Net Ultrafiltration Prescription and Practice Among Critically Ill Patients Receiving Renal Replacement Therapy: A Multinational Survey of Critical Care Practitioners

Raghavan Murugan, MD, MS, FRCP, FCCM[1,2]; Marlies Ostermann, MD, PhD[3]; Zhiyong Peng, MD, PhD[4]; Koichi Kitamura, MD[5]; Shigeki Fujitani, MD, PhD[6]; Stefano Romagnoli, MD, PhD[7,8]; Luca Di Lullo, MD, PhD[9]; Nattachai Srisawat, MD, MS[10]; Subhash Todi, MD, MRCP[11]; Nagarajan Ramakrishnan, MD, MMM, FCCM, FISCCM[12]; Eric Hoste, MD, PhD[13]; Chethan M. Puttarajappa, MD, MS[14]; Sean M. Bagshaw, MD, MSc[15]; Steven Weisbord, MD, MSc[1,14,16]; Paul M. Palevsky, MD[1,14,16]; John A. Kellum, MD, MCCM[1,2]; Rinaldo Bellomo, MD, PhD[17]; Claudio Ronco, MD, PhD[18]

[1]The Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA.

[2]The Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA.

[3]Department of Critical Care, King's College London, Guy's & St Thomas' Hospital, London, United Kingdom.

[4]Department of Critical Care Medicine, Wuhan University Zhongnan Hospital, Wuhan, Hubei Province, China.

[5]Department of Nephrology, Endocrinology and Diabetes, Tokyo Bay Urayasu Ichikawa Medical Center, Urayasu, Chiba, Japan.

[6]Emergency and Critical Care Medicine Department, St. Marianna University, Kawasaki-city, Kanagawa, Japan.

[7]Department of Health Science, University of Florence, Florence, Italy.

[8]Department of Anesthesia and Critical Care, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy.

[9]Department of Nephrology and Dialysis, L. Parodi-Delfino Hospital, Colleferro, Italy.

[10]Excellence Center for Critical Care Nephrology, Division of Nephrology, Department of Medicine, Chulalongkorn University, Bangkok, Thailand.

[11]Department of Critical Care, AMRI Hospitals, Kolkata, West Bengal, India.

[12]Department of Critical Care Medicine, Apollo Hospitals, Chennai, Tamil Nadu, India.

[13]Department of Intensive Care Medicine, Ghent University, Ghent, Belgium.

[14]Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh, Pittsburgh, PA.

[15]Department of Critical Care Medicine, Faculty of Medicine and Dentistry and School of Public Health, University of Alberta, Edmonton, AB, Canada.

[16]Renal Section, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA.

DOI: 10.1097/CCM.0000000000004092

[17]Department of Intensive Care Medicine, Austin Hospital, The University of Melbourne, Melbourne, VIC, Australia.

[18]Department of Medicine, University of Padova, International Renal Research Institute of Vicenza and Department of Clinical Nephrology, San Bortolo Hospital, Vicenza, Italy.

Dr. Murugan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and involved in drafting of the article, statistical analysis, and study supervision. Drs. Murugan, Ostermann, Peng, Puttarajappa, Weisbord, Palevsky, Kellum, and Bellomo were involved in study concept and design. Drs. Murugan, Ostermann, Peng, Kitamura, Romagnoli, Di Lullo, Srisawat, Todi, Bellomo, and Ronco were involved in acquisition of data. Drs. Murugan, Ostermann, Weisbord, Palevsky, Kellum, Bellomo, and Ronco were involved in analysis and interpretation of data. Drs. Murugan, Ostermann, Peng, and Kitamura were involved in administrative, technical, or material support. All authors were involved in critical revision of the article for important intellectual content.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Murugan received grant funding from the National Institute of Diabetes and Digestive and Kidney Diseases and Bioporto and funding from AM Pharma and La Jolla unrelated to this study. Dr. Romagnoli received funding from Baxter, MSD, and Masimo. Dr. Hoste's institution received funding from AM Pharma and Sopachem. Dr. Bagshaw received funding from Baxter. Dr. Weisbord received funding from Saghmos Therapeutics. Drs. Weisbord and Palevsky disclosed government work. Dr. Palevsky's institution received funding from Dascena, and he received funding from Baxter, Novartis, and GE Healthcare. Dr. Kellum received funding from Baxter (grant and consulting) and NxStage (consulting). The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: muruganr@upmc.edu

Objectives: To assess the attitudes of practitioners with respect to net ultrafiltration prescription and practice among critically ill patients with acute kidney injury treated with renal replacement therapy.

Design: Multinational internet-assisted survey.

Setting: Critical care practitioners involved with 14 societies in 80 countries.

Subjects: Intensivists, nephrologists, advanced practice providers, ICU and dialysis nurses.

Intervention: A cross-sectional survey.

Measurement and Main Results: Of 2,567 practitioners who initiated the survey, 1,569 (61.1%) completed the survey. Most practitioners were intensivists (72.7%) with a median duration of 13.2 years of practice (interquartile range, 7.2–22.0 yr). Two third of practitioners (71.0%; regional range, 55.0–95.5%) reported using continuous renal replacement therapy with a net ultrafiltration rate prescription of median 80.0 mL/hr (interquartile range, 49.0–111.0 mL/hr) for hemodynamically unstable and a maximal rate of 299.0 mL/hr (interquartile range, 200.0–365.0 mL/hr) for hemodynamically stable patients, with regional variation. Only a third of practitioners (31.5%; range, 13.7–47.8%) assessed hourly net fluid balance during continuous renal replacement therapy. Hemodynamic instability was reported in 20% (range, 20–38%) of patients and practitioners decreased the rate of fluid removal (70.3%); started or increased the dose of a vasopressor (51.5%); completely stopped fluid removal (35.8%); and administered a fluid bolus (31.6%), with significant regional variation. Compared with physicians, nurses were most likely to report patient intolerance to net ultrafiltration (73.4% vs 81.3%; $p = 0.002$), frequent interruptions (40.4% vs 54.5%; $p < 0.001$), and unavailability of trained staff (11.9% vs 15.6%; $p = 0.04$), whereas physicians reported unavailability of dialysis machines (14.3% vs 6.1%; $p < 0.001$) and costs associated with treatment as barriers (12.1% vs 3.0%; $p < 0.001$) with significant regional variation.

Conclusions: Our study provides new knowledge about the presence and extent of international practice variation in net ultrafiltration. We also identified barriers and specific targets for quality improvement initiatives. Our data reflect the need for evidence-based practice guidelines for net ultrafiltration. (*Crit Care Med* 2019; XX:00–00)

Key Words: fluid overload; net ultrafiltration; prescription; renal replacement therapy; survey

Fluid overload (FO) is prevalent in more than two thirds of critically ill patients with acute kidney injury and is independently associated with mortality (1–4). When FO is resistant to treatment with diuretics, clinicians frequently use net ultrafiltration (UF^{NET}) during renal replacement therapy (RRT). This practice is based on studies (3, 5) that suggest UF^{NET} may reduce morbidity and mortality and is supported by clinical practice guidelines (6). Nevertheless, several aspects of UF^{NET} including the optimal timing, rate, or how to manage complications are unclear.

