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Continuous Renal Replacement Therapy and the COVID Pandemic

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Abstract

Severe COVID-19 illness and the consequent cytokine storm and vasodilatory shock commonly leads to ischemic acute kidney injury. The need for renal replacement therapies in those with the most severe forms of AKI is considerable and risks overwhelming healthcare systems at the peak of a surge. Here, we detail the challenges and considerations involved in the preparation of steps a disaster response plan in situations such as the COVID-19 pandemic which would dramatically increase demand for nephrology services. Taking careful inventory of all aspects of an RRT program (personnel, consumables, machines) before a surge in RRT arises and developing disaster contingency protocols anticoagulation and for shared RRT models when absolutely necessary is paramount to a successful response to such a disaster.

Keywords

CRRT; Pandemic; COVID-19; SARS-CoV-2; disaster response; Acute kidney injury

COVID-19 and kidney injury

The ongoing SARS-Coronavirus-2 pandemic leading to widespread Coronavirus-2019 disease (COVID-19) brings into the focus the paramount need for disaster planning within the nephrology community.[1] While the dramatic burden of respiratory failure and need for mechanical ventilation among patients with SARS-CoV-2 infection was recognized early in the pandemic and led to appropriate disaster planning, the recognition of the high rates of

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acute kidney injury (AKI) and subsequent need for renal replacement therapies (RRT) in COVID-19 were delayed.[1]

Early reports out of China appeared to have incomplete reporting of AKI with incidences as low as 0.5–3%.[2,3] Later reports including some from ICU cohorts reported wider variations in the incidence of AKI 5–23% but direct comparisons were limited by the absence of granular reporting on clinical information to compare the underlying severity of these cohorts.[4–7] One large cohort in New York City (the hotspot early in the pandemic) reported an overall AKI incidence of 47%, with 31% stage 3 severity.[8] Similarly, a single-center report from New Orleans, another city heavily affected during the early days of the pandemic, reported 28% incidence of AKI with 55% requirement of renal replacement therapy (RRT) and 50% in-hospital mortality.[9] Differences in admissions criteria and frequent absence of preadmission measures of kidney function limited the ability to draw precise conclusions on the burden of severe kidney disease.[8] A detailed systematic review and meta-analysis estimated the incidence of AKI among hospitalized patients to be as high as 17%.[10] The predominant mechanism of renal injury appears to be acute tubular necrosis, as evidenced by pathological evaluation of urinary sediment microscopy,[11] kidney biopsies,[12,13] and autopsies[14,15] of patients with COVID-19 and AKI. Collapsing glomerulopathy (COVID-19 associated nephropathy - COVAN) and other podocytopathies have also been reported in individuals with African and other ancestry.[16–18] Whether there is a direct impact of SARS-CoV2 infection on the kidney remains uncertain with some investigators reporting on the identification on the viral particles on electron microscopy.[19]

Surge in RRT needs

In the most severe disease usually characterized by circulatory shock and ARDS requiring mechanical ventilation, severe AKI requiring RRT is quite common. It is now estimated that nearly 5% of hospitalized patients require some form of RRT for AKI,[10] while 20–31% of critically ill patients were develop indications for RRT.[10,20,21] Not surprisingly kidney injury among critically ill patients with COVID-19 is also associated with a particularly poor outcome. This dramatic increase in demand in the face of unprecedented hospitalization rates and ICU censuses to accommodate the surge of patients has presented a unique challenge to the healthcare system and in particular for nephrology services, as a surge in demand of this scale has not been seen outside of crush-injuries from natural disasters. The absence of early estimates of the true burden of kidney injury created a situation where RRT resource planning did not occur ahead of time. It should be noted that this increased need for RRT does not include the increase in dialysis dependent patients with end stage kidney disease needing hospitalization and continued maintenance RRT. Providing RRT both in the ICU and outside is a resource intense procedure that requires significant capital investments (dialysis machines), consumables (filters, blood lines), dialysate fluids (either continuous produced or in prepacked sterile bags) and healthcare workers (dialysis nurses and technicians) with appropriate advanced training. As a result, RRT is dependent on a robust supply chain that had not previously been faced with such a rapid, sustained and widespread increase in demand. As an example, the projected shortfall in CRRT machines across just 6 states in the United States with a COVID surge was nearly 1000 machines.[22]

