current evidence that passive antibody therapy is contraindicated in patients with CKD stage 4, though more specific research does need to be done
COVID-19 vaccines	Important in prevention of infection and spread of COVID-19	Recommended, though need more research specifically involving patients with CKD stage 4-5

Anti-coagulation	Decreased DVT/PE risk	Patients with CKD stages 1-3 should be given direct oral anticoagulants or heparin which do not require any dose adjustments. In patients with CKD stage 4, the dosages of these direct oral anticoagulants need to be adjusted and in CKD stage 5 and patients on dialysis, warfarin is the preferred anticoagulant

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DOI: 10.36959/832/405