INTRODUCTION

Coronavirus disease 2019 (COVID-19) has posed many challenges to healthcare systems worldwide, resulting in over 590,000 deaths in the U.S. alone. Despite this, there is a paucity of data regarding COVID-19 and its impact on psychiatric treatment. Lithium is a commonly used mood stabilizer and is one of the few psychiatric treatments shown to decrease suicidality. This medication has a narrow therapeutic index and requires routine monitoring of blood levels to avoid toxicity. Lithium toxicity can result from minor adjustments in lithium dose or alterations in its excretion, such as in acute kidney injury (AKI). Lithium toxicity can cause neurological symptoms, cardiac arrhythmias, endocrine abnormalities, and kidney failure, which can in some cases be fatal.

Preclinical studies have speculated that lithium may be a potential treatment for coronavirus given its neuroprotective effects due to inhibition of glycogen synthase kinase-3 and its ability to inhibit viral replication of different Coronaviridae. Lithium may also be dangerous in COVID-19 infection, as COVID-19 can present with gastrointestinal symptoms and decreased oral intake resulting in dehydration and acute kidney injury, thus predisposing patients to lithium toxicity. We present a case series of two patients with COVID-19 who developed elevated lithium levels, after which lithium titration proved to be challenging.

CASE REPORT #1

Ms. A, a 34-year-old woman, presented to the emergency department with weakness, dyspnea, poor oral intake, and inability to ambulate. Her medical and psychiatric histories include schizoaffective disorder, intellectual disability, self-injurious behaviors, asthma, diabetes, polycystic ovarian syndrome, and hypothyroidism. Her psychiatric medications consisted of clonazepam 1 mg twice daily (BID), valproic acid extended-release 250 mg BID, lithium carbonate 600 mg BID, quetiapine 400 mg BID, and topiramate 50 mg nightly. Non-psychiatric medications consisted of pantoprazole 40 mg daily, levothyroxine 12.5 mcg daily, and montelukast 10 mg daily.

In the emergency department, her oxygen saturation was normal. Labs were notable for creatinine (Cr) elevation to 1.36 mg/dl (baseline Cr 0.7–0.8 mg/dl), and elevated D-dimer 1.09 mg/L (<0.50 mg/L). Thyroid and liver function tests, sodium, potassium, and glucose levels were unremarkable. Urine toxicology screen was negative, and urinalysis showed microalbuminuria of 240 mg/dl. Her chest radiography showed hazy bilateral opacities. SARS CoV-2 PCR was positive.

Ms. A was admitted for acute kidney injury. Trough lithium levels were supratherapeutic at 1.36 mmol/L. Lithium was held, psychiatric consultation was requested, and intravenous fluids were started. Ms. A experienced a rapid improvement in her creatinine (1.18–0.86 mg/dl) and improved oral intake by hospitalization day (HD) 2.

Psychiatric examination revealed impairments in orientation and attention, with the patient not knowing the date or day of the week and being unable to complete attention tasks such as serial sevens or spelling “world” backwards. She was unable to provide a coherent narrative of events preceding the admission. She denied mood, anxiety, and psychotic symptoms as well as suicidal or homicidal
thoughts. Information from her family suggested that she was not at her psychiatric baseline. She is usually fully oriented, conversant, and able to maintain employment by working in a store. Her outpatient psychiatrist noted that the patient decompensates psychologically when lithium levels drop below 0.9–1.0 mmol/L, with resultant aggression and self-injurious behavior.

Additional workup revealed hyperammonemia of 64 umol/L and a normal valproic acid level. Due to hyperammonemia, valproic acid and topiramate were held, and levcarnitine supplementation was started, resulting in normalization of ammonia levels after 8 days. By HD 3, Ms. A’s inattention and disorientation resolved, and she returned to her psychiatric baseline.

Initially, the patient’s presentation was thought to be due to delirium secondary to AKI, decreased renal clearance of lithium, hyperammonemia, and COVID-19. Her lithium dose was reduced to 300 mg daily with a plan to titrate her dose, as her AKI had resolved by HD 2. Ms. A did not receive diuretics, nonsteroidal anti-inflammatories, angiotensin-converting enzyme (ACE) inhibitors, or other medications that can cause lithium toxicity.

By HD 16, a steady-state trough lithium level was supratherapeutic at 1.25 mmol/L, despite the patient being on 450 mg BID, which was 75% of her home dose (see Table 1). Her lithium dose was decreased to 300 mg daily and 450 mg nightly, with a repeat lithium trough level of 0.97 mmol/L on HD 19.

## CASE REPORT #2

Ms. B, a 24-year-old woman, presented to the emergency department with 2 weeks of fever, cough, and fatigue. She had a history of asthma, obstructive sleep apnea, selective mutism, ADHD, schizoaffective disorder, and borderline personality disorder. Her psychiatric medications consisted of chlorpromazine 50 mg daily as needed for agitation, clozapine 100 mg in the morning and 200 mg at night, lithium 450 mg in the morning and 750 mg at night, and lisdexamfetamine 40 mg daily. She had been on a stable lithium dose for at least a year. A lithium level 3 months prior was 0.73 mEq/L.

In the emergency department, her oxygen saturation was 98% on room air. SARS CoV-2 PCR was positive. Laboratory results were notable for C-reactive protein 34.7 mg/L, ferritin 384 ng/ml, and fibrinogen 509 mg/dl. Creatinine was 0.95 mg/dl (baseline 0.7 mg/dl). She was not tested for proteinuria. Urine toxicology was positive for amphetamines due to her lisdexamfetamine prescription. Sodium, potassium, glucose, white blood cell count, D-dimer, PT, INR, and liver function tests were unremarkable. Chest X-ray showed a left lower lobe airspace consolidation. She was admitted for COVID-19 pneumonia.

