Optimizing continuous renal replacement therapy in the ICU

Nurmohamed, S.A.

2012

Chapter 5

Delivered dose of continuous venovenous hemofiltration predicts outcome in septic patients with acute kidney injury: a retrospective study

S.A. Nurmohamed

M.V. Koning

M.G. Vervloet

A.B.J. Groeneveld

J Crit Care

2011; 26(2):213-220

Abstract

Purpose. In continuous venovenous hemofiltration (CVVH) issues like timing and dose remain controversial, particularly in sepsis. The objective of this study is to examine which CVVH characteristic best predicts mortality in sepsis-induced acute kidney injury (AKI).

Materials and methods. We retrospectively studied all consecutive patients with sepsis-induced AKI requiring CVVH in a 1.5-year period. Patient, sepsis and CVVH characteristics, including timing, dose, mode, type of substitution fluid and of anticoagulation, and azotemic control were evaluated. Primary outcome was survival at day 28 after start of CVVH.

Results. Of the 97 patients, 43 (44%) died up to day 28 after start of CVVH. In univariate analyses, the delivered dose of CVVH was about 10% higher in survivors than non-survivors (median 23 vs 20 mL/kg/h, P=0.01). In multivariate analyses, a lower delivered CVVH dose contributed to predict higher mortality, independently of disease severity, type of substitution fluid and azotemic control. In a Kaplan-Meier curve, a delivered dose <19.7 mL/kg/h was associated with shorter survival (P=0.006).

Conclusion. Our retrospective data suggest that in sepsis-induced AKI requiring CVVH, delivered dose, rather than timing, mode of administration and azotemic control is an independent predictor of mortality. A lower delivered dose is associated with higher mortality.

Keywords

- acute kidney injury - azotemic control - continuous renal replacement therapy - dose - mortality - sepsis

Introduction

The incidence of acute kidney injury (AKI) in the intensive care unit (ICU) varies from 1-25% with a hospital mortality of 28-90%.[1,2] While the leading cause of AKI is sepsis, AKI independently contributes to morbidity and mortality.[1-4] In European ICU's, some form of continuous renal replacement therapy is often applied for stage 3 AKI, mostly continuous venovenous hemofiltration (CVVH).[5-8] There is, however, ongoing controversy on optimal timing, dose and modality of CVVH, the role of azotemic and fluid control, the type of substitution fluid, and of the anticoagulants needed to keep the filter open, particularly in sepsis.[9-16] Not only the optimum upper dose but also the minimum allowable one is not well established. Furthermore, even in the large observational studies and prospective randomized clinical trials on CVVH, sepsis and non-sepsis were lumped together.[6,8,17-19] However, the randomized clinical trials conducted by Ronco et al. and the Australia and New Zealand Intensive Care Society clinical trials group suggest in post hoc analyses that septic patients may particularly benefit from high (vs standard) dose CVVH,[6,18] though these findings did not reach significance. Although septic shock as a non-renal indication for (early) initiation of (high-dose) CVVH is highly controversial, observational studies suggest some hemodynamic benefit.[5,7,20,21] The mechanisms remain unclear, however. In a meta-analysis of prospective studies, high-intensity renal replacement therapy did not confer a survival benefit in sepsis.[15]

The objective of the current study is to retrospectively examine if CVVH characteristics are associated with mortality, in critically ill patients with sepsis-induced AKI. Our hypothesis is that dose rather than timing of CVVH is a determinant of outcome of septic AKI.

Materials and methods

All consecutive patients admitted in the 30-bed adult and mixed ICU of our university hospital with AKI treated by CVVH between November 2004 and January 2006 were retrospectively studied. Patients were included in the study if fulfilling sepsis criteria within a 48 hours window of start of CVVH. Sepsis was defined as the presence of an infection combined with two of the following conditions: temperature >38.0 °C or <36.0 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min or mechanical ventilation, and white blood cell count >12.0 $x10^9$/L or <4.0 $x10^9$/L.[22]

Treatment protocol. In our ICU, CVVH is started by treating intensivists and consulting nephrologists on the basis of standard clinical guidelines including AKI with hemodynamic instability, ongoing hypercatabolism, hyperkalemia, severe acidosis, diuretic-resistant volume overload, respiratory distress, multi-organ failure, or some combinations of these factors. In order to warrant filter patency, patients are treated per protocol by heparin in order to reach an activated partial thromboplastin time (aPTT) between 55-65 seconds. Patients with an increased bleeding risk (defined as a platelet count below 40 $x10^9$/L, or an activated partial thromboplastin time (aPTT) of more than 60 seconds or a prothrombin time test (PT-INR) of more than 2.0, a recent major bleeding or significant active bleeding) are treated with regional anticoagulation with citrate-buffered substitution fluid.[23] Patients are routinely treated by CVVH with lactate-buffered substitution fluid, usually in predilution mode. In case of severe lactic acidosis (plasma lactate >5 mmol/L) bicarbonate-buffered solution is preferred. The composition of the different substitution fluids is outlined in Table 1.

