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Refractoriness of Hyperkalemia and Hyperphosphatemia in Dialysis-Dependent Acute Kidney Injury Associated with COVID-19

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Key Points:

* Refractory hyperK and hyperP are more frequent in CoV-AKI-RRT compared to pre-COVID-19 era.

* Patients with CoV-AKI-RRT had elevated serum potassium and serum phosphate that corresponded with lactate dehydrogenase levels.

* Intracellular ion release due to cytokine storm and RRT interruptions in CoV-AKI pts may account for elevated serum potassium and phosphate.

Abstract:

Background: Persistent hyperkalemia (hyperK) and hyperphosphatemia (hyperP) despite renal replacement therapy (RRT) was anecdotally reported in COVID-19 and acute kidney injury (AKI) requiring RRT (CoV-AKI-RRT). However, observation bias could have accounted for the reports. Thus, we systematically examined the rate and severity of hyperK and hyperP in patients with CoV-AKI-RRT in comparison with pre-COVID-19 era. Methods: We identified patients with CoV-AKI-RRT treated with sustained low-efficiency dialysis (SLED) for >2 days in March-April 2020. As pre-COVID-19 control, we included patients with AKI treated with SLED who were part of a research database (2018-2019). We examined the rates of hyperK [serum potassium (sK) >=5.5 mEq/L], severe hyperK [sK >=6.5 mEq/L], hyperP [serum phosphate (sP) >=4.5 mg/dL] and moderate or severe hyperP [sP >=7.0-10.0 and >10.0 mg/dL, respectively] as %SLED-days with an event. Results: Along the duration of SLED, the incidence of hyperK was greater in CoV-AKI-RRT (n=64) [mean 19(2)% vs. 14(3)% SLED-days, p=0.002] compared to control (n=60). The proportion of patients with >=1 event of severe hyperK was greater in CoV-AKI [33% vs. 7%, p=0.0004]. The incidence of hyperP was similar between groups [mean 56(4)% vs. 53(5)% SLED-days, p=0.49]. However, the proportion of patients with >=1 event of moderate and severe hyperP was greater in CoV-AKI-RRT [86% vs. 60% (p=0.001) and 50% vs. 18% (p=0.0002), respectively]. Among those with CoV-AKI-RRT, sK and sP correlated with lactate dehydrogenase (LDH) [r=0.31 (p=0.044) and r=0.31 (p=0.043), respectively] whereas hyperP also correlated with shorter SLED runs (hours/run) (r=-0.27, p=0.055). Conclusion: Refractory hyperK and hyperP were more frequent in CoV-AKI-RRT compared to pre-COVID-19 era. Because of the correlation of sK and sP with higher LDH and sP with shorter SLED runs, intracellular ion release from cell injury due to cytokine storm and RRT interruptions may account for the findings.

Disclosures: J.C.Q. Velez has participated in advisory board/consulting engagements with Mallinckrodt Pharmaceuticals, Bayer and Travere Therapeutics, and has been a member of a Speaker Bureau for Otsuka Pharmaceuticals. All remaining authors have nothing to disclose.

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Refractoriness of Hyperkalemia and Hyperphosphatemia in Dialysis-Dependent Acute Kidney Injury Associated with COVID-19

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- Refractory hyperK and hyperP are more frequent in CoV-AKI-RRT compared to pre-COVID-19 era.
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Methods: We identified patients with CoV-AKI-RRT treated with sustained low-efficiency dialysis (SLED) for ≥2 days in March-April 2020. As pre-COVID-19 control, we included patients with AKI treated with SLED in December of 2019. We examined the rates of hyperK [serum potassium (sK) ≥5.5 mEq/L], severe hyperK [sK ≥6.5 mEq/L], hyperP [serum phosphate (sP) ≥4.5 mg/dL] and moderate or severe hyperP [sP ≥7.0-10.0 and >10.0 mg/dL, respectively] as %SLED-days with an event.

Results: Along the duration of SLED, the incidence of hyperK was greater in CoV-AKI-RRT (n=64) [mean 19 ± 2% vs. 14 ± 3% SLED-days, p=0.002] compared to control (n=60). The proportion of patients with ≥1 event of severe hyperK was greater in CoV-AKI [33% vs. 7%,
The incidence of hyperP was similar between groups [mean 56 ± 4% vs. 53 ± 5% SLED-days, p=0.49]. However, the proportion of patients with ≥1 event of moderate and severe hyperP was greater in CoV-AKI-RRT [86% vs. 60% (p=0.001) and 50% vs. 18% (p=0.0002), respectively]. Among those with CoV-AKI-RRT, sK and sP correlated with lactate dehydrogenase (LDH) [r=0.31 (p=0.044) and r=0.31 (p=0.043), respectively] whereas hyperP also correlated with shorter SLED runs (hours/run) (r=-0.27, p=0.055).

