DIY: Ultrapure Home Brew Dialysate for the ICU?

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During the last quarter century, unlike most hospitals, the Cleveland Clinic has produced its own dialysate for continuous venovenous hemodialysis (CVVHD).[1,2] In this issue of *Kidney Medicine*, Taliercio et al[3] make a strong

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case for the safety and economy of this effort in their hands. During the past year, the spike in demand for kidney replacement therapy associated with the coronavirus disease 2019 (COVID-19) pandemic demonstrated the vulnerability of traditional supply chains.[4] In the United States, the supply chains have recovered, and with luck, the worst of this pandemic is behind us. However, we do not know what other catastrophes the future holds: infectious, geologic, weather-related, or more directly caused by human omission or commission. Under what circumstances should the rest of us try the Cleveland Clinic approach?

The idea is elegantly simple: every hemodialysis machine already produces dialysate. To produce CVVHD fluid, rather than attaching what would usually be the blood compartment of the dialyzer to blood lines, one attaches it to an effluent line that delivers the dialysate, which has passed through the dialyzer, out to sterile bags. Potassium, calcium, and sodium concentrations can be customized, as they are when the machine is used as intended for hemodialysis. One labels and seals the bags, stores them, and delivers them to the intensive care unit. The Cleveland group has posted a YouTube video that demonstrates the steps. "But, *is it really safe to treat critically ill patients with homebrew dialysate?*" you might imagine the hospital administrator or the Joint Commission surveyor asking.

The answer is that, as implemented at the Cleveland Clinic, this method appears to be very safe. Its key novel features are the careful collection, storage, and redelivery of dialysate. Chemical stability and microbiological safety are the obvious concerns. Over time, even despite acetate buffer, fluids containing bicarbonate with calcium can be expected to have precipitation and to increase in pH as carbon dioxide diffuses out. The quality measures reported by the authors demonstrate electrolyte stability over the storage period.

Corradi et al,[5] evaluating a similar method, also showed no clinically relevant change in electrolytes over a much longer storage period, 96 hours, and assert lack of clinically relevant change to 168 hours. In any case, most CVVHD treatments involve frequent blood chemistry monitoring, and the effect of even major electrolyte deficits in the fluid would probably be detected long before adverse clinical impact. Microcrystallization has been reported in similar fluids[6]; however, in CVVHD, the dialysis filter should effectively prevent transit of any microcrystals into the patient. The reported microbiological data are likewise reassuring. Furthermore, the authors report patient blood chemistry changes similar to those observed in association with the use of commercial solutions. They observed no difference in patient mortality compared with similarly ill patients using a model derived from a population using commercial fluids.

Therefore, the Cleveland Clinic has a robust and apparently safe protocol. How might this translate to a new location and a different program? Several key points need emphasis. As the authors note, this protocol is intended specifically for the generation of dialysate, not of infusate for hemofiltration, which must meet standards for sterility.[7] Another is that mitigating any potential safety issues depends not only on details of the fluid preparation, but also on investment in a robust quality monitoring protocol, with sampling that accurately simulates the conditions under which the fluids are being used for patient therapy.

On an emergency basis, with the alternative being the complete inability to provide continuous kidney replacement therapy (CKRT) because of a fluid shortage, the Cleveland Clinic protocol would seem to easily meet the goals of safety and appropriateness. We make this judgment not only as academic evaluators, but also with operational experience gained from preparing to use it ourselves. At the height of the spring 2020 COVID-19 surge in the Northeast, with the assistance of a local dialysis technical expert and after consultation with 2 of the report's authors, we produced several bags of dialysate using the Cleveland Clinic technique and prepared to implement the practice at scale. Though ultimately not required, we judged at that time, and continue to believe, that it is sound.

Several logistical points emerged from this exploration. Any such enterprise should involve hospital legal staff, any other organizations supporting the hospital's dialysis program and their technical and legal staff, infection prevention (particularly with regard to safely re-accessing the bags for use), and the hospital pharmacy (for their expertise regarding issues regarding stocking, transport, and labeling). One particular detail is that the large collection bags used in Cleveland have the appropriate blood line connectors for dialysis tubing, but are not designed specifically for being sealed and then re-accessed. Although it appears they can be accessed in a safe manner, to do so likely requires additional planning and education of the intensive care unit nursing staff. (A future possibility: there are already multiport large bags with a high-

volume filling port and a separate "spike" port for end-user access, eg, for total parenteral nutrition compounding. If an enterprising bag manufacturer replaced the pharmacy-compounder fitting with a standard dialysis blood line connector, it would seem a perfect fit for this need).