Psychiatric examination revealed a woman who was fully oriented and oddly related with a concrete thought process. She endorsed depressive symptoms and chronic suicidal ideation without intent or plan. She denied other psychiatric symptoms. Staff at her group home confirmed that this was her psychiatric baseline.
Ms. B received four doses of hydroxychloroquine, after which the hydroxychloroquine was discontinued due to QTc prolongation of 469 ms. Ms. B did not receive diuretics, nonsteroidal anti-inflammatory agents, ACE inhibitors, or other medications that can cause lithium toxicity. Sodium levels were 138–141 mmol/L, and creatinine levels were 0.7–0.9 mg/dL throughout her hospitalization. On HD 5, a non-trough lithium level was inadvertently drawn 30 min after her morning dose instead of immediately prior and was supratherapeutic at 1.61 mEq/L. On this day, Ms. B reported increased nausea without emesis, and subjective confusion. Her selective mutism precluded a complete cognitive evaluation. A trough lithium level was obtained in the evening and was supratherapeutic at 1.31 mEq/L, so lithium was held. Lithium levels on HD 6 and 7 were 1.22 mEq/L and 0.95 mEq/L. Lithium was restarted at 300 mg BID on HD 7. Nausea resolved by HD 12. On HD 12, despite Ms. B being on a dose of lithium approximately half her outpatient dose, trough lithium level was elevated to 1.24 mEq/L, warranting an additional decrease in lithium dose from 300 mg PO BID to 450 mg nightly. A trough lithium level drawn before discharge on HD 16 was 0.88 mEq/L.

4 | DISCUSSION

These cases raise concerns about lithium physiology and potential for toxicity after COVID-19 infection after resolution of AKI or in patients with normal creatinine levels. Lithium is absorbed in the gastrointestinal tract, freely filtered in the glomerulus, and is reabsorbed mostly in the proximal tubule. Therefore, alterations in renal function from pre-renal or renal causes can result in lithium toxicity, as lithium has a narrow therapeutic index. While the reference range for lithium blood levels varies between laboratories and countries, our hospital’s therapeutic reference range is 0.8 to 1.2 mEq/L. The American Psychiatric Association Practice Guidelines for the treatment of bipolar disorder mention that blood lithium levels above 1.5 mEq/L are associated with toxicity.

In our two patients, attempts to titrate lithium dose resulted in supratherapeutic blood levels despite minimal or no alteration in creatinine levels. Ms. A’s blood lithium level became elevated even after resolution of AKI despite being on a reduced dose. In Ms. B’s case, the lithium dose was decreased by more than half due to ongoing elevated levels, despite the patient having no evidence of AKI and having adequate oral intake. Both patients were lost to follow-up, thus, we do not have information regarding longitudinal lithium level measurements.

Lithium toxicity can result from medications that alter renal excretion, such as ACE inhibitors, NSAIDs, and diuretics, but neither of our patients were on these medications. In our two cases we do not suspect that clozapine, chlorpromazine, clozapine, lisdexamfetamine, montelukast, or pantoprazole resulted in supratherapeutic lithium levels, as these do not affect renal excretion of lithium. In Ms. A’s case, she was taking lamotrigine at 50 mg at bedtime prior to admission. There is one case report suggesting that topiramate can result in lithium toxicity, but this case report does describe the dose topiramate or lithium the patient was receiving, and it appears that toxicity was precipitated by addition of topiramate. Our patient was receiving both lithium and low-dose topiramate for long-term psychiatric management and did not experience lithium toxicity. Furthermore, topiramate was discontinued due to hyperammonemia, and repeat lithium levels continued to be elevated despite decreasing its dose, suggesting that the main cause for this abnormality was COVID-19. In both patients, the benefits of continuing lithium treatment outweighed potential risks, as both patients had a history of severe self-injurious behaviors, mood instability, and suicidal ideation that were minimized with lithium.

There are only two prior publications describing lithium toxicity in the setting of AKI and COVID-19 infection. To our knowledge, there are no reports of COVID-19-associated supratherapeutic lithium levels in patients with mild kidney injury or without clinical evidence of kidney injury.

Acute kidney injury is common with COVID-19, affecting 33.6% of hospitalized patients; it often occurs early in the disease course and is associated with respiratory failure and poor prognosis. Multiple etiologies have been proposed, including SARS-CoV-2-related autoimmune dysregulation, microemboli, hypercoagulability, and direct damage to the renal endothelium. SARS-CoV-2 can directly infect the renal tubular endothelium through angiotensin-converting enzyme 2 (ACE2) receptors. ACE2 converts angiotensin II into angiotensin, which has vasodilatory, anti-inflammatory, and antioxidative properties. On the other hand, angiotensin II mediates vasoconstriction and inflammation. SARS-CoV-2 infection results in downregulation of ACE2 and an increase of angiotensin II, leading to vasoconstriction and a pro-inflammatory state. At this time, there is a gap in the medical literature regarding renal consequences of COVID-19 and their effects on lithium reabsorption and excretion and further studies are warranted to elucidate this matter.

5 | CONCLUSION

Lithium titration can be challenging in patients with COVID-19, even in patients with mild or no AKI. Psychiatrists should be aware of the need to monitor lithium levels longitudinally in COVID-19 patients to avoid lithium toxicity. Future studies are warranted to elucidate potential mechanisms of renal damage from COVID-19, its effects on lithium pharmacophysiology, and long-term effects.

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CONFLICT OF INTEREST
The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
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