Adapting to resource shortages

At the height of the first COVID-19 surge in NYC, the number of patients with indications for RRT exceeded the availability of CRRT resources.[1] Different strategies for delivering RRT to these critically-ill patients needed to be explored, and factors that influenced our decisions to adopt different strategies are summarized in Table 1. Given the paucity of devices and the challenges of intermittent hemodialysis in hemodynamically unstable patients, several large academic centers shifted to protocols that allowed devices to be shared between patients resulting in the use of traditionally continuous therapies in a non-continuous manner – an approach that has previously been referred to as either prolonged-intermittent renal replacement therapy (PIRRT) or accelerated veno-venous hemofiltration (AVVH).[23–25] While prior intermittent strategies have utilized a 12 hour on and 12 hour off strategy, often to facilitate early mobilization of ICU patients, this frequent change results in a dramatic increase in consumable burn rate where filters are discarded evert 12 hours instead of every 48–72 hours. In contrast, a 24 hour on/off strategy is associated with a much lower rate of filter usage, still allows for adequate clearance at similar dialysate flow rates and similar volume management achieved of the 12hr on/ 12 hr off strategy.[1] Notably, however, this approach also allowed for a lower nursing burden by decreasing the frequency of changes for the patients, less down time for each device associated with priming/return of blood, and simplifying the logistic challenges associated with coordinating the movement of machines amongst an ever changing cohort of critically ill patients across a large geographical footprint of the hospital. Using novel tracking tools such as a CRRT sharing tool allowed for regionalization of machines and geographical patient pairings and facilitated the orchestration of efficient and accurate machine movement across the hospital and across multiple hospitals in a healthcare system.[26]

While this sharing protocol strategy addresses the dearth of available CRRT resources during a surge in need, it does not address vulnerabilities in the supply chain of therapy fluid (dialysate and replacement fluid). Such a protocol allows for 2 patients to receive RRT with one device, ensuring that they are receiving adequate clearance averaged over 48 hours, but this requires using increased flow rates to achieve adequate clearance. In other words, the amount of dialysis or replacement fluid being used per machine is doubled – while still at recommended clearance goals per patient. One approach to conserve commercially available therapy fluid that was utilized by some during the pandemic surge is a nomogram to prescribe a specific number of 5L therapy fluid bags per patient per day rather than prescribing only in mL/min.[1] During any sharing protocol, this prevents the waste of partially used therapy fluid bags at the end of the treatment session. Another strategy employed was dropping the therapy fluid dosing down to the lower limit of the recommended range (20 vs. 25mL/kg/hr) in patients who were not hypercatabolic in order to prolong the lifespan of the supply.[1] Finally, in order to be less reliant on a stretched supply chain which other institutions are competing for, some centers developed protocols for on-site dialysate production for CRRT using a conventional hemodialysis machine to generate dialysate for use on CRRT.

Importantly, some institutions have access to other CRRT or prolonged intermittent RRT (PIRRT) platforms that provide alternative ways to handle the increased need. In one report, sustained low efficiency dialysis (SLED) was the modality of choice.[27] Because of its higher dialysis dose delivery, SLED allows for 8–10 hour treatments, thus freeing a dialysis machine to be used for 2 patients within the same day. In addition, SLED does not require consumable dialysis solutions because it utilizes the hospital water supply. While SLED may offer some of those advantages, it also requires allocation of reverse osmosis machines for water purification as well as effective nursing. In the absence of SLED-trained ICU nurses, its implementation may be hindered by the need of a dialysis nurse at the bedside for prolonged periods of time. Finally, at the height of the surge some New York City hospitals turned to acute peritoneal dialysis to expand their dialytic capacity beyond the confines of CRRT and HD machines. There are important caveats to patient selection detailed in the description of their experiences utilizing low volume dwells (to avoid ventilatory compromise) and acute PD in patients with severe COVID-19 illness.[28–31]Importantly, patients with high oxygen or positive expiratory end-pressures and patients requiring proning were in general not considered candidates for acute PD at our institution.