Emerging evidence from observational studies in critically ill patients suggests that higher UF^{NET} rates, compared with lower UF^{NET} rates, are associated with lower mortality in some studies (7) and increased mortality in others (8). Data from outpatients with end-stage renal disease also suggest that higher UF^{NET} rates are associated with increased mortality (9–12). Thus, we conducted a multinational survey of critical care practitioners to ascertain attitudes in prescription and practice of UF^{NET} with the ultimate goal to inform research and quality improvement initiatives.

Specifically, we assessed 1) how practitioners determined diuretic resistance and criteria used for initiation and prescription of UF^{NET}; 2) modality of RRT, typical UF^{NET} prescription, assessment of prescribed-to-delivered dose of UF^{NET}, and evaluation of net fluid balance; 3) hemodynamic instability and management; 4) perceived barriers; and 5) attitudes related to timing of initiation of UF^{NET}, need for a protocol, and equipoise to enroll patients in a clinical trial of protocol-based UF^{NET} versus usual care.

METHODS

Survey Development and Testing

We conducted a worldwide, self-administered, cross-sectional, internet-assisted, open survey of adult intensivists and nephrologists including trainees, advanced practice providers (i.e., nurse practitioners), and ICU and dialysis nurses, involving 14 critical care and nephrology societies in 80 countries. We used rigorous survey methodology to design, test, and administer the survey instrument (13, 14). First, we conducted an unstructured interview with intensivists ($n = 3$), nephrologists ($n = 2$), advanced practice providers ($n = 2$), ICU ($n = 2$), and dialysis nurses ($n = 2$) at the University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, to understand their attitudes toward fluid removal and drafted the instrument (phase I testing). Second, we piloted the instrument on critical care medicine ($n = 2$) and nephrology ($n = 2$) trainees, intensivists ($n = 2$), nephrologists ($n = 2$), advanced practice providers ($n = 2$), ICU ($n = 2$), and dialysis nurses ($n = 2$) at UPMC and Guy's & St Thomas' Hospital, London, United Kingdom, making revisions for readability and clarity (phase II testing).

The instrument was then pretested by the survey steering committee, who provided feedback on "Face-, Content-, and Criterion validity." We assessed "test-retest reliability" by administering the instrument to four practitioners on two occasions separated by 2 weeks, and the final instrument consisted of 25 questions examining five domains (**eMethods 1**, **Supplemental Digital Content 1**, http://links.lww.com/CCM/F64). We used branched logic within the instrument to ask questions that are only appropriate for nurses (**eMethods 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64). The final instrument (**eMethods 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64) was approved by the University of Pittsburgh's Human Research Protection Office and was endorsed by the European Society of Intensive Care Medicine (ESICM), Chinese Society of Critical Care Medicine (CSCCM), Japanese Society of Critical Care Medicine (JSCCM), the Society of Critical Care Medicine (SCCM), the Comprehensive Local Research Network (CLRN), and the National Institute of Health Research in the United Kingdom.

Survey Administration

The survey prefaced by an invitation letter was administered using an online software (Qualtrics, Provo, UT). The survey was disseminated between January 6, 2018, and January 10, 2019, via email to the members of the Australasian and New Zealand Intensive Care Society, British Association of Critical Care Nurses (BACCN), Canadian Critical Care Society, CSCCM, ESICM, Indian Society of Critical Care Medicine, Italian Society of Intensive Care, JSCCM, National Kidney Foundation, SCCM, Thailand Society of Critical Care Medicine, and the CLRN (eMethods 2, Supplemental Digital Content 1, http://links.lww.com/CCM/F64). To expand the survey distribution and improve the response rates, individual societies sent reminders according to their policies and procedures.

The survey was also displayed on the website of the ESICM, American Association of Critical Care Nurses, CSCCM, Italian Society of Nephrology, as well as in the newsletter of BACCN. In China and Japan, the survey instrument was translated in Chinese and Japanese by two investigators (Z.P., K.K.). The survey was administered anonymously, and the IP addresses of individuals and information related to identity were not collected. The survey was voluntary, and consent was implied if the participants responded, and no incentives were offered for survey completion. We adhered to the Checklist for Reporting Results of Internet E-surveys to report the data (15).

Statistical Analysis

Only complete questionnaires were included in the final analyses. We present descriptive statistics as either proportions or median (interquartile range [IQR]), as appropriate and regional data as range. In assessing proportions, we excluded "I do not prescribe/make decision," "Other," "I don't know," and "Not applicable" items. We assessed practice variation using the chi-square test and Wilcoxon rank sum or K-sample equality of medians test for binary and continuous outcomes, respectively. To compare regional differences for seven-point Likert-type responses, we collapsed ordinal categories into three groups (agree, neither agree nor disagree, and disagree). We did not impute any missing data and considered p values less than 0.05 to be statistically significant. All analyses were performed using STATA 15.0 (STATA Corp, College Station, TX) software. Thematic analysis was performed for the free-text comments and lexical analysis for comments in English (**eMethods 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64) (16).

RESULTS

Practitioner Characteristics

The survey was disseminated to 56,840 members belonging to nine societies (eMethods 2, Supplemental Digital Content 1, http://links.lww.com/CCM/F64). However, many practitioners were members of multiple societies and received the survey more than once. Of 2,567 practitioners who initiated the survey, 1,569 practitioners (61.1%) completed and 998 practitioners (38.9%) did not complete the questionnaire (**eTable 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64) including 62 (2.4%) who opted out of the survey. Practitioners were from North America (34.1%), Europe (30.9%), Asia (28.9%), Oceania (2.9%), South America (2.7%), and Africa (0.5%; **Table 1**; and **eTable 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64). The most represented countries were the United States (29.6%), United Kingdom (11.5%), Japan (10.3%), China (10.1%), Italy (5.0%), India (3.2%), Canada (2.9%), and Australia (2.5%; **Fig. 1**; and **eTable 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64). Majority of practitioners were intensivists (72.7%) and ICU nurses (22.0%), and the median duration of clinical practice was 13.2 years (IQR, 7.2–22.0 yr). More than half (57.5%) practiced in a university-based hospital. **eTable 4** (Supplemental Digital Content 1, http://links.lww.com/CCM/F64) shows the distribution of responses by physicians and nurses.