**Conclusion:** Refractory hyperK and hyperP were more frequent in CoV-AKI-RRT compared to pre-COVID-19 era. Because of the correlation of sK and sP with higher LDH and sP with shorter SLED runs, intracellular ion release from cell injury due to cytokine storm and RRT interruptions may account for the findings.

**Introduction**

Continuous renal replacement therapy (CRRT) and sustained low-efficacy dialysis (SLED) are common dialytic modalities indicated in critically ill patients with acute kidney injury (AKI) and hemodynamic instability. Electrolyte abnormalities can be life threatening and require prompt renal support. By providing convective and diffusive clearances, these dialytic modalities mediate mass clearances of solutes and electrolytes. In contrast to intermittent hemodialysis, the continuous nature of CRRT and SLED delivers more effective clearance of electrolytes. SLED can be used as CRRT or as prolonged intermittent RRT (PIRRT). Because of the ample time during which patients are exposed to removal of solutes and electrolytes during CRRT/PIRRT, it is not uncommon to encounter hypokalemia and hypophosphatemia as a result of effective clearance of potassium and phosphorus. This phenomenon has resulted
in standard protocols that include frequent monitoring and supplementation of potassium and phosphorus for patients treated with CRRT/SLED despite being in kidney failure. 6-8.

COVID-19 can lead to AKI due to acute tubular injury in conjunction with multiorgan dysfunction 9,10. During the early days of the pandemic, there were anecdotal reports of an unusual incidence of persistent hyperkalemia and hyperphosphatemia associated with severe catabolic state in patients with COVID-19 and acute kidney injury (AKI) (CoV-AKI 11. Additionally, this phenomenon was noted among kidney transplant patients affected with COVID-19 needing daily hemodialysis to control resistant hyperkalemia and hyperphosphatemia12. However, objective demonstration of the frequency of those events is still lacking. Thus, we conducted a retrospective study to examine the rate and severity of hyperkalemia and hyperphosphatemia in patients with CoV-AKI- RRT in comparison with pre-COVID-19 era and assessed for potential factors associated with it.

Methods

With approval of the Institutional Review board (IRB), with waiver of informed consent and in accordance with the Declaration of Helsinki, we conducted a retrospective single-center study to examine the incidence of refractory hyperkalemia and hyperphosphatemia in patients with COVID-19 and AKI-RRT. This is an ancillary study from our previously reported cohort of AKI in COVID-19 13. Among 161 patients with CoV-AKI, we identified patients with CoV-AKI who underwent RRT by SLED 14 for ≥ 2 days in an intensive care unit (ICU) between March and April of 2020. We excluded patients dialyzed under CRRT, continuous venovenous hemodiafiltration (CVVHDF) or conventional intermittent hemodialysis (IHD). Patients on CVVHDF and IHD were excluded because they represented a very small subset of our cohort.
As pre-COVID-19 control, we included consecutive patients (reverse chronological order) with AKI without COVID-19 who underwent SLED in December of 2019.

Electronic medical records were accessed to obtain pertinent demographic and clinical data. SLED flowsheets were manually reviewed to extract data entered by nursing personnel both from nephrology and intensive care regarding timing of initiation and interruption, blood flow rate (BFR), dialysate flow rate (DFR). Standard BFR was 200 ml/min and standard DFR was 200 ml/min. Pre-filter saline solution was 200 ml/hr. Net ultrafiltration rate was tailored to the individual needs (range 0 - 400 ml/hr). The protocols for anticoagulation used in our cohort were previously reported\textsuperscript{15}. Briefly, we utilized regional citrate, prefilter heparin, minimally intensive heparin, systemic low-intensity heparin, systemic high-intensity heparin and combined systemic high-intensity heparin plus regional citrate. There were no major differences in the SLED management in historical controls as compared to the patients during the initial months of the pandemic, except that after the first week of the study period, BFR was increased to 250 ml/min as an attempt to reduce the risk of circuit failure in patients with COVID-19.

The indications to start SLED were routine indications for RRT initiation including volume overload, hyperkalemia, metabolic acidosis and uremic encephalopathy. Similarly, SLED was discontinued when renal recovery was observed based on urine output and/or serum creatinine trends.

