Protocol for local on-site dialysate production for continuous renal replacement therapy during the COVID-19 pandemic

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Key Points:

- Dialysate production in a hospital is not commonly performed, and therefore 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 COVID-19 pandemic
- This technique can be easily and widely applied to most hospitals with commonly available materials

Abstract:

Acute kidney injury frequently occurs in patients with COVID-19 and injury severe enough to require renal replacement therapy (RRT) is a common complication among critically-ill patients.1–3 During the surge, 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 Federal Drug Administration (FDA) 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 produced dialysate. Dialysate made in house was tested and 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 vs. supply of dialysate.
Acute kidney injury is a common complication among patients with COVID-19 and severe acute kidney injury (AKI) requiring renal replacement therapy (RRT) is a particularly common complication among patients with severe kidney disease. In our experience, 34% of patients hospitalized with COVID-19 and 78% of those admitted to the ICU developed AKI during their hospitalization with 35% of critically-ill patients requiring continuous RRT (CRRT). In the midst of a surge of patients, this led to an unprecedented number of patients with AKI and need for CRRT. 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.

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 2 patients, with a 12 hour on/off model. 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, while one machine was being used to support 2 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 2 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 4-fold increase the dialysate consumption rate thus rapidly depleting 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. This was done to ensure that we would be able to adequately provide appropriate therapy fluid volumes to COVID-19 patients on 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 that was subsequently used to fill commercially available 4-liter sterile bags. These bags were selected in part because they have a “large-bore” or “DIN” luer lock connection that could be used to fill and subsequently be permanently sealed, and a spike port that could be used at the time of patient treatment. As per FDA guidance, the non-sterile nature of the fluid limited the duration that 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 CVVHD circuit and could not be used as a replacement fluid in either a CVVH or CVVHDF 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 that were used to obtain a sample for testing should not be then 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 a sodium of 140 mEq/L, Bicarbonate of 32 mEq/L and potassium of 3 mEq/L. 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 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 on to 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 at the state to ensure that there is no more ethylene oxide in the filter, and that the conductivity is now stable.

7. Attach a spare Hansen (M43611 Dialyzer 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 800mL/min and a sterile 5L bag (Baxter TPN Exactamix bags (H938743) are attached to the single bloodline port on the filter that is open. This can be done 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 the use of multiple Y connectors (Figure 1) Crucially, sterile tubing that can connect the DIN luer lock connectors common to both dialyzers and dialysate bags is specialized and thus uncommon, presenting a procurement challenge.

Using the outlined approach, we then completed the process of filling sterile bags for use and performed chemical testing to confirm that the composition of the dialysate solution was as expected. Composition was tested using 3 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 that we tested. Visual inspection of the fluid on all bags produced on a dark background did not reveal any perceptible precipitation at 30 hours. Microbiologic testing including testing for endotoxins and fluid cultures were 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. Our testing protocol was developed in collaboration with our hospital’s clinical laboratory. Amato et. al 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 use of emergency produced dialysate past 24 hours, which is comparable to recommendations provided for commercially produced dialysate after mixing has occurred. In addition, while the dialysate is considered ultrapure, it is not considered sterile and should not be used as replacement fluid.

While 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, as sterile bags need to be swapped out with regular frequency. Frequent chemistry and microbiological testing need to occur at regular frequency and be accompanied by increased monitoring of the central reverse osmosis (RO) system for the dialysis machines. For these reasons, close monitoring of all aspects of in-house dialysate production and use is essential. While we were fortunate to not have needed 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 during times of extreme supply constraints as an effective stop gap measure. Given the constraints of hemodialysis which requires specially trained nurses, and the influx of patients with end stage renal disease, reverting to a program of only hemodialysis for renal replacement therapy in the face of CRRT dialysate shortage was not an option.
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 infection tested the supply chain and created shortages that could adversely impact patient care. We hope that the description of our method to generate dialysate to support a CRRT program in the midst of a pandemic surge provides the necessary blueprint to replicate our system in the unfortunate event of a dialysate fluid supply disruption.

Disclosures

C. Parikh reports the following: Consultancy Agreements: Genfit Biopharmaceutical Company; Ownership Interest: Renaltix AI; Research Funding: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Heart, Lung and Blood Institute (NHLBI); Scientific Advisor or Membership: Genfit Biopharmaceutical Company, RenalytixD. Fine reports the following: Consultancy Agreements: GlaxoSmithKline – DSMB; Scientific Advisor or Membership: Medical Advisory Board - Fresenius Medical Corporation. S. Mohan reports the following: Consultancy Agreements: Angion Biomedica; Research Funding: Angion Biomedica; Scientific Advisor or Membership: Deputy Editor, Kidney International Reports (ISN), Vice Chair, UNOS, Data advisory committee, Member, SRTR Visiting Committee, Member, ASN Quality committee, Angion Pharma scientific advisory board; Other Interests/Relationships: Research Funding from NIH (NIDDK, NIHMD and NIBIB). All remaining authors have nothing to disclose.

Funding

Dr. Chirag R. Parikh was supported by NIH grants RO1HL085757
Author Contributions

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A Li: Investigation; Methodology; Writing - original draft; Writing - review and editing

C Parikh: Methodology; Writing - review and editing

S Mohan: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing - original draft; Writing - review and editing

Supplementary Material

Pictorial Step by step guide PDF: “Method for repurposing dialysis machines for dialysate production.PDF”
References


Table 1.

Dialysate Chemistry Testing over time

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<tr>
<th>Time</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
<th>5 hr</th>
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hr, Hours. 1 dialysate bag tested over 30 hours
Table 2.
Endotoxin Testing and Repeat Chemistry for three samples

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<td>Cl (mmol/L)</td>
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<td>(EU/mL)</td>
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<tr>
<td>Cultures (48 hours)</td>
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<td>Negative</td>
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3 randomly selected dialysate bags tested at 48 hours
Figure 1: Multiple bag filling method of dialysate production