Diuretic Resistance and Criteria Used for Initiation and Prescription of UF^{NET}

Of intensivists, nephrologists, and advanced practice providers (77.1%), 44.2% (regional range, 33.3–55.0%) affirmed that they used a maximum 100–250 mg of furosemide equivalent per day before determining diuretic resistance with regional variation. Although more than half of practitioners in North America (55%) used 100–250 mg/d of furosemide, only a third in Europe (33.5%) and Oceania (33.3%) used this dose. For initiation of UF^{NET}, practitioners considered persistent oliguria/anuria (42.4%; range, 22.2–51.1%) and pulmonary edema (16.0%; range, 13.3–37.5%). Although prescribing UF^{NET}, half (52.2%; range, 44.8–75.0%) considered patient hemodynamic status and 19.0% (range, 10.5–22.3%) cumulative fluid balance with regional variation.

RRT Modality, UF^{NET} Prescription, Assessment of Prescribed-to-Delivered UF^{NET} Dose, and Evaluation of Net Fluid Balance

Intermittent Hemodialysis. Across regions, practitioners reported that they treated a median of 10% (range, 1.0–45.5%) of patients with intermittent hemodialysis (IHD) (**Table 2**; and eTable 4, Supplemental Digital Content 1, http://links.lww.com/CCM/F64) and 6.0% (range, 0.5–60%) with "slow" forms of IHD such as sustained low-efficiency dialysis, prolonged intermittent RRT, or extended daily dialysis. The typical median UF^{NET} rate prescription was 2.0 L (IQR, 2.0–3.0; regional range, 2.0–2.5) per session. Only two third (70.0%; range, 50.0–97.5%) reported assessing prescribed-to-delivered dose of UF^{NET} with significant regional variation.

Continuous RRT. Although two third (71.0%; range, 20.0–95.5%) of practitioners indicated that they used continuous RRT (CRRT) as the first modality for UF^{NET}, there was regional variation (Table 2). Respondents from Europe and Oceania reported using CRRT in more than 90.0% of patients, whereas only 20.0% of patients in South America. For a hemodynamically stable patient, typical initial UF^{NET} prescription, as reported by practitioners, was 125.0 mL/hr (IQR, 100.0–200.0;

TABLE 1. Practitioner Characteristics, Diuretic Dose, and Criteria Used for Initiation and Prescription of Net Ultrafiltration

Characteristic	Africa (*n* = 8)	Asia (*n* = 453)	Europe (*n* = 485)	North America (*n* = 535)	Oceania (*n* = 45)	South America (*n* = 43)	All (*n* = 1,569)
Practitioner type, *n* (%)							
Intensivist	8 (100)	397 (87.6)	365 (75.3)	246 (46)	34 (75.6)	36 (83.7)	1,086 (69.2)
Nephrologist	0	14 (3.1)	4 (0.8)	11 (2.1)	1 (2.2)	2 (4.6)	32 (2.0)
Intensivist and nephrologist	0	22 (4.9)	19 (3.9)	9 (1.7)	0	5 (11.6)	55 (3.5)
Advanced practice provider	0	5 (1.1)	7 (1.4)	28 (5.2)	1 (2.2)	0	41 (2.6)
ICU nurse	0	10 (2.2)	89 (18.3)	239 (44.7)	8 (17.8)	0	346 (22.0)
Dialysis nurse	0	5 (1.1)	1 (0.2)	2 (0.4)	1 (2.2)	0	9 (0.6)
Years of practice, median (IQR)	16.8 (14.0–21.0)	13.9 (9.0–21.2)	16.3 (10.0–23.9)	9.0 (4.4–20.0)	20.0 (15.0–27.0)	15.0 (10.0–19.5)	13.2 (7.2–22.0)
Hospital type, *n* (%)							
University based	4 (50.0)	210 (46.4)	306 (63.1)	343 (64.1)	22 (48.9)	18 (41.9)	903 (57.5)
Community based	1 (12.5)	112 (24.7)	110 (22.7)	149 (27.8)	2 (4.4)	11 (25.6)	385 (24.5)
Government	3 (37.5)	96 (21.2)	42 (8.6)	28 (5.2)	18 (40.0)	7 (16.3)	194 (12.4)
Other	0	35 (7.7)	27 (5.6)	15 (2.8)	3 (6.7)	7 (16.3)	87 (5.5)
Maximum dose of loop diuretic prescribed (furosemide equivalent), mg/d,[a,b,c] *n* (%)							
< 100	0	115 (26.3)	41 (10.4)	19 (6.5)	4 (11.1)	6 (14.0)	185 (15.3)
100–250	3 (37.5)	209 (47.7)	132 (33.5)	160 (55.0)	12 (33.3)	19 (44.2)	535 (44.2)
251–500	3 (37.5)	60 (13.7)	69 (17.5)	68 (23.4)	9 (25.0)	8 (18.6)	217 (18.0)
501–750	0	14 (3.2)	25 (6.3)	9 (3.1)	1 (2.8)	2 (4.6)	51 (4.2)
751–1,000	1 (12.5)	14 (3.2)	66 (16.7)	14 (4.8)	3 (8.3)	5 (11.6)	103 (8.5)
> 1,000	1 (12.5)	11 (2.5)	30 (7.6)	5 (1.7)	1 (2.8)	1 (2.3)	49 (4.0)
Criteria used for UF^{NET} initiation,[a,c,d] *n* (%)							
Persistent oliguria/anuria (urine output < 0.5 mL/kg/hr for ≥ 12 hr)	2 (25.0)	224 (51.1)	180 (45.6)	80 (27.2)	8 (22.2)	21 (48.8)	515 (42.4)
Severe hypoxemia (Pao_2/Fio_2 ratio < 150)	0	38 (8.7)	38 (9.6)	74 (25.2)	1 (2.8)	1 (2.3)	152 (12.5)
Pulmonary edema with or without hypoxemia	3 (37.5)	72 (16.4)	66 (16.7)	39 (13.3)	7 (19.4)	7 (16.3)	194 (16.0)
Cumulative fluid balance (> 1,000 mL)	0	11 (2.5)	19 (4.8)	16 (5.4)	5 (13.9)	3 (7.0)	54 (4.4)
Fluid overload > 10% of body weight	0	15 (3.4)	21 (5.3)	19 (6.5)	2 (5.6)	3 (7.0)	60 (5.0)
Ongoing need for fluids in the presence of oliguria	2 (25.0)	50 (11.4)	26 (6.6)	23 (7.8)	3 (8.3)	2 (4.6)	106 (8.7)

(*Continued*)

TABLE 1. (*Continued*). Practitioner Characteristics, Diuretic Dose, and Criteria Used for Initiation and Prescription of Net Ultrafiltration

Characteristic	Africa (*n* = 8)	Asia (*n* = 453)	Europe (*n* = 485)	North America (*n* = 535)	Oceania (*n* = 45)	South America (*n* = 43)	All (*n* = 1,569)
Criteria used for UF^{NET} prescription,[a,d,e] *n* (%)							
24-hr fluid balance	1 (12.5)	45 (10.3)	63 (15.9)	36 (12.2)	6 (16.7)	5 (11.6)	156 (12.8)
Cumulative fluid balance	0	94 (21.5)	88 (22.3)	31 (10.5)	8 (22.2)	9 (20.9)	230 (18.9)
Weight gain	0	28 (6.4)	31 (7.8)	9 (3.1)	0	1 (2.3)	69 (5.7)
Radiographic features of fluid overload	0	16 (3.6)	7 (1.8)	6 (2.0)	0	2 (4.6)	31 (2.5)
Hemodynamic status (heart rate, blood pressure, central venous pressure, pulse pressure variation, dose of vasopressors)	6 (75)	231 (52.7)	177 (44.8)	179 (60.8)	18 (50.0)	23 (53.5)	634 (52.2)
Volume of anticipated fluid use in the next 24 hr	0	8 (1.8)	10 (2.5)	3 (1.0)	1 (2.8)	1 (2.3)	23 (1.9)
Arterial lactate	0	6 (1.4)	1 (0.2)	0	0	1 (2.3)	8 (0.7)

IQR = interquartile range, UT^{NET} = net ultrafiltration.