Potential complications

There are a number of unique factors to take into consideration when reorganizing a CRRT program as we have described so far. First is the hypercoagulability seen in COVID-19 disease, and the challenges this places on a vulnerable supply of cartridges and blood products and trying to minimize nursing to patient contact time to protect nurses from occupational COVID exposure. One group described their experience using different forms of circuit anticoagulation in 80 COVID patients on CRRT, with a median filter life of only 21 hours. The three strategies that resulted in the longest filter lifespans in descending order were: 1) regional citrate anticoagulation plus systemic heparin (for non-CRRT indications), 2) argatroban and 3) systemic heparin. Utilizingpre-filter heparin strategies or no anticoagulation at all led to the shortest filter lifespans. Another group described their experience using protocolized systemic heparin dosing by following anti-factor Xa levels (targeting 0.3 – 0.7 IU/mL) rather than PTT.[34] Compared to standard of care (i.e. adjusting by PTT), the anti-factor Xa protocol did not lead to differences in filter losses until the third filter clotting event (event rates for first 2 clotting events remained the same).[34] SLED-based protocols also were associated with increased heparin usage.[27] Our institution adopted a CRRT anticoagulation protocol which directs clinicians to initiate pre-filter heparin as a default when no clinical contraindications exist. If filter clotting persists then to start regional citrate anticoagulation if available. If RCA not available to initiate full systemic anticoagulation with unfractionated heparin monitoring anti-Xa levels targeting 0.3–0.7 units/mL (requires availability of anti-Xa levels with rapid turnaround). If the circuit continues to clot to transition to systemic argatroban and finally if the circuit continues to clot despite all of the above and therapeutic PTT on argatroban to consult Hematology for guidance (Supplemental Figure S1). This highlights the extreme hypercoagulability in this group of patients and the unique demands it places on CRRT resource consumption and RN workload in an already vulnerable system.

Line placement site is another additional factor that needs to be careful consideration. Given the spatial complexities with proning patients, internal jugular dialysis access sites are preferred over femoral or subclavian sites.[35] The CRRT blood circuit is disconnected from the patient during the actual process of proning and supinating patients in order to prevent kinking and wrapping around the advanced airway. While there are anectodal reports of using blood line extension tubing in order to allow the CRRT machine to remain outside of the ICU room to minimize nursing exposure and conserve PPE, there are no studies examining whether this leads to increased machine alarms, performance of pressure monitors and filter clotting. it is for this theoretical concern that while our institution did use therapy fluid extension lines to allow for therapy fluid bag exchanges to occur outside of the patient room, we actively decided not to pursue blood line extenders given the high rates of clotting we were already experiencing. Of note, certain device cartridges are already incorporate extended tubing to facilitate use with citrate anticoagulation which would also lend themselves well to the placing the CRRT device outside the patient rooms

For patients receiving medications that are renally or extracorporeally cleared by RRT, hybrid therapies with shared protocols complicates medication dosing. These “accelerated” therapies provide faster clearance than traditional CRRT therapies but less than conventional HD and leaves the provider to make difficult decisions about appropriate dosing with a lack of evidence-based resources to inform their decision. While time averaged clearance of small molecules are largely unchanged, medications that are dosed once daily or more frequently are going to be impacted by the variations in drug clearances underscoring the need for careful attention to drug dosing. Therapeutic drug monitoring should be utilized when possible, and clinical ICU pharmacists should be involved in selecting the most appropriate dosing regimen when utilizing accelerated RRT protocols. Additionally, there is a compendium of dosing strategies in the literature as a starting point for clinicians faced with this challenge.[36]

Finally, the discussion on role of extracorporeal cytokine clearance has been revived by the cytokine storm that is seen in critically-ill patients with COVID-19. Case reports and small case series have described hemadsorption and convective clearance of cytokines in COVID-19 using CVVH, CVVHDF, and novel membrane technologies[37–39], however, given the observational reporting on these strategies it remains unclear what (if any) role these therapies have on outcomes in patients with AKI requiring CRRT in the setting of cytokine storm.

Outcomes – death, kidney recovery and dialysis dependency

Amongst survivors, careful monitoring for renal recovery is paramount, not only during the index hospitalization but even after discharge given that survivors experience continued renal recovery. While definitions for renal recovery vary substantially, it is usually heralded by an increase in urine output, which is the best predictor of renal recovery and successful discontinuation of RRT.[28,40–42] The reported volumes of UOP that best predict recovery also varies in the literature: >0.5–1L/d unassisted or >2L/d with diuretics in clinical trials and ~0.4L/d unassisted or >2.3L/d with diuretics in observational studies. Other clinical changes that should alert providers to imminent recovery are: a spontaneous decline in SCr, a decrease in interdialytic weight gain (suggesting undocumented urine output), or an increase in calculated native renal clearance with timed urine collections.[40] What, if any impact dialysis dependent AKI will have on the long term prevalence of ESKD or the rates of renal recovery among patients who remain dialysis dependent for longer duration remains to be seen.[44]