We examined the rates of hyperkalemia [serum potassium ≥ 5.5 mEq/L], severe hyperkalemia [serum potassium ≥ 6.5 mEq/L], mild hyperphosphatemia [serum phosphate ≥ 4.5 mg/dL], moderate hyperphosphatemia [serum phosphate ≥ 7.0-10.0 mg/dL] and severe hyperphosphatemia [serum phosphate > 10.0 mg/dL] as % SLED-days with an event. We
reported the incidence of overall hyperkalemia and severe hyperkalemia, overall hyperphosphatemia and severe hyperphosphatemia along the duration of SLED that are reported as days of hyperkalemia and hyperphosphatemia per days of SLED in CoV-AKI-RRT cohort as compared to the control cohort. Hyperkalemia and hyperphosphatemia on the first day of SLED were also considered as an event. We additionally examined the correlation of hyperkalemic and hyperphosphatemic events (percentage of days with hyperkalemia and hyperphosphatemia per days of SLED) with the duration of SLED, serum lactate dehydrogenase (LDH), creatinine phosphokinase (CPK) levels respectively.

Statistical analyses were performed utilizing GraphPad Prism 7 software (New Orleans, Louisiana, United States).

Results

Among 161 patients with CoV-AKI, 89 patients received RRT (55%). Of the 89 patients who received RRT, we excluded 3 treated with IHD and 3 treated with CRRT. Nineteen patients were excluded due to death within 48 hours of initiation of SLED. Thus, 64 patients with CoV-AKI-RRT dialyzed as SLED were included. The median age was 60 (39 – 84), 77% (49 patients) were of black race and 23% (15 patients) were women (Table 1). The cause of AKI was presumably ischemic acute tubular injury in 85% (54 patients). For the control group, we extracted data from 60 patients from an existing database with AKI without a diagnosis of COVID-19 who were dialyzed by SLED between January of 2018 and December of 2019. The CoV-AKI-RRT group and the control group were comparable with respect to age and gender (Table 1). However, more patients self-identified as black were included in the CoV-AKI-RRT (77%) versus the control cohort (30%).
The median duration of SLED in the CoV-AKI-RRT cohort were 19 days (Table 1). Along the duration of SLED, the incidence of hyperK was greater in the CoV-AKI-RRT group compared to control [mean 19 ± 2% vs. 14 ± 3% SLED-days, respectively; p = 0.002] (Figure 1A). In the CoV-AKI-RRT cohort, 86% (55 patients) experienced at least 1 episode of hyperkalemia while on SLED, compared with 57% (34 patients) in the control group (p = 0.0003). Furthermore, the proportion of patients with ≥ 1 event of severe hyperkalemia was greater in the CoV-AKI-RRT cohort [21 (33%) vs. 4 (7%), p = 0.0004]. The overall incidence of hyperphosphatemia was similar between groups [mean 56 ± 4% vs. 53 ± 5% SLED-days, p = 0.49] (Figure 1B). However, the proportion of patients with ≥ 1 event of moderate and severe hyperphosphatemia were greater in CoV-AKI-RRT compared to control [86% vs. 60% (p = 0.001) and 50% vs. 18% (p=0.0002); for moderate and severe hyperphosphatemia, respectively] (Figure 1B).

In the CoV-AKI-RRT cohort, serum potassium and serum phosphate significantly correlated with the level of LDH [r = 0.305 (p = 0.044) and r = 0.307 (p = 0.043); respectively] (Figure 2B-C). In addition, hyperphosphatemia also correlated with shorter SLED runs (hours/run) (r = -0.268, p = 0.055) (Figure 2D) whereas hyperkalemia did not correlate with duration of SLED (r = -0.07, p = 0.61) (Figure 2A). Serum CPK levels did not correlate with either hyperkalemic (r = 0.06, p =0.69) or hyperphosphatemic events (r = 0.16, p = 0.32). Similarly, no significant correlation was found between serum pH, serum lactate, blood urea nitrogen (BUN) or serum carbon dioxide (CO₂) and either hyperkalemia (pH: r = -0.23, p = 0.07; lactate: r = 0.03, p = 0.83; BUN: r = 0.07, p = 0.58; CO₂: r = 0.09, p = 0.48) or hyperphosphatemia (pH: r = -0.20, p = 0.12; lactate: r = 0.19, p = 0.14; BUN: r = 0.14, p = 0.27; CO₂: r = 0.01, p = 0.94). Presence of anticoagulation was not associated with greater number of hyperkalemic (p=0.93) or hyperphosphatemic (p=0.24) events.
**Discussion**