[a]Practitioners included intensivists, nephrologists, intensivists and nephrologists, and advanced practice providers. ICU and dialysis nurses were excluded from these questions.

[b]Practitioners include 1,210 (77.1%) from Africa (*n* = 8), Asia (*n* = 438), Europe (*n* = 394), North America (*n* = 291), Oceania (*n* = 36), and South America (*n* = 43).

[c]$p < 0.001$.

[d]Practitioners include 1,214 (77.3%) from Africa (*n* = 8), Asia (*n* = 438), Europe (*n* = 395), North America (*n* = 294), Oceania (*n* = 36), and South America (*n* = 43).

[e]$p = 0.002$.

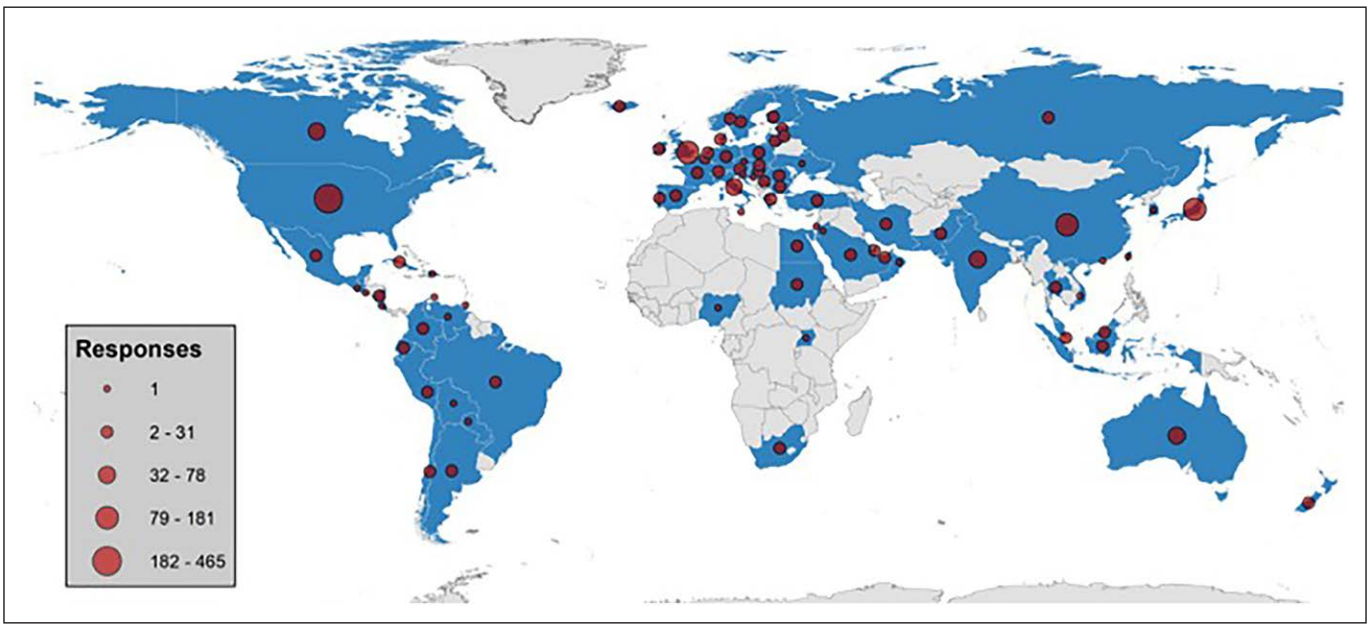

Figure 1. Geospatial distribution of survey responses. *Blue shade* represents the country of practice. *Red circles* represent the practitioners, and the size of the *circle* represents the number of practitioners per country who completed the survey. Total number of practitioners who completed the survey was 1,569.

TABLE 2. Modality of Renal Replacement Therapy, Typical Net Ultrafiltration Prescription, and Evaluation of Net Fluid Balance