Prior studies have found that acute tubular injury (ATN) on biopsy is one predictor of renal recovery.[45] The high rates of renal recovery now being seen in COVID-19 AKI survivors is in line with the predominant pathological finding of ATN previously described, where the authors describe a pattern of tubular injury that appears less severe than the clinical phenotype and has been described as a “recoverable” finding. Other factors affecting recovery vs. dependency include both the severity and duration of the AKI episode, the length of time on RRT, baseline CKD, age, comorbid diabetes mellitus, comorbid congestive heart failure, and the number of pre-existing comorbidities.[40,44,47]

Between 27–64% of COVID-19 patients who required RRT were able to have RRT discontinued by 28 days or by ICU discharge.[21,48,49] Another study reported a 42% rate of renal recovery after needing RRT, however, the length of follow-up is unclear.[50] Furthermore, one study reported that among 216 patients with COVID-19 discharged from the hospital, 73 (34%) were still RRT-dependent, and among 69 of those patients who were still alive by day 60, 39 (57%) were still RRT-dependent.[4] Longer term follow-up in COVID-19 AKI survivors beyond 60 days is not yet reported, however we can learn from the experiences of prior observational studies of severe AKI requiring RRT. Among patients hospitalized with AKI requiring RRT, only 15–30% of survivors still required RRT at discharge (70–85% recovery in survivors),[51,52] and by 30 days after discharge 43% of patients who were RRT-dependent at discharge had recovered renal function. The majority of post-discharge renal recovery occurs within 3 months (73% of all recovery)[45] with a 78% recovery rate at 1 year of survivors of severe AKI in the ICU.[53]

Conclusions

Acute kidney injury is a common complication among patients hospitalized with COVID-19 especially among those with more severe infections. The need for renal replacement therapies in those with the most severe forms of AKI is considerable and risks overwhelming healthcare systems at the peak of a surge. Careful planning with shared protocols and an awareness of the consumable supply are essential prerequisites for a successful RRT strategy. Taking careful inventory of all aspects of an RRT program (personnel, consumables, machines) before a surge in RRT arises and developing disaster contingency protocols for sharing CRRT and utilizing acute PD when absolutely necessary is paramount to a successful response to such a disaster Long term outcomes among survivors including the extent and duration of renal recovery remains to be seen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1 –

Different RRT modalities and strategies with factors that influence decisions

Modality	Intermittent HD	24 hours CRRT	Hybrid RRT	Acute PD
Strategy	Conventional thrice weekly hemodialysis.	Conventional CRRT (CVVHD, CVVH, or CVVHDF)	Accelerated RRT or PIRRT (6 – 24 hours out of 48 hours)	Emergent bedside PD catheter placement and rapid start PD in the ICU
Personnel	HD Technicians HD RNs	ICU RNs	ICU or HD RNs (depending on institution)	ICU or PD RNs (depending on institution)
Pros	• provides sufficient clearance in a short amount of time, allowing for more than 1 patient treatment in a 24 hour period	• limits unnecessary exposure of HD RNs when ICU RNs already entering room	• maximizes the number of patients able to provide RRT to during pandemics/ disasters (i.e. >1 patient per machine per day)	• allows for expansion of an RRT program beyond the confines of HD machines, CRRT machines, and PD cyclers (by utilizing CAPD)
Cons	• not recommended in hemodynamically unstable patients • unnecessary exposure of HD RNs in addition to already exposed ICU RNs • unnecessary PPE use for dedicated HD RN to also enter the room • does nothing to address the mismatch in demand vs. supply	• limits the capacity of a CRRT program to 1 patient per machine per day and does not increase capacity during a disaster • prolonged filter exposure time may lead to increased clotting	• logistic challenges sharing machines in a large CRRT program • uncertainty with medication dosing in accelerated RRT and PIRRT modalities	• patients requiring proning for severe ARDS not suitable candidates • patients requiring high O2 or high positive end-expiratory pressures may not be suitable candidates • peritoneal leaks • unnecessary PD RN exposure and PPE consumption for frequency of entering the room for CAPD