Confirming anecdotal observations of unexpected rates of hyperkalemia and hyperphosphatemia in patients with COVID-19 and AKI undergoing CRRT/PIRRT, we found an unusually high rate of hyperkalemic and hyperphosphatemic events among patients with CoV-AKI-RRT while on SLED. This observation is in contrast to common occurrence of hypokalemia and hypophosphatemia in patients with AKI requiring SLED for other causes not related to COVID-19.16

The exact mechanism contributing to the observed phenomena is not completely understood. Importantly, patients in the CoV-AKI-RRT cohort started with higher serum phosphate level, factor that could have contributed to the observed increase rate of severe hyperphosphatemia despite ongoing SLED. A report by Patel et al.11 described development of hyperphosphatemia, hyperkalemia and elevated LDH levels in patients with COVID19. Importantly, this case series included only 3 patients. Another study 12 described cases of refractory hyperkalemia and hyperphosphatemia among patients with kidney allografts affected with COVID-19 who necessitated daily hemodialysis. Refractoriness of hyperkalemia and hyperphosphatemia despite effective CRRT/SLED can lead to increased utilization of dialysis-related resources. Hyperkalemia can lead to cardiac instability and precipitate cardiac arrest. In one report17, patients with CoV-AKI had elevated BUN and serum phosphate levels before initiation of dialysis (150 and 9.8 mg/dL, respectively) while the mean CPK levels were within normal limits (200, range 72-830 U/L), suggesting a hypercatabolic state resulting in excessive generation of urea nitrogen from muscle protein break down without evidence of rhabdomyolysis. Upon quantification using urea kinetics, patients with CoV-AKI requiring acute peritoneal dialysis (PD) had 2-fold higher rates of urea nitrogen generation (10.2 ± 5 g/d) when compared to patients on maintenance PD (4.7 ± 3 g/d) despite similar protein intake. The
magnitude of muscle protein breakdown was equivalent to 315 g/d with a cumulative of 2.5 kg muscle breakdown secondary to hypercatabolic state in patients with CoV-AKI.

As previously reported, patients with COVID-19 and AKI-RRT are at greater risk of filter clotting/clogging and decreased filter life leading to shorter SLED runs. Thus, a potential explanation for the electrolyte abnormalities could have been ineffective delivery of dialysis due to frequent interruption. In fact, the development of hyperphosphatemia in the CoV-AKI-RRT cohort correlated with shorter SLED runs suggesting that the reduced duration/efficiency of SLED partly explained the results. However, events of hyperkalemia did not correlate with shorter SLED runs suggesting that other mechanisms were involved in the observed refractoriness of hyperkalemia.

Elevated LDH levels reflect high inflammatory cell turnover characteristic of the acute inflammatory state of COVID-19, rather than muscle breakdown. Release of LDH likely denotes cell breakdown and flux of intracellular product. The cytokine storm secondary to immune dysregulation in patients with COVID-19 leads to cell injury with subsequent release of acute inflammatory markers and intracellular electrolytes. Supporting this hypothesis, the frequency of both hyperkalemic and hyperphosphatemic events significantly correlated with the level of serum LDH. Although rhabdomyolysis has been reported to be a cause of AKI in patients with COVID-19, the lack of correlation between CPK level and the hyperkalemic and hyperphosphatemic events suggest that rhabdomyolysis did not drive the observations.

This study has limitations. The data reported herein pertains to the early days of the COVID-19 pandemic and does not necessarily reflect the phenotype of AKI cases observed during subsequent waves of other variants of SARS-CoV-2 virus, such as the delta and omicron.
variants. We were unable to explore other mechanistic aspects because data on additional serum markers of cell injury like uric acid and bilirubin were not consistently available. This study reflects the occurrence of hyperkalemia and hyperphosphatemia during SLED and not necessarily on CVVHDF. However, because the dialysis dose delivered via CVVHDF is lesser than that via SLED, it is reasonable to conclude that these results are also applicable to CVVHDF. Finally, the use of a historical control may not account for the intensiveness of care during the COVID-19 pandemic. Conversely, COVID-19-related contact precautions may have limited nurses in promptly responding to alarms and addressing positioning and access issues.

In conclusion, we observed refractory hyperkalemia and hyperphosphatemia in patients CoV-AKI-RRT managed by SLED as compared to what was observed during the pre-COVID-19 era. Although the current state of the pandemic and the more recently observed incidence and severity of AKI associated with COVID-19 does not seem to be as alarming as it was during the beginning of the pandemic, the results of this study provide relevant information that should prompt nephrologists and intensivists to be alert for the possibility of observing this phenomenon during other states of hyper-catabolism or acute inflammatory response to severe viral infections.
Disclosures: J.C.Q. Velez has participated in advisory board/consulting engagements with Mallinckrodt Pharmaceuticals, Bayer, Calliditas and Travere Therapeutics, and has been a member of a Speaker Bureau for Otsuka Pharmaceuticals. All remaining authors have nothing to disclose.