Practice Characteristics	Africa (*n* = 8)	Asia (*n* = 453)	Europe (*n* = 485)	North America (*n* = 535)	Oceania (*n* = 45)	South America (*n* = 43)	All (*n* = 1,569)
IHD, median (IQR)							
Percent use in the last month[a]	45.5 (40.0–51.0)	20.0 (9.0–43.0)	5.0 (0–25.0)	10 (2.0–30.0)	1.0 (0–10.0)	29.5 (11.0–80.0)	10.0 (2.0–30.0)
Typical UF^{NET} prescription, liters per session[b]	2.5 (2.3–3.1)	2.2 (2.0–3.0)	2.0 (1.5–3.0)	2.0 (2.0–3.0)	2.2 (2.0–3.0)	2.5 (2.0–3.0)	2.0 (2.0–3.0)
Slow forms of IHD,[c] median (IQR)							
Percent use in the last month[a]	60.0 (5.0–81.0)	30.0 (6.0–64.0)	1.0 (0–20.0)	1.0 (0–20.0)	0.5 (0-20.0)	20.0 (5.0–51.0)	6.0 (0–34.0)
Typical UF^{NET} prescription, liters per session[d]	4.0 (1.5–6.0)	2.0 (1.2–3.0)	2.0 (1.0–2.9)	2.0 (1.2–3.0)	2.0 (1.5–3.0)	2.5 (1.1–3.0)	2.0 (1.1–3.0)
Percent of assessment of prescription-to-delivered UF^{NET}[a]	97.5 (88.0–100.0)	50.0 (27.0–80.0)	79.5 (21.0–100.0)	90.0 (21.0–100.0)	90.0 (12.0–100.0)	70.0 (35.0–100.0)	70.0 (25.0–100.0)
CRRT, median (IQR)							
Percent use in the last month[a]	55.0 (30.0–80.0)	66.5 (29.0–90.0)	90.0 (30.0–100.0)	60.0 (20.0–90.0)	95.5 (70.5–100.0)	20.0 (0–50.0)	71.0 (25.0–96.0)
Initial UF^{NET} rate for hemodynamically stable patient, mL/hr[a]	300.0 (204.0–301.0)	152.0 (100.0–230.0)	149.0 (100.0–200.0)	100.0 (80.0 – 200.0)	151.0 (100.0–201.0)	152.0 (105.0 – 306.0)	125.0 (100.0–200.0)
Maximal UF^{NET} rate for hemodynamically stable patient, mL/hr[e]	501.0 (500.0–502.0)	300.0 (200.0–407.0)	300.0 (201.0–352.0)	252.0 (200.0–324.0)	300.5 (251.0 – 400.0)	300.0 (201.0–403.0)	299.0 (200.0–365.0)
UF^{NET} rate for hemodynamically unstable patient, mL/hr[a]	200.0 (106.0–297.0)	99.0 (49.0–161.0)	98.0 (51.0–108.0)	51.0 (25.0–100.0)	92.5 (51.0–148.0)	100.0 (51.0–215.0)	80.0 (49.0–111.0)
Method used to achieve UF^{NET} using CRRT, *n* (%)[a]							
By varying ultrafiltration rate only	1 (25.0)	171 (42.9)	191 (41.2)	223 (47.5)	18 (42.9)	9 (40.9)	613 (43.8)
By varying replacement fluid rate only	0	22 (5.5)	32 (6.9)	17 (3.6)	9 (21.4)	0	80 (5.7)
By varying both ultrafiltration and replacement fluid rate	2 (50.0)	191 (47.9)	191 (41.2)	143 (30.5)	13 (30.9)	13 (59.1)	553 (39.5)
How frequently did you check net fluid balance during CRRT? (hr), *n* (%)[a]							
1	1 (25.0)	76 (19.0)	121 (26.1)	224 (47.8)	16 (38.1)	3 (13.7)	441 (31.5)
2	0	85 (21.3)	20 (4.3)	22 (4.7)	2 (4.8)	1 (4.5)	130 (9.3)
4	1 (25.0)	88 (22.1)	40 (8.6)	42 (9.0)	3 (7.1)	4 (18.2)	178 (12.7)
6	0	40 (10.0)	57 (12.3)	20 (4.3)	4 (9.5)	6 (27.3)	127 (9.1)
8	0	45 (11.3)	63 (13.6)	25 (5.3)	1 (2.4)	1 (4.5)	135 (9.6)
12	0	22 (5.5)	67 (14.5)	43 (9.2)	6 (14.3)	2 (9.1)	140 (10.0)
24	0	27 (6.8)	55 (11.8)	45 (9.6)	6 (14.3)	3 (13.6)	136 (9.7)

CRRT, continuous renal replacement therapy, IHD, intermittent hemodialysis, IQR = interquartile range, UF^{NET} = net ultrafiltration.

[a]$p < 0.001$.

[b]$p = 0.07$.

[c]Slow forms of IHD include sustained low-efficiency dialysis, prolonged intermittent renal replacement therapy, or extended daily dialysis.

[d]$p = 0.06$.

[e]$p = 0.19$.

range, 100.0–300.0). However, this varied across regions and also by practitioner type with physicians reporting higher rates than nurses (median rate, 149.0 vs 100.0 mL/hr; $p < 0.001$; and eTable 4, Supplemental Digital Content 1, http://links.lww.com/CCM/F64). The maximal UF^{NET} rate prescribed was 299.0 mL/hr (IQR, 200.0–365.0; range, 300.0–501.0).

For hemodynamically unstable patients, the reported median UF^{NET} rate was 80.0 mL/hr (IQR, 49.0–111.0; range, 51.0–200.0) with regional variation. Among the top eight respondent countries, the median UF^{NET} prescription was lowest in Japan (40.0 mL/hr; IQR, 0–52.0), Canada, and the United States (51.0 mL/hr; IQR, 25.0–100.0) and highest in China (169.0 mL/hr; IQR, 102.0–243.0; **Fig. 2*A***; and **eTable 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64). Across regions, physicians reported higher median rates than nurses (92.0 vs 52.0 mL/hr; $p < 0.001$). Practitioners achieved UF^{NET} by varying the ultrafiltration rate alone in 43.8% (range, 25.0–47.5%) and by varying both the ultrafiltration and replacement fluid rates in 39.5% (range, 30.5–59.1%) with regional variation.

Only one third (31.5%; range, 13.7–47.8%) of practitioners reported evaluating the net fluid balance every 1 hour. Hourly net fluid balance was evaluated only by 48.0% of practitioners in North America and 19.0% in Asia. Among the top eight respondent countries, only 51.0% of practitioners in the United States and the United Kingdom, 40.5% in Australia, and 5.3% in Italy evaluated hourly fluid balance. Physicians evaluated less frequently than nurses (19.2% vs 66.9%; $p < 0.001$) (eTable 4 and **eFig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64).

Hemodynamic Instability and Its Management

Practitioners reported new hemodynamic instability as characterized by onset or worsening of tachycardia, hypotension, or a need to start or increase the dose of vasopressors in 20.0% of patients (range, 20.0–38.0%; **Table 3**). When hemodynamic instability occurred, two third of practitioners (70.3%; range, 60.4–75.0%) reported that they decreased the rate of fluid removal; half (51.5%; range, 37.5–57.2%) started a new or increased the dose of a vasopressor; one third (35.8%; range, 25.0–43.5%) completely stopped fluid removal, and a third (31.6%; range, 25.0–36.5%) administered a fluid bolus with significant regional variation.

Compared with physicians, nurses were more likely to report the following interventions: decrease fluid removal

