Protocol for Local On-Site Dialysate Production for Continuous Renal Replacement Therapy during the COVID-19 Pandemic

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Abstract
AKI frequently occurs in patients with COVID-19, and kidney injury severe enough to require RRT is a common complication among patients who are critically ill. During the surge of the pandemic, there was a high demand for dialysate for continuous RRT, and this increase in demand, coupled with vulnerabilities in the supply chain, necessitated alternative approaches, including internal production of dialysate. Using a standard hemodialysis machine and off-the-shelf supplies, as per Food and Drug Administration guidelines, we developed a method for on-site dialysate production that is adaptable and can be used to fill multiple bags at once. The use of a central reverse osmosis unit, dedicated hemodialysis machine, sterile bags with separate ports for fill and use, and frequent testing will ensure stability, sterility, and—therefore—safety of the produced dialysate. The dialysate made in house was tested and it showed both stability and sterility for at least 30 hours. This detailed description of our process for generating dialysate can serve as a guide for other programs experiencing similar vulnerabilities in the demand versus supply of dialysate.

Key Points
- Because dialysate production in a hospital is not commonly performed, the technique has not been generalized to commonly available materials.
- On-site dialysate production may be necessary when demand is high, as it was during the coronavirus disease 2019 pandemic.
- This technique can be easily and widely applied to most hospitals using commonly available materials.

AKI is a common complication among patients with coronavirus disease 2019 (COVID-19), and severe AKI requiring RRT is a particularly common complication among patients with severe kidney disease (1–3). In our experience, 34% of patients hospitalized with COVID-19, and 78% of those admitted to the intensive care unit, developed AKI during their hospitalization, with 35% of patients who were critically ill requiring continuous RRT (CRRT) (3). In the midst of a surge of patients, this led to an unprecedented number of patients with AKI and need for CRRT (2). The increased demand was met with a rapid procurement of additional machines and the use of novel sharing protocols, which allowed us to provide RRT to twice the number of patients that we would have otherwise been able to accommodate (4).

The increased strain on resources was particularly critical for CRRT dialysate. Even with a doubling in the number of machines, most machines had to be shared in a 2:1 ratio between two patients, with a 12-hour on/off model (5). The use of shared protocols does not obviate the need for weight-based therapy fluid delivery to these patients (i.e., the prescription is prorated for the given amount of time they are receiving therapy). As a result, although one machine was being used to support two patients on an alternating 12-hour on/off model, the total amount of dialysate fluid required to deliver an adequate prescribed clearance dose for these two patients in a 24-hour period doubled. This doubling of fluid consumption, coupled with a near doubling of the number of CRRT machines in use during the surge, resulted in a nearly four-fold
increase the dialysate consumption rate, which thus rapidly depleted our CRRT dialysate stockpile.

In light of this and given concerns about the ability of our supply chain to maintain an adequate stockpile of CRRT fluids, we developed an internal approach to the production of dialysate solution to augment commercial solutions. We based our approach on the work by the Cleveland Clinic, with modifications to suit our institution (6,7). This was done to ensure that we would be able to adequately provide appropriate therapy fluid volumes to patients with COVID-19 who required CRRT.

A standard, volumetric, single-pass hemodialysis machine (Fresenius 2008T Hemodialysis Machine) and high-flux, hollow membrane, polysulfone membrane hemodialyzer (Fresenius Optiflux F180NRe) were used to generate bag dialysate for CRRT. The water supply from the central reverse-osmosis unit for the hospital dialysis unit was used to generate dialysate fluid, which was subsequently used to fill commercially available 4-L sterile bags. These bags were selected, in part, because they have a “large-bore” or “Deutsches Institut für Normung” (DIN) Luer lock connection that could be used to fill and then be permanently sealed, and a spike port that could be used at the time of patient treatment. As per Food and Drug Administration (FDA) guidance, the nonsterile nature of the fluid limited the duration the bags could be stored to no more than 24 hours, and preferably closer to 4–6 hours, and the fluid was used only as dialysate in a continuous venovenous hemodialysis circuit and could not be used as a replacement fluid in either a continuous venovenous hemofiltration or continuous venovenous hemodiafiltration circuit. In addition to using only off-the-shelf, approved medical products, the FDA suggested the use of frequent monitoring of the chemistry and microbiology, using fluid culture and endotoxin measurements. They also recommended that the bags used to obtain a sample for testing should not then be used for patient care.

The step-by-step approach used is outlined as follows:

1. Connect the hemodialysis machine to the central reverse osmosis unit, which undergoes routine chlorine and chloramine testing with every dialysis shift. (Testing frequency was increased when producing CRRT dialysate.)

2. Use the appropriate acid and bicarbonate concentrates, with a goal of achieving 140 mEq/L sodium, 32 mEq/L bicarbonate, and 3 mEq/L potassium. The conductivity alarms should be set to 14.1 mS/cm, with the lowest tolerance for deviation (0.3 mS/cm).

3. Attach the dialysate outflow (blue) Hansen connector (M43611 Dialyzer Connector) to the dialyzer at one end, while partially capping the dialysate outflow port on the polysulfone dialyzer.

4. Capping the outflow port on the filter tightly will force the dialysate to cross the membrane, onto the blood side of the filter, and flow out from the bloodline connection ports.

5. Attach a regular hemodialysis bloodline to one of the ports and clamp the line. This will now force the dialysate being produced and flowing into the filter to cross the membrane and out the remaining bloodline port.

6. Allow enough fluid to drain to ensure there is no more ethylene oxide in the filter, and that the conductivity is now stable.

