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SARS-CoV-2 Shedding in Dialysis Patients With COVID-19

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The impact of COVID-19 on patients with end-stage kidney disease (ESKD) on dialysis is substantial. Dialysis patients are especially vulnerable to COVID-19 because of their significant comorbidities, impaired immune function, and frequent face-to-face interactions as part of their life-sustaining therapy. Consistent with this premise, dialysis units are prone to COVID-19 outbreaks, and ESKD patients with COVID-19 experience higher morbidity and mortality compared to the general population, with a reported case fatality rate of 20% to 30%.[1] In response to this risk, multiple guidelines and protocols have been developed by individual groups and nephrology societies to limit SARS-CoV-2 transmission and COVID-19 outbreaks in dialysis units.[2]

SARS-CoV-2 infection prevention and control measures for dialysis units are extrapolated from protocols that are derived from epidemiologic and respiratory viral transmission studies in the general population. For immunocompetent patients diagnosed with COVID-19, maintenance of contact and droplet isolation is recommended for 10 days from symptom onset.[3] These recommendations are supported by studies that have correlated shedding of cultivatable virus with viral copy number estimated by the cycle threshold (Ct) value from SARS-CoV-2 polymerase chain reaction (PCR) nucleic acid detection tests, the current gold standard for diagnosing COVID-19.[4–6] Cultivatable virus and the likelihood of forward transmission are inversely correlated with SARS-CoV-2 PCR Ct values. Consensus is emerging that no cultivatable SARS-CoV-2 can be recovered from COVID-19–positive patients with PCR Ct values above 25 to 30, depending on the assay used.[4–6] In patients with intact immune systems, Ct values generally rise to this level within 7 to 10 days after symptom onset; however, because of the sensitivity of the assay, the COVID-19 PCR itself may remain positive for weeks following the acute illness.[3] Thus, patients recovering from COVID-19 can shed SARS-CoV-2 nucleic acid for prolonged periods of time without harboring viable virus and may be considered noninfectious. Consequently, conversion to a negative COVID-19 PCR should not be used to guide public health and hospital isolation protocols for the general population. In contrast, COVID-19 patients who are immunosuppressed or who experience critical illness may shed cultivatable virus and remain infectious for even longer periods of time, in some cases up to 2 months after infection,[7] and therefore require special consideration.

Patients with ESKD have impaired innate and adaptive immune systems that result in an increased risk of bacterial infection as well as generally blunted responses to vaccination.[8] The ability of COVID-19–positive ESKD patients to clear SARS-CoV-2 and thus the risk of infectious virus shedding is unknown. Thus, isolation protocols for COVID-19 dialysis patients are not clearly established. Given the possibility of extended shedding of noninfectious viral nucleic acid, prolonged isolation becomes impractical, especially if conversion to a negative COVID-19 PCR is used as a criterion for discontinuing precautions.

We performed a quality assurance/quality improvement project using COVID-19 PCR Ct values as a surrogate to assess the risk of infectious virus shedding in COVID-19–positive ESKD patients, with the objective of informing a discontinuation of isolation protocol for patients in our dialysis units. Alberta Kidney Care South reported 49 cases of COVID-19 in a population of 1332 ESKD patients on dialysis (3.7%) from March 2020 to December 2020. This corresponded to 36 of 1031 (3.5%) hemodialysis and 13 of 301 (4.3%) peritoneal dialysis patients. There were 7 deaths, giving a case-fatality rate of 14.2%. Of 49 COVID-19 dialysis patients, 20 had at least 2 COVID-19 PCR tests over 10 days or longer and were included in the analysis. Baseline characteristics of these patients are shown in Table 1. The median age was 61 years (range 31–86 years), 75% were male, and 80% were on hemodialysis. We used the Ct values of the COVID-19 PCR as a surrogate for the presence of cultivatable SARS-CoV-2. Of the 20 patients with serial COVID-19 PCR tests, 4 patients (20%) required admission to the intensive care unit (ICU) with mechanical ventilation, and 2 patients (10%) died. The Ct values as measured over time for the 20 patients are presented in Figure 1. Approximately 2 weeks from the first positive COVID-19 PCR, 19 of 20 patients reached Ct values >28, consistent with no infectivity or infectivity with no forward transmission potential. One patient with a persistent COVID-19 PCR Ct value <28 was a solid organ allograft recipient and chronically immunosuppressed with prednisone and mycophenolate mofetil. Two COVID-19–positive patients on prednisone monotherapy had adequate recovery in their Ct value to consider them unlikely to be carrying viable virus and hence noninfectious within a 14-day timeframe. In 4 patients, Ct values appear to have had an initial downward trend, presumably due to testing in the very early phase of the disease when viral copy numbers are still relatively low. Finally, only 1 patient had a nondetectable COVID-19 PCR after 14 days. Despite these results, half the patients were still symptomatic or hospitalized at the time of follow-up testing (Table 1).