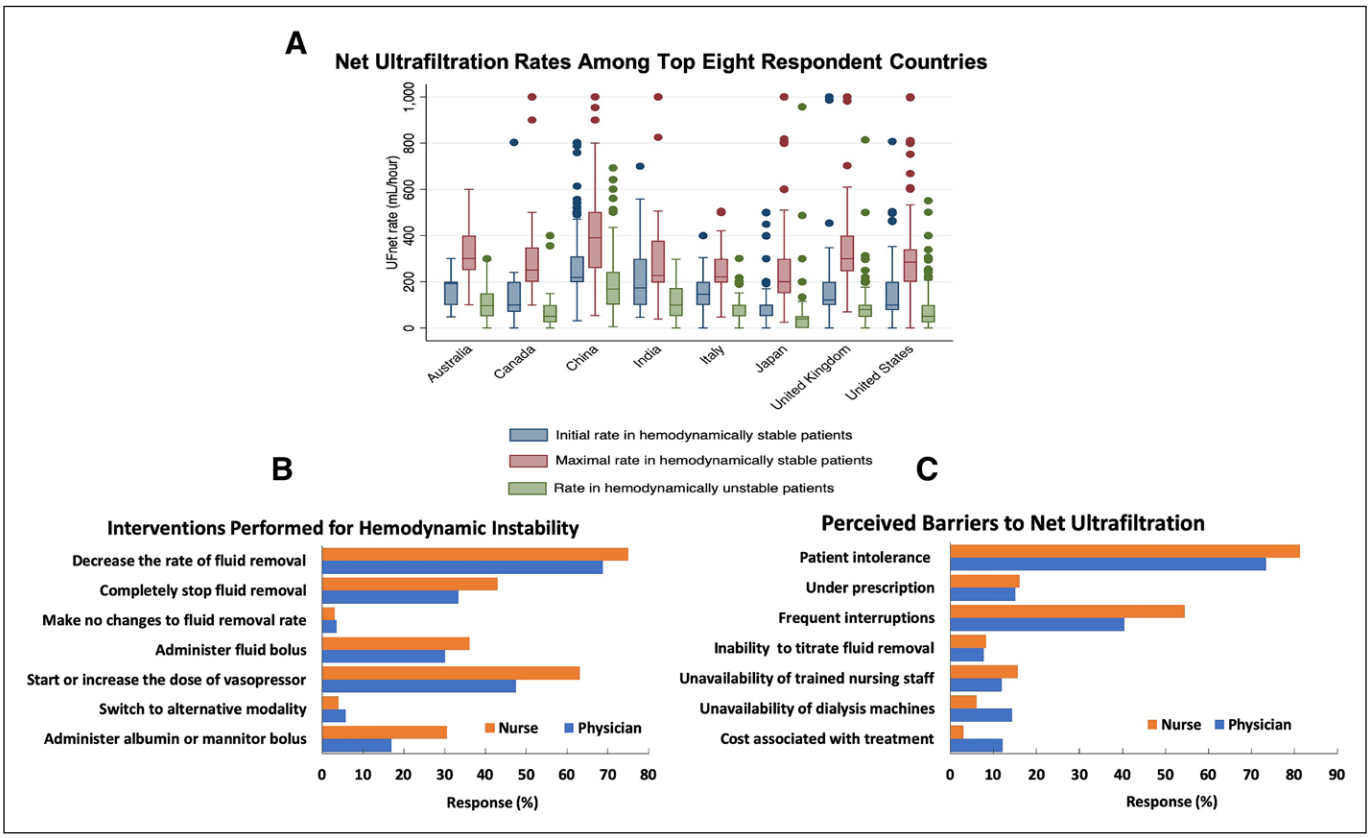

Figure 2. Net ultrafiltration rates and attitudes by practitioner type. **A**, Boxplot summaries of initial and maximal net ultrafiltration rates for hemodynamically stable patients and typical net ultrafiltration rates for hemodynamically unstable patients for the top eight respondent countries. The *vertical box* represents the 25th percentile (*bottom line*), median (*middle line*), and 75th percentile (*top line*) values. The lowest datum (*lower whisker*) represents 1.5 times the interquartile range of the lower quartile, and the highest datum (*upper whisker*) represents 1.5 times the interquartile range of the upper quartile. *Circles* represent outliers. Net ultrafiltration rates varied significantly across countries ($p < 0.001$ for all three groups). **B**, Interventions performed for hemodynamic instability during net ultrafiltration. Compared with physicians, nurses were more likely to cite interventions such as decrease or stop fluid removal, administer a fluid bolus, start or increase the dose of vasopressors, or administer albumin or mannitol bolus ($p < 0.05$ for all responses). **C**, Perceptions related to barriers for successful implementation of net ultrafiltration. Compared with physicians, nurses were more likely to cite barriers such as patient intolerance, frequent interruptions, and unavailability of trained staff ($p < 0.05$ for all responses), whereas physicians were more likely to cite unavailability of dialysis machines and cost ($p < 0.001$).

TABLE 3. Hemodynamic Instability, Interventions Performed, and Perceived Barriers to Net Ultrafiltration

Practice Characteristics	Africa (*n* = 8)	Asia (*n* = 453)	Europe (*n* = 485)	North America (*n* = 535)	Oceania (*n* = 45)	South America (*n* = 43)	All (*n* = 1,569)
Percentage of patients developing new hemodynamic instability during UF^{NET},[a] median (IQR)	38.0 (20.0–50.0)	25.0 (10.0–40.0)	20.0 (10.0–30.0)	25.0 (10.0–41.0)	20.0 (10.0–25.0)	30.0 (17.5–50.0)	20.0 (10.0–35.0)
Interventions performed for hemodynamic instability,[b] *n* (%)							
Decrease the rate of fluid removal[a]	6 (75.0)	320 (70.6)	340 (70.1)	379 (70.8)	32 (71.1)	26 (60.4)	1,103 (70.3)
Completely stop fluid removal[a]	2 (25.0)	139 (30.6)	164 (33.8)	233 (43.5)	13 (28.8)	11 (25.6)	562 (35.8)
Make no changes to fluid removal rate[c]	0	11 (2.4)	18 (3.7)	19 (3.5)	5 (11.1)	0	52 (3.3)
Administer a fluid bolus[d]	2 (25.0)	131 (28.9)	177 (36.5)	158 (29.5)	14 (31.1)	14 (32.5)	496 (31.6)
Start or increase the dose of a vasopressor[e]	3 (37.5)	204 (45.0)	249 (51.3)	306 (57.2)	24 (53.3)	22 (51.2)	808 (51.5)
Switch to alternative modality[f]	0	27 (5.9)	16 (3.3)	31 (5.8)	3 (6.6)	6 (13.9)	83 (5.3)
Administer albumin or mannitol bolus[a]	0	62 (13.6)	65 (13.4)	174 (32.5)	12 (26.7)	6 (13.9)	319 (20.3)
Perceived barriers to UF^{NET},[b] *n* (%)							
Patient intolerance (e.g., hypotension)[a]	6 (75.0)	336 (74.1)	352 (72.6)	425 (79.4)	34 (75.5)	31 (72.1)	1,184 (75.4)
Under prescription[g]	3 (37.5)	55 (12.1)	74 (15.2)	94 (17.5)	13 (28.9)	2 (4.6)	241 (15.3)
Frequent interruptions (e.g., trip to CT scan, operating room, filter clotting, catheter malfunction)[a]	3 (37.5)	164 (36.2)	220 (45.3)	263 (49.1)	32 (71.1)	8 (18.6)	690 (44)
Inability to titrate fluid removal[h]	0	41 (9.0)	22 (4.5)	52 (9.7)	4 (8.9)	5 (11.6)	124 (7.9)
Unavailability of adequately trained nursing staff[i]	3 (37.5)	67 (14.7)	36 (7.4)	89 (16.6)	1 (2.2)	6 (14.0)	202 (12.8)
Unavailability of dialysis machines[j]	2 (25.0)	101 (22.2)	30 (6.2)	50 (9.1)	0	9 (21.0)	192 (12.2)
Cost associated with treatment[a]	2 (25.0)	110 (24.2)	23 (4.7)	16 (3.0)	0	3 (6.9)	154 (9.8)

IQR = interquartile range, UF^{NET} = net ultrafiltration.
[a]$p < 0.001$.
[b]Multiple responses possible.
[c]$p = 0.30$.
[d]$p = 0.04$.
[e]$p = 0.002$.
[f]$p = 0.04$.
[g]$p = 0.21$.
[h]$p = 0.83$.
[i]$p = 0.04$.
[j]$p = 0.01$.

rate (68.7% vs 75.0%; $p = 0.01$); stop fluid removal (42.9% vs 33.4%; $p = 0.001$); administer fluid bolus (36.1% vs 30.1%; $p = 0.02$); start or increase vasopressor dose (63.1% vs 47.5%; $p < 0.001$); and administer albumin or mannitol bolus (30.6% vs 16.9%; $p < 0.001$) (**Fig. 2*B***; and **eTable 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64).