7. Attach a spare Hansen connector to the second supply line on the machine. This will prevent the dialysis machine from going into bypass mode.

8. Once ready, the dialysate flow rate should be increased to 800 ml/min, and a sterile 5-L bag (TPN Exactamix bags, H938743; Baxter) are attached to the single bloodline port on the filter that is open. This can be done in either direction, using a DIN connector or via a female-to-male DIN connector.

Given the speed at which the bags would be expected to fill, it may be advantageous to have multiple bags fill simultaneously. This can be achieved by using multiple Y connectors (Figure 1, Supplemental Material). It is important to note that the sterile tubing that connects the DIN Luer lock connectors to both dialyzers and dialysate bags is specialized and, thus, uncommon, which presents a procurement challenge.

### Table 1. Dialysate chemistry testing over time

| Time | 1 Hr | 2 Hr | 3 Hr | 4 Hr | 5 Hr | 24 Hr | 30 Hr |
|------|------|------|------|------|------|-------|-------|
| Sodium (mmol/L) | 140  | 141  | 140  | 140  | 141  | 143   | 142   |
| Potassium (mmol/L) | 3.2  | 3.2  | 3.2  | 3.2  | 3.2  | 3.2   | 3.2   |
| Chlorine (mmol/L) | 113  | 113  | 113  | 113  | 113  | 114   | 114   |
| Carbon dioxide (mmol/L) | 30   | 29   | 29   | 29   | 29   | —     | —     |
| Calcium (mg/dl) | 4.8  | 4.8  | 4.7  | 4.8  | 4.8  | 4.8   | 4.8   |
| Lactate (mmol/L) | 0    | 0    | 0    | 0    | 0    | 0     | 0     |
| pH | 7.29 | 7.29 | 7.317| 7.379| 7.425| —     | 7.492 |

One dialysate bag tested over 30 hours.
Using the outlined approach, we then completed the process of filling sterile bags for use and performed chemical testing to confirm the composition of the dialysate solution was as expected. Composition was tested using three randomly selected bags. One bag of dialysate solution was then subjected to serial testing to confirm that the chemical composition did not degrade over the first 30 hours after the initial testing (Table 1). Visual inspection, on a dark background, of the fluid on all produced bags did not reveal any perceptible precipitation at 30 hours. Microbiologic testing, including testing for endotoxins and fluid cultures, was performed to ensure sterility of the fluid. Multiple bags were tested to determine if the process of disconnecting filled bags and reconnecting fresh sterile bags was likely to introduce contamination (Table 2). Our testing protocol was developed in collaboration with our hospital’s clinical laboratory. Layman-Amato et al. (8) provides a recent review of dialysate testing standards that may be of use for others developing and approving their own testing protocol. FDA guidance precluded the use of emergency-produced dialysate past 24 hours after production, which is comparable with recommendations provided for commercially produced dialysate after mixing has occurred. In addition, although the dialysate is considered ultrapure, it is not considered sterile and should not be used as replacement fluid.

Although our system was designed to use off-the-shelf equipment and to scale to the needs of a large academic medical center, we acknowledge that it is not without challenges. Our process is labor intensive, because sterile bags need to be swapped out with regular frequency. Frequent chemistry and microbiologic testing needs to occur at regular frequencies and must be accompanied by increased monitoring of the central reverse osmosis system for the dialysis machines. For these reasons, close monitoring of all aspects of in-house dialysate production and use is essential. Although we were fortunate enough to avoid having to use the produced dialysate for our patients, severe strain on supply chains created a situation that required a secondary solution to be in place. Our procedures and testing provide a blueprint process that can be used as an effective stop-gap measure during times of extreme supply constraints. Given the constraints of hemodialysis, which requires specially trained nurses, and the influx of patients with ESKD, reverting to a program of only hemodialysis for RRT in the face of CRRT dialysate shortage was not an option (4).

In summary, we describe a simple, reproducible means of producing dialysate solutions to maintain a utilitarian approach to maintain a large CRRT program during a pandemic. The high incidence of severe AKI among patients hospitalized with COVID-19 tested the supply chain and created shortages that could adversely affect patient care. We hope that the description of our method for generating dialysate to support a CRRT program in the midst of a pandemic surge
Disclosures
C.R. Parikh reports having consultancy agreements with Genfit Biopharmaceutical Company; serving as a scientific advisor for, or member of, Genfit Biopharmaceutical Company and RenalytixAI; having ownership interest in RenalytixAI; and receiving research funding from the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). D. Fine reports serving on the medical advisory board for Fresenius Medical Corporation, and having consultancy agreements with GlaxoSmithKline (data and safety monitoring board). S. Mohan reports serving as a member of the Angion Pharma scientific advisory board, as deputy editor for Kidney International Reports (International Society of Nephrology), receiving research funding from Angion Biomedica; receiving research funding from NIH (National Institute of Biomedical Imaging and Bioengineering, National Institute on Minority Health and Health Disparities, and NIDDK). All remaining authors have nothing to disclose.

Author Contributions
R. Carrera, A. Li, S. Mohan, and A.A. Moses were responsible for investigation; R. Carrera, A. Li, S. Mohan, A.A. Moses, and J.S. Stevens wrote the original draft; S. Mohan, and A.A. Moses were responsible for data curation; S. Mohan, and C.R. Parikh were responsible for methodology; S. Mohan provided supervision and was responsible for formal analysis, project administration, resources, and validation; S. Mohan conceptualized the study; and all authors reviewed and edited the manuscript.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000652021/-/DCSupplemental.
Supplemental Material. Pictorial step by step guide PDF: “Method for repurposing dialysis machines for dialysate production.PDF.”

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