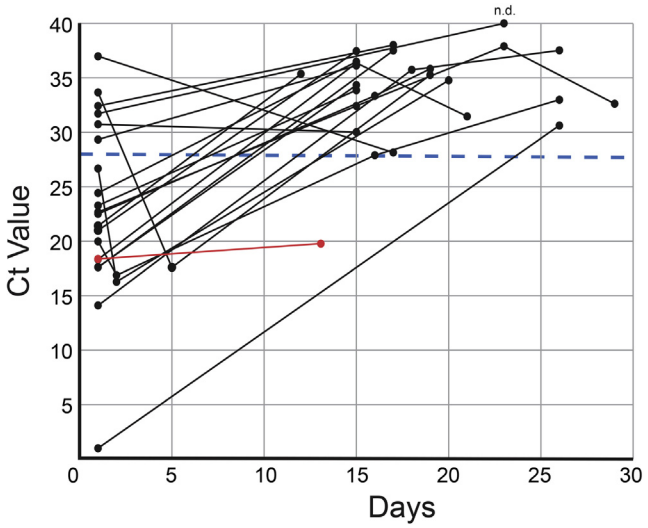

Figure 1. Cycle threshold (Ct) values of the 20 patients over time from their initial diagnosis. Hashed line is 28. Only 1 transplant patient (red line) did not achieve a Ct value of ≥28 within 14 days. One patient with a Ct value of 1 (recorded as such with no actual Ct value) had testing at the onset of the pandemic when these data were not yet recorded. One patient had a negative COVID-19 polymerase chain reaction result on day 23 (n.d.).

Table 1. Characteristics of the study population (N = 20)

Demographics	Value
Age, yr, median (range)	61 (30–86)
Male:Female	15:5
Hemodialysis: peritoneal dialysis	16:4
Cause of kidney disease[a]	
Hypertension/diabetes (%)	14 (70)
Glomerulonephritis (%)	4 (20)
Other (%)	5 (25)
Diabetes	15 (75)
Medications	
ACEI/ARB (%)	11 (55)
Immunosuppressants[b] (%)	3 (15)
Immunocompromising comorbidity	
Solid organ transplant (%)	1 (5)
Other[c] (%)	2 (10)
Symptoms at presentation	
Yes (%)	18 (90)
Unknown (%)	2 (10)
Intensive care unit admission	4 (20)
Status at follow-up testing	
Symptoms	
Yes (%)	5 (25)
No (%)	6 (30)
Unknown (%)	4 (20)
Hospitalized	5 (25)

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Some patients had multiple listed etiologies of kidney disease.
[b]Immunosuppressant medications were prednisone (2), prednisone, and mycophenolate mofetil (1).
[c]Other immunocompromising comorbidities including autoimmune conditions requiring treatment.

In a retrospective study of 90 SARS-CoV-2–positive *in vitro* samples probed for the E-gene, Bullard *et al.* could not demonstrate infectivity of patients with Ct values >24 and symptom duration of >8 days.[4] Their study was limited primarily to non-immunocompromised adult patients in a community context. In a similar report limited to patients with mild COVID-19, Wolfel *et al.* also concluded that cultivatable virus could not be detected more than 14 days after onset of symptoms.[6] Although van Kampen *et al.* further suggest that symptom severity should be considered, they concluded that both quantitative viral RNA load assays and serological assays may be

sufficient to step down infection control precautions.[5] Finally, a study in cardiac transplant patients found nonviable virus correlated with Ct values between 25 and 30.[7] Several studies have reported prolonged (>2 weeks) COVID-19 PCR positivity in patients on dialysis. Dudreuilh *et al*. found that 41.2% of their patients had persistent positive PCR testing at 14 days, whereas De Vriese and Reynders noticed that COVID-19 survivors needed 34 to 44 days from symptom onset to first negative test.[2,9] Only De Vriese and Reynders reported Ct values, with most patients reaching a Ct value of ~25 by 15 to 21 days, although the specific test characteristics were not disclosed. Interestingly, effective production of anti−SARS-CoV-2 IgG levels correlated directly with rising COVID-19 PCR Ct values in these patients.[9] Both groups have also recommended specific de-escalation plans for COVID-19−positive patients on hemodialysis. Dudreuilh *et al*. recommended serial testing in afebrile patients starting at 7 days after initiation until at least 2 negative tests (48 hours apart).[5]

Based on this review of Ct values in a COVID-19−positive chronic dialysis cohort, all patients without immunosuppressive therapy were found to have levels above 28 at 14 days from the first positive COVID-19 PCR test, suggesting a very low likelihood of infectivity. Our results and those of De Vriese and Reynders[9] suggest that SARS-CoV-2 kinetics in ESKD patients are similar to those in the general population, and that dialysis patients with mild to moderate COVID-19 infection mount a sufficient immune response to this virus. Thus, contact and droplet isolation procedures can be safely discontinued for COVID-19−positive patients in the dialysis unit as per the general population, without the requirement for conversion to a negative COVID-19 PCR. Special consideration, however, must be given to ESKD patients on immunosuppressive therapy, with severe disease or ongoing symptoms.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods

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