Perceived Barriers to UF^{NET}

Patient intolerance, as reported by practitioners, was the most common barrier (75.4%; range, 72.1–79.4%) followed by frequent interruptions (44.0%; range, 18.6–71.1%) and under prescription of UF^{NET} (15.3%; range, 4.6–37.5%). Compared with physicians, nurses were most likely to report patient intolerance (73.4% vs 81.3%; $p = 0.002$),

interruptions (40.4% vs 54.5%; $p < 0.001$), and unavailability of staff (11.9% vs 15.6%; $p = 0.04$), whereas physicians reported unavailability of dialysis machines (14.3% vs 6.1%; $p < 0.001$) and cost as barriers (12.1% vs 3.0%; $p < 0.001$) (**Fig. 2*C***; and eTable 6, Supplemental Digital Content 1, http://links.lww.com/CCM/F64).

Across regions, there was variation in perceived barriers (Table 3). For instance, unavailability of trained nursing staff was a barrier in China (25.3%), India (15.7%), and the United States (16.6%), and unavailability of dialysis machines in china (29.7), Japan (20.0%), United Kingdom (17.2%), and India (17.6%). Whereas, cost was a barrier in China (46.8%) and India (27.4%).

Attitudes Related to Timing, Use of Protocol, and Enrolling Patients in a Clinical Trial of Protocol-Based UF^{NET}

Across regions, most practitioners (90.0%; range, 84.5–91.7%) agreed that early UF^{NET} would be beneficial (**eTables 7** and **8** and **eFig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64), and a protocol (81.4%; range, 62.3–88.3%) outlining the rate, volume, and duration of UF^{NET} would be useful, with significant regional variation. Although two thirds (78.3%; range, 72.7–83.7%) indicated that they would be agreeable to enroll patients in a clinical trial comparing protocol-based UF^{NET} versus usual care with physicians more willing to enroll than nurses (82.3% vs 66.1%; $p < 0.001$) (eFig. 2*B*, Supplemental Digital Content 1, http://links.lww.com/CCM/F64).

Thematic Analysis of Comments

Of 1,173 physicians and 396 nurses, 355 (30.3%) and 103 (26.0%) provided comments. Thematic analysis revealed five common themes (**eTable 9**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64) including tools to facilitate UF^{NET}, organizational-, clinician-, patient-, and RRT-related factors. Of these, prescription-related factors (9.8%) and the use of functional hemodynamic monitoring (8.7%) were predominant themes. Several comments also revealed suggestions for research and quality improvement initiatives (**eTable 10**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64). Lexical analysis revealed top five nonconjunctive terms: "fluid" (168 words), "patient" (132), "removal" (93), "CRRT" (78), and "treatment" (42) (**eFig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F64).

DISCUSSION

In this multinational survey, we found significant regional variation in diuretic dosing, criteria used for initiation and prescription of UF^{NET}, modality of RRT, assessment of prescribed-to-delivered dose during IHD, rate of UF^{NET} during CRRT, evaluation of net fluid balance and method used to achieve UF^{NET}, frequency and management of hemodynamic instability, perceived barriers, benefit of using a protocol, and willingness to enroll in a clinical trial of protocol-based UF^{NET} versus usual care.

There was also variation in practice as reported by physicians and nurses. Physicians reported higher UF^{NET} rates, whereas nurses reported higher interventions for managing hemodynamic instability. Nurses reported patient intolerance, frequent interruptions, and unavailability of staff as barriers, whereas physicians reported unavailability of dialysis machines and cost. Physicians were more willing to enroll patients in clinical trials. Thematic analysis revealed predominantly prescription-related issues and the need for functional hemodynamic monitoring to guide UF^{NET}.

Our survey findings have several implications. First, understanding and addressing practice variation in UF^{NET} are important because it might be associated with poor outcomes. Practice variation in other ICU care processes such as mechanical ventilation and sedation use has been associated with poor outcomes, and interventions to reduce practice variation have resulted in improved outcomes (17, 18). Second, we found suboptimal practice patterns such as infrequent assessment of net fluid balance during CRRT; use of high UF^{NET} rates, which has been associated with poor outcomes; and barriers such as frequent interruptions, lack of trained staff, unavailability of dialysis machines, and cost. By increasing clinician awareness about these issues, our survey is likely to result in quality improvement initiatives. Third, by providing normative data on practice patterns, our survey will inform future trial design and aid development of evidence-based guidelines.

Although most practitioners used CRRT, there was variation in prescription of rate of UF^{NET}. Unlike prescription for solute clearance, the optimal rate of UF^{NET} for critically ill patients is unclear and one recent observational study found that UF^{NET} rate greater than 1.75 mL/kg/hr was associated with increased risk of mortality compared with rate less than 1.01 mL/kg/hr (8), whereas other study found that rate greater than 25 mL/kg/d compared with rate less than 20 mL/kg/d was associated with lower mortality (7). These differential findings suggest a need for clinical trials to determine optimal UF^{NET} rate in various patient populations. Furthermore, there was a discrepancy between the prescribed-to-delivered dose of UF^{NET} rate between physicians and nurses with nurses reporting lower rates. This finding may either represent true challenges to implementing the prescribed UF^{NET} rates due to various reasons (e.g., hemodynamic instability). Only one third of practitioners assessed hourly net fluid balance during CRRT with significant variation among practitioners with respect to timing of assessment of net fluid balance, which may be due to lack of evidence-based guidelines and constraints related to staffing.

Practitioners used a multipronged approach to tackle hemodynamic instability with wide variation in practice, which has also been noted in prior studies (19). Such variation might be attributable to the absence of robust evidence to support treatment recommendations among critically ill patients. This is in stark contrast to the management of dialysis in the long-term setting, where there are well-established practice guidelines (20). Aside from patient intolerance, the most common barrier to achieving the target UF^{NET} was interruptions,

unavailability of adequately trained staff, dialysis machines, and cost, a finding consistent with other studies (21, 22).

