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EDITORIAL COMMENTARY

Role of pediatric nephrologists in managing adults with AKI due to COVID-19

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Introduction

To date, SARS-CoV-2 virus has infected over 7 million people and claimed more than 400,000 lives worldwide. In addition to pneumonia and respiratory failure, the disease also causes multiple organ injuries including the kidney [1]. Although the true incidence of acute kidney injury (AKI) at the global level is currently unknown, observational studies in Wuhan City of China report that 25–30% of critically ill patients suffered from AKI [2, 3]. Similarly, data from patients admitted to the hospitals in New York City, the epicenter of COVID-19 in the USA, show that about 30% developed AKI. More strikingly, 75% of ICU patients had AKI and 31% required renal replacement therapy (Argenziano et al., medRxiv, April 20, 2020). Furthermore, a high death rate is observed when AKI is more severe [4]. This resulted in an unprecedented shortage of dialysis equipment, supplies, and care providers.

Pediatric response to COVID-19

With over 50,000 COVID-19 patients in New York City requiring hospitalization, many health care providers became involved, performing roles ordinarily not in the scope of their practice [5]. Among these were pediatricians. As COVID-19 infection overwhelmingly affects adults over children, adult patients occupied pediatric beds [6]. Our NewYork Presbyterian (NYP) hospital system has several pediatric locations, in addition to its largest pediatric service at Columbia Irving Medical Center (NYP/CUIMC). To make space to care for more adult patients in other facilities, all pediatric inpatients were swiftly transferred to our children's hospital, which was then designated as the admitting hospital for all children in the entire hospital system for more than 2 months. Although these changes resulted in an initial increase in patient volume, pediatric hospitalizations were overall decreased given the cancelation of elective surgeries and "New York on PAUSE" stay-at-home order that curtailed other admissions. This allowed our children's hospital to reengage in the disaster response by accepting adult patients.

The capacity of the Pediatric Intensive Care Unit (PICU) expanded by 50% (from 41 to 60 beds) and all levels of pediatric providers worked on the front line. To specifically offload the volume of adults requiring continuous renal replacement therapy (CRRT) at the adult hospital at CUIMC, we strategically accepted adults who needed CRRT since our children's hospital stocks six PrismaFlex machines and maintained a robust CRRT service prior to COVID-19. Relatively younger age (52 years or under) and fewer comorbidities (obesity, hypertension, diabetes) were also among the selection criteria. As such, all physicians in the Division of Pediatric Nephrology, consisting of four faculty members and three fellows, were reassigned to care for adults with AKI in addition to caring for children, representing an example of "all hands on deck" during the critical time of saving human lives.

Strategies to care for adults with AKI due to COVID-19

The influx of adults with AKI necessitated an increase in staffing and dialysis resources. The capacity of various renal replacement modalities (i.e., CRRT, hemodialysis, and peritoneal dialysis) increased rapidly. At the peak, 67 CRRT machines were utilized per day in April 2020, compared to fewer than 24 the previous April. Despite being on the same campus, the children's and the adult hospitals use different

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CRRT equipment; the children's hospital uses the PrismaFlex whereas the adult hospital uses NxStage, and nursing staff is not cross trained. However, the medical crisis triggered adaptive responses. Both PrismaFlex machines and PICU nurses were redeployed promptly to the adult nephrology service. As the pandemic worsened, it became necessary to expand the number of PICU beds to accept transfers of adult COVID-19 patients from the adult to the children's hospital. PICU nurses with expertise in PrismaFlex returned to the children's hospital.

From April 1 to May 15, 2020, the PICU assumed care of 29 adult COVID-19 patients with 26 needing mechanical ventilation. Seven of the 26 suffered AKI, 5 required CRRT following ventilator placement, and 2 also required ECMO. In general, the indications for CRRT were oliguria, fluid overload, and electrolyte abnormalities such as metabolic acidosis and hyperkalemia refractory to medical management. The acceleration of the pandemic peak created a sudden resource scarcity. Although there were a sufficient number of PrismaFlex machines at the children's hospital, replacement fluids were in short supply throughout the hospital system. The utilization of CRRT fluids was increased fivefold. Despite many efforts, the hospital was unable to secure adequate shipments from suppliers expeditiously. After NxStage replacement fluids were exhausted, PrismaSATE and PrismaSOL fluids manufactured by Baxter were used for both NxStage and PrismaFlex equipment. To conserve the supply in fluids and hemofiltration filters, a monitoring system was developed collaboratively among care providers, hospital procurement, and strategic sourcing departments for daily inventory and distribution. Accordingly, we made adaptive changes to CRRT. We chose CVVHDF as the modality and used both PrismaSATE and PrismaSOL to avoid depleting PrismaSOL. To provide adequate clearance, the starting dialysis dose was 20–30 cc/kg/h and then reduced to 15–20 cc/kg/h when patients were metabolically stable. Once the hospital secured an adequate supply, patients were transitioned to CVVH and PrismaSOL fluids were primarily used, as it is our division's common practice.