We turn now to the consideration of this process on a nonemergency basis: electively forgoing commercial solutions and thereby assuming responsibility for quality of the product. It is worth noting that the Cleveland Clinic has a very large CKRT program, with approximately 15 dedicated CKRT technicians who produce the dialysate, among other duties (Demirjian, personal communication, March 2021). Such an environment is conducive to the ongoing training and process control required for a high-quality industrial process and represents a substantial institutional commitment. Although we have no reason to doubt the accuracy of the reported estimate of technician time required to directly produce the dialysate, it seems possible that this calculation understates the investment in staff selection, training, and continuing education, particularly at startup. Finally, although the authors do not describe the process of medical and administrative leadership and of quality oversight, it too has a cost. It is important to emphasize that this program is neither an orphan nor an afterthought.

The authors have dubbed the dialysate they produce Cleveland Clinic UltraPure Solution, and the name deserves comment. Standards for the composition of water and dialysate used in extracorporeal blood purification are set by the International Standards Organization (ISO). With respect to infectious agents, ISO defines 2 standards for dialysate: "standard" and "ultrapure." Standard dialysate yields a total viable microbial count of <100 colony-forming units (CFU)/mL, whereas ultrapure dialysate yields <0.1 CFU/mL, a difference of 3 orders of magnitude. Standard dialysate contains <0.5 endotoxin unit (EU) per mL, whereas ultrapure dialysate contains <0.03 EU/mL of endotoxin, 1 order of magnitude less.[8]

In Japan, where ultrapure dialysate is widely used for conventional hemodialysis, there is evidence of a dose response between endotoxin concentrations and mortality even within the range of endotoxin concentrations meeting the ultrapure standard.[9] The testing techniques required to establish adherence to the standard and ultrapure levels differ. To establish that dialysate contains <100 CFU/mL, qualifying as satisfactory standard dialysate, one can use the pour plate or spread plate method. However, a laboratory report of "no growth" or "0 CFU/mL" by this technique cannot demonstrate that the fluid qualifies as ultrapure because culture of a small volume, whether by the pour plate or the spread plate technique, is not sensitive enough. To demonstrate that dialysate qualifies as ultrapure, it must be cultured using membrane filtration of 10 to 1,000 mL, and the equipment used to measure endotoxin concentration must be equipped so as to detect endotoxin at 0.03 EU/mL.[7]

There are 3 points to make about the circumstance that the Cleveland Clinic dialysate qualifies as ultrapure: first, it represents a level of investment in ensuring dialysate quality that is higher than is common in US dialysis programs, whether outpatient or inpatient. The authors presumably figured this cost into their calculations, but if we propose to emulate them, we should keep it in mind. Second, it may not matter that the dialysate qualifies as ultrapure rather than as standard. It is widely thought that exposure to bacteria, endotoxin, and other bacterial products is associated with chronic inflammation; a number of inflammatory parameters are improved by using ultrapure dialysate and there is observational evidence that patients with end-stage kidney disease treated by hemodialysis live longer if they are treated using lower-endotoxin dialysate.[10] However, it would seem much less likely that brief exposure to standard rather than ultrapure dialysate would make much difference in patients as inflamed as those who undergo CVVHD. In addition, the CVVHD dialysate circuit is not a sterile compartment and may be routinely microbiologically contaminated.[11,12] Nevertheless, showing that ultrapure dialysate can be achieved by the Cleveland Clinic method is still useful because it suggests that there is a microbiological margin of safety to the technique.

Quality and safety aside, any consideration of nonemergency use also involves considerations of cost. The Cleveland Clinic method is relatively inexpensive. Although the authors suggest eye-popping savings relative to wholesale purchase of commercial dialysis fluid, institutions already buying large volumes of commercial fluid at a discount would probably realize smaller (but still real) savings relative to their existing contracts. There may also be startup labor costs beyond the steady-state values reported by Cleveland. Finally, any proposal should plan to reinvest some of the anticipated cost savings to robust quality control to ensure the quality and safety of the process.

In summary: the Cleveland Clinic method seems safe and practical as described. In an emergency, it can render a hospital independent of the supply chain for CVVHD fluid, although the Cleveland Clinic method still depends on supplies of plastic bags and tubing. This dispassionate description, at its heart, means that the Cleveland Clinic process could save lives in a time of shortage. Independent of emergency measures, their experience describes a feasible, flexible, and scalable process that deserves consideration. It essentially redistributes resources from fluid suppliers and their employees and shareholders to hospitals and their employees. However, with that resource transfer comes the responsibility for the oversight of fluid production. Pharmaceutical factory production of fluid for intravenous and intraperitoneal infusion has proved very safe during the past 90 years, and as a convenience, we have used the same approach for CVVHD fluid. For some institutions, the savings and the flexibility of the alternate Cleveland Clinic approach described here may well be worth the responsibility.

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