Practitioners favored early UF^{NET} despite lack of evidence for such practice. Although FO was the main reason for starting RRT among those allocated to the late arms of several randomized trials that examined the timing of initiation of RRT (23–25), none exclusively examined timing with respect to initiation of UF^{NET}. Although many practitioners believed that a protocol would be beneficial, thematic analysis revealed that practitioners preferred use of functional hemodynamic monitoring and precision medicine approaches to individualize UF^{NET}. Thus, further research is required to examine and validate functional hemodynamic monitoring and other approaches such as lactate to guide UF^{NET}. Nevertheless, the majority of practitioners were willing to enroll patients in a clinical trial of protocol-based UF^{NET}.

Our study has limitations. First, we were unable to determine the precise response rate as practitioners belonged to multiple societies and we were unable to track individual identities as well as due to challenges in conducting a web-based multinational survey. Thus, there is a potential for selection bias due to nonrespondents. Nevertheless, our survey is the first to explore the international practice variation in UF^{NET}. Second, the practitioners were mostly intensivists and ICU nurses; thus, we were unable to compare the responses with nephrologists and dialysis nurses, who may have different perspectives. Third, an inherent limitation of "self-reporting" is that the reliability of individual responses cannot be ensured and there is a possibility of multiple similar responses from several participants from the same institution as well as potential for recall bias.

Fourth, the higher number of responses collected from some countries potentially reflect the care practices in those specific countries rather than the continent. Fifth, we did not study practice patterns in specific patient populations such as those on extracorporeal membrane oxygenation, medical/surgical patients, or those with varying degrees of FO because our goal was to describe most common practice patterns in the ICU. Despite these limitations, this survey provides insight into the UF^{NET} prescription and practice, which may help plan future research and quality implementation initiatives.

CONCLUSIONS

In this multinational survey, we found significant regional variation in prescription and practice of UF^{NET}, which may be partly due to the absence of evidence-based recommendations and guidelines. Thus, there remains a compelling need for further research to generate evidence to define best practices that improve patient outcomes and subsequently, interventions that reduce variation in practice.

ACKNOWLEDGMENTS

We thank the following international societies who helped in the dissemination of the surveys to its members: The Australian and New Zealand Intensive Care Society, The American Association of Critical Care Nursing, The British Association of Critical Care Nurses, The Canadian Critical Care Society, The Chinese Society of Critical Care Medicine, The European Society of Intensive Care Medicine, The Indian Society of Critical Care Medicine, The Italian Society of Intensive Care, The Italian Society of Nephrology, The Japanese Society of Critical Care Medicine, The National Kidney Foundation, The Society of Critical Care Medicine, The Thailand Society of Critical Care Medicine, and the U.K. Comprehensive Local Research Network. We also thank the intensivists, nephrologists, trainees, ICU and dialysis nurses, and advanced practice providers who contributed to this survey and David Wallace who contributed to the geospatial figure.

REFERENCES

1. Balakumar V, Murugan R, Sileanu FE, et al: Both positive and negative fluid balance may be associated with reduced long-term survival in the critically ill. *Crit Care Med* 2017; 45:e749–e757
2. Garzotto F, Ostermann M, Martín-Langerwerf D, et al; DoReMIFA study group: The Dose Response Multicentre Investigation on Fluid Assessment (DoReMIFA) in critically ill patients. *Crit Care* 2016; 20:196
3. Bouchard J, Soroko SB, Chertow GM, et al; Program to Improve Care in Acute Renal Disease (PICARD) Study Group: Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; 76:422–427
4. Payen D, de Pont AC, Sakr Y, et al; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators: A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008; 12:R74
5. Bellomo R, Cass A, Cole L, et al; RENAL Replacement Therapy Study Investigators: An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial. *Crit Care Med* 2012; 40:1753–1760
6. Kidney Disease Improving Global Outcomes (KDIGO): Clinical practice guideline for acute kidney injury. *Kidney Int* 2012; 2(Suppl):1–138
7. Murugan R, Balakumar V, Kerti SJ, et al: Net ultrafiltration intensity and mortality in critically ill patients with fluid overload. *Crit Care* 2018; 22:223
8. Murugan R, Kerti SJ, Chang CH, et al: Association of net ultrafiltration rate with mortality among critically ill adults with acute kidney injury receiving continuous venovenous hemodiafiltration: A secondary analysis of the Randomized Evaluation of Normal vs Augmented Level (RENAL) of renal replacement therapy trial. *JAMA Netw Open* 2019; 2:e195418
9. Flythe JE, Kimmel SE, Brunelli SM: Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. *Kidney Int* 2011; 79:250–257
10. Kim TW, Chang TI, Kim TH, et al: Association of ultrafiltration rate with mortality in incident hemodialysis patients. *Nephron* 2018; 139:13–22
11. Movilli E, Gaggia P, Zubani R, et al: Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. *Nephrol Dial Transplant* 2007; 22:3547–3552
12. Saran R, Bragg-Gresham JL, Levin NW, et al: Longer treatment time and slower ultrafiltration in hemodialysis: Associations with reduced mortality in the DOPPS. *Kidney Int* 2006; 69:1222–1228
13. Burns KE, Duffett M, Kho ME, et al; ACCADEMY Group: A guide for the design and conduct of self-administered surveys of clinicians. *CMAJ* 2008; 179:245–252
14. Burns KEA, Kho ME: How to assess a survey report: A guide for readers and peer reviewers. *CMAJ* 2015; 187:E198–E205
15. Eysenbach G: Improving the quality of Web surveys: The Checklist for Reporting Results of Internet E-Surveys (CHERRIES). *J Med Internet Res* 2004; 6:e34
16. Braun V, Clarke V: What can "thematic analysis" offer health and wellbeing researchers? *Int J Qual Stud Health Well-being* 2014; 9:26152

17. Jackson DL, Proudfoot CW, Cann KF, et al: A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. *Crit Care* 2010; 14:R59
18. Young MP, Manning HL, Wilson DL, et al: Ventilation of patients with acute lung injury and acute respiratory distress syndrome: Has new evidence changed clinical practice? *Crit Care Med* 2004; 32: 1260–1265
19. Douvris A, Malhi G, Hiremath S, et al: Interventions to prevent hemodynamic instability during renal replacement therapy in critically ill patients: A systematic review. *Crit Care* 2018; 22:41
20. National Kidney F: KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis* 2015; 66:884–930
21. Chua HR, Baldwin I, Bailey M, et al: Circuit lifespan during continuous renal replacement therapy for combined liver and kidney failure. *J Crit Care* 2012; 27:744.e7–744.15
22. Uchino S, Fealy N, Baldwin I, et al: Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. *Intensive Care Med* 2003; 29:575–578
23. Barbar SD, Clere-Jehl R, Bourredjem A, et al; IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network: Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018; 379:1431–1442
24. Gaudry S, Hajage D, Schortgen F, et al; AKIKI Study Group: Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016; 375:122–133
25. Zarbock A, Kellum JA, Schmidt C, et al: Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. *JAMA* 2016; 315:2190–2199