Hyper-coagulation is a common manifestation in COVID-19 [7] and is believed to be secondary to inflammatory responses to viral infection. Pro-inflammatory cytokines and complement factors activate pro-coagulation pathways [8]. Elevations of D-dimer and fibrinogen degradation products are seen early in COVID-19 [9]. The endothelialopathy also appears contributory. Viral replication causes inflammatory cell infiltration, endothelial apoptosis, and microvascular thrombosis [10]. As a result, CRRT circuit clotting was a frequent complication. To ensure effective therapy, we started unfractionated heparin 1000 units/h pre-filter via the circuit and monitored both aPTT and anti-Xa levels. The initial goal for anti-Xa level was 0.1–0.3 units/mL. If clotting persisted, then systemic heparin was instituted with target anti-Xa levels at 0.3–0.7 units/mL. These approaches were generally successful without the need for citrate regional anticoagulation or argatroban intravenous infusion. All 5 adult COVID-19 patients on CRRT were transferred back to the adult hospital by May as the adult ICU census declined. At the time of transfer, 3 patients were extubated and off renal replacement therapies. There were no deaths in the 29 adults cared for in the PICU.

Mutually beneficial experience through pediatric to adult redeployment

Despite relocating adults into the children's hospital, the excessive number of adult patients presented an urgent need for health care personnel expansion. Seventeen pediatric fellows of various subspecialties were redeployed to general wards or medical ICU at the adult hospital, with the exception of two pediatric nephrology fellows who were diverted specifically to adult nephrology that needed to expand the number of primary and consultation services drastically. The increase in AKI patients yielded the tasks of assessing patients, prescribing CRRT, and monitoring treatment responses. The pediatric nephrology fellows' matched skill sets were able to contribute meaningfully to this effort.

The redeployment experience was uniquely beneficial to the fellows' training. While most pediatric fellows' specialty training was paused, as they were participating in medical care they would unlikely practice following fellowship, pediatric nephrology fellows were able to enhance their learning. The strain in resources necessitated utilization of less frequently used treatment modalities such as prolonged intermittent renal replacement therapy (PIRRT), acute peritoneal dialysis in the ICU setting, and intermittent hemodialysis while on inotropic supports. By having pediatric members embedded within the adult division, we were able to consistently communicate about the best strategies in treating patients and utilizing common resources. The pediatric fellows rotated back to the children's hospital, bringing with them the experiences and knowledge gained from their time on the adult nephrology service. This collaborative effort led to modifications of CRRT to provide treatment to as many patients as possible during the public health crisis.

In addition, one of our faculty members was redeployed to the adult ICU after review of COVID-19 management guidelines with respect to ventilators, thrombosis, cardiac manifestations, and infectious disease treatments. Returning to the adult ICU care required adaptation of medical prowess in basic procedures such as placing feeding tubes, obtaining blood samples, interpretating blood gas results required for ventilator adjustments, and managing dysrhythmias. Nonetheless, strategies for management of AKI, blood pressure, and immunotherapy in pediatric practice were generally applicable to

adults, especially as our skillset had been adapted through the experience of consulting on adults in the PICU.

Possible etiologies of AKI in COVID-19

The reasons for the high AKI rate and the etiology of AKI in COVID-19 patients are not completely understood but likely to be multifactorial [11]. Of patients who had AKI and needed mechanical ventilation, more than half developed AKI within the first 24 h of intubation [4]. The early, dramatic, and abrupt cessation of kidney function may not be simply explained by cardiopulmonary compromise even in critically ill patients of non-COVID causes when the etiology of AKI is commonly due to hypotension, hypoxia, ischemia, sepsis, and nephrotoxic medications. This raises the concern that there might be additional pathogenic factors. Cytokine storm, hyperinflammation, and complement dysregulation have been shown to be a prominent feature in subgroups of COVID-19 patients [12, 13]. Due to the lack of sufficient renal biopsy information in COVID-19, the significance of the cytokine storm and its downstream effects in renal injury is not clear at this time. Alternatively, a direct viral infection could result in cytopathy to the kidney.