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Author Contributions: J.C.Q. Velez: Conceptualization; Data curation; Investigation; Methodology; Formal analysis; Software; Supervision; Validation; Writing – review and editing. Aakash Ramanand, Vipin Varghese: Data curation; Investigation; Writing – original draft. Swetha Kanduri: Writing – original draft; Writing – review and editing. Yuang Wen, Muner Mohamed: Data curation; Investigation, writing – review and editing. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Data Sharing Statement: All data is included in the manuscript and/or supporting information.


Data are presented as n (%) [median (range)], CoV-AKI-RRT: acute kidney injury requiring renal replacement therapy in patients with COVID-19; AKI: acute kidney injury; ATN: acute tubular necrosis.

<table>
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<th>Control AKI-RRT (n = 60)</th>
<th>CoV-AKI-RRT (n = 64)</th>
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<tbody>
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<tr>
<td>Sex, Female</td>
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<td>49 (82)</td>
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<td>Number of Days on SLED</td>
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<td>Phosphate (mg/dL)</td>
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<td>2787 (8-40000)</td>
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<td>Peak LDH (U/L) (n=46)</td>
<td>182 (23-&gt;40000)</td>
<td>832 (300-3499)</td>
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</table>
Figure Legends

Figure 1. Comparison of frequency of elevated serum potassium and phosphate concentration between CoV-AKI-RRT and control. **Panel A.** Incidence of overall hyperkalemia [serum potassium (sK) ≥ 5.5 mEq/L] and severe hyperkalemia [serum potassium (sK) ≥ 6.5 mEq/L] along the duration of sustained low efficacy dialysis (SLED), reported as days of hyperkalemia per days of SLED in CoV-AKI-RRT cohort as compared to the control cohort. **Panel B.** Incidence of overall hyperphosphatemia [serum phosphate (sP) ≥ 4.5 mg/dL] and severe hyperphosphatemia [serum phosphate (sP) > 10.0 mg/dL] along the duration of sustained low efficacy dialysis (SLED), reported as days of hyperphosphatemia per days of SLED in CoV-AKI-RRT cohort as compared to the control cohort.

Figure 2. Factors associated with elevated serum potassium and phosphate concentration in the CoV-AKI-RRT cohort. Correlation of hyperkalemic events (percentage of days with hyperkalemia per days of sustained low efficacy dialysis (SLED)) with duration of per session of SLED (**Panel A**). Correlation between serum lactate dehydrogenase (LDH) level (**Panel B**) or serum pH (**Panel C**) and proportion of hyperkalemic events per SLED sessions. Correlation of hyperphosphatemic events (percentage of days with hyperphosphatemia per days of SLED) with duration of SLED (**Panel D**). Correlation between LDH level (**Panel E**) or serum pH (**Panel F**) and proportion of hyperphosphatemic events per session of SLED.
Figure 1

A  
- Control AKI-RRT  
- CoV-AKI-RRT

Incidence of hyperK (days of hyperK per days of SLED)  
- 14%  
- 19%

Incidence of Severe HyperK (days of severe hyperK per days of SLED)  
- 7%  
- 33%

p = 0.002  
p = 0.0004

B  
- Control AKI-RRT  
- CoV-AKI-RRT

Incidence of hyperPO4 (days of hyperPO4 per days of SLED)  
- 53%  
- 56%

Incidence of Severe HyperPO4 (days of severe hyperPO4 per days of SLED)  
- 18%  
- 50%

p = 0.49  
p = 0.0002
Figure 2

Graph A: Percentage of days with HyperK per days of SLED versus total hours of SLED/start. 
- R = -0.07; p = 0.61

Graph B: LDH (U/L) versus days HyperK / days SLED. 
- R = 0.30; p = 0.04

Graph C: pH versus days HyperK / days SLED. 
- R = -0.23; p = 0.07

Graph D: Percentage of days with HyperPO4 per days of SLED versus total hours of SLED/start. 
- R = -0.27; p = 0.05

Graph E: LDH (U/L) versus days HyperPO4 / days SLED. 
- R = 0.31; p = 0.04

Graph F: pH versus days HyperPO4 / days SLED. 
- R = -0.21; p = 0.12