The SARS-CoV-2 virus uses the envelope-located trimeric spike (S) glycoprotein to bind to its receptor ACE2 that is widely expressed in human tissues such as the respiratory and GI tracts, the heart, and endothelial cells, for host cell entry through the mechanism of membrane fusion and/or endocytosis [14–17]. The S1 domain of the S protein is responsible for receptor binding while the S2 domain mediates membrane fusion after cleavage by host proteases, such as TMPRSS2 [15]. Similar to mouse kidneys, human kidneys have been shown to have a high level of ACE2 expression in glomerular podocytes and proximal tubules [18, 19]. TMPRSS2 is also expressed in the proximal tubules [20] where a robust endocytic recycling system exists [21]. The presence of the viral entry machinery in the kidney suggests that the SARS-CoV-2 virus could invade and injure the kidney cells, like other known host cells such as epithelial cells in the upper airway and type II pneumocytes of the lung.

Indeed, SARS-CoV-2 virion and viral protein have been detected in the kidney. Electron microscopy examination of postmortem kidneys of 9 out of 26 COVID-19 patients from Wuhan revealed virions (65–136 nm in size) with characteristics of coronavirus located in the cytoplasm of renal proximal tubules and glomerular podocytes. SARS-CoV-2 nucleocapsid protein was detected by immunostaining in some kidney samples [22]. Most recently, viral particles resembling SARS-coV-2 have also been shown in injured proximal tubules of a single patient in Michigan infected by the virus [23]. In addition, SARS-CoV-2 viruses have been found in the urine of Chinese COVID-19 patients [24]. These findings indicate that SARS-CoV-2 can directly infect tubular epithelial cells and podocytes. However, more studies need to be performed to confirm whether a viral infection of the kidney contributes to the pathogenesis of AKI.

Summary and conclusions

As members of the medical profession, we have pledged to dedicate our lives to the service of humanity. We have witnessed how humanity shines through during the toughest times. Like countless volunteers who stood up to the challenge and helped conquer the pandemic, a small team of pediatric nephrologists responded when duty called. While other institutions accepted adults into pediatric units or redeployed pediatric providers to adult units, our division used a mixed model in mobilization necessitated by the significant need. Through this process, we have also learned that cross-training of physicians and nurses in caring for both adults and children should be integrated into better preparedness for public health emergencies should they arise again.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

References

1. Richardson S et al (2020) Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA
2. Chen T et al (2020) Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 368: m1091
3. Yang X et al (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med
4. Hirsch JS et al (2020) Acute kidney injury in patients hospitalized with Covid-19. Kidney Int
5. Sarpong NO, Forrester LA, Levine WN (2020) What's important: redeployment of the orthopaedic surgeon during the COVID-19 pandemic: perspectives from the trenches. J Bone Joint Surg Am
6. Philips K et al (2020) Rapid implementation of an adult coronavirus disease 2019 unit in a children's hospital. J Pediatr
7. Connors JM, Levy JH (2020) COVID-19 and its implications for thrombosis and anticoagulation. Blood
8. Magro C et al (2020) Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res
9. Tang N et al (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 18(4):844–847

10. Varga Z et al (2020) Endothelial cell infection and endotheliitis in COVID-19. Lancet 395(10234):1417–1418
11. Batlle D et al (2020) Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology. J Am Soc Nephrol
12. Mehta P et al (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 395(10229):1033–1034
13. Risitano AM et al (2020) Complement as a target in COVID-19? Nat Rev Immunol
14. Zhou P et al (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579(7798):270–273
15. Hoffmann M et al (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell
16. Wan Y et al (2020) Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 94(7)
17. Yuan M et al (2020) A highly conserved cryptic epitope in the receptor-binding domains of SARS-CoV-2 and SARS-CoV. Science
18. Soler MJ, Wysocki J, Batlle D (2013) ACE2 alterations in kidney disease. Nephrol Dial Transplant 28(11):2687–2697
19. Lely AT et al (2004) Renal ACE2 expression in human kidney disease. J Pathol 204(5):587–593
20. Vaarala MH et al (2001) Expression of transmembrane serine protease TMPRSS2 in mouse and human tissues. J Pathol 193(1):134–140
21. Christensen EI, Nielsen S (1991) Structural and functional features of protein handling in the kidney proximal tubule. Semin Nephrol 11(4):414–439
22. Su H et al (2020) Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int
23. Farkash EA, Wilson AM, Jentzen JM (2020) Ultrastructural evidence for direct renal infection with SARS-CoV-2. J Am Soc Nephrol
24. Wang L et al (2020) Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol:1–6