Table 1. Composition of substitution fluids.

	BH 504®	HF 32 Bic®	HF CitPre®
Sodium	140	140	139.9
Potassium	1.5	2.0	3.0
Magnesium	0.5	0.5	0.5
Calcium	1.5	1.75	-
Chloride	103	111.5	104.0
Glucose	11.0	1.0	5.0
Citrate	-	-	13.3
Bicarbonate	-	32.0	-
Lactate	42.0	3.0	-

In mmol/L.

CVVH was performed using a hemofiltration machine (Diapact™, B.Braun, Melsungen, Germany). Vascular access was secured by inserting an 11-French double lumen catheter (GamCath, Gambro, Hechingen, Germany) into one of the large veins (jugular, femoral or subclavian). In all patients, a 1.9 m^2 highly permeable cellulose triacetate hemofilter was used (Nipro UF205, Nissho corporation, Osaka, Japan). Filters were routinely changed after 72 hours. Blood flow and flow of lactate- or bicarbonate-buffered substitution fluid were routinely set at 180 mL/min and 2 L/h, respectively, with the ultrafiltrate flow set by treating physicians. When using citrate-buffered substitution fluid, the blood and substitution fluid flows were set per protocol at 180 mL/min and 2.4 L/h, respectively. CVVH was discontinued at the discretion of treating physicians and patients were otherwise treated according to institutional guidelines.

Patients were monitored with help of daily determinations in plasma of creatinine, urea, blood gas analysis and pH. A multichannel analyzer was used to measure creatinine and urea (Hitachi Modular P800, Roche Diagnostics, Mannheim, Germany). Blood gas analysis was performed on the ICU using a Bayer RapidLab 865 Blood Gas Analyser (Bayer, Leverkusen, Germany), or in the hospitals clinical laboratory, using a Radiometer ABL800 Flex (Radiometer, Copenhagen, Denmark). When needing renal replacement therapy after discharge from the ICU, patients received intermittent hemodialysis.

All patients diagnosed with sepsis received standard supportive treatment, including prompt fluid resuscitation, vasoactive drugs, mechanical ventilation and empirical antimicrobial therapy, which was chosen by the attending intensivist. Intravenous hydrocortisone was used in patients in septic shock who, despite fluid replacement, required vasopressor agents. The culture results were used to guide antibiotic prescriptions.

Data collection. We designed a predefined checklist for this retrospective study. Our ICU has an electronic patient file where patients' details are stored. Baseline characteristics were retrieved, including age, gender, weight, height (to calculate body mass index, BMI, kg/m^2), co-morbidity, and date and reason of admission. Co-morbid conditions were defined as follows: hypertension: a diagnosis of hypertension mentioned in the medical record or the use of blood pressure lowering agents; diabetes mellitus: a diagnosis of diabetes mellitus mentioned in the medical record or the use of insulin or oral glucose lowering agents; chronic renal failure: a diagnosis of chronic renal failure mentioned in the medical record, without the need of renal replacement therapy (stages 1-4 chronic kidney disease); coronary artery disease: a prior diagnosis of coronary artery disease or history of angina pectoris or myocardial infarction any time in the past or a history of percutaneous coronary intervention or coronary artery bypass grafting; chronic obstructive pulmonary disease: a diagnosis of chronic obstructive pulmonary disease mentioned in the medical record or the use of medication for this indication. The reasons of ICU admission were grouped in six major categories: respiratory insufficiency, septic shock, gastrointestinal surgery, cardiac surgery, aortic repair and congestive heart failure. The defining criteria for sepsis were retrieved. The infection site was recorded as well as the presence of bacteremia. The isolated micro-organisms were grouped in the following categories: Gram-positive and –negative cocci, Gram-positive and –negative rods, anaerobes, yeasts, fungi and miscellaneous. A severity of illness score at the time of ICU admission was generated by the acute physiology and chronic health evaluation (APACHE II). The sequential organ failure assessment (SOFA) score was obtained at admission and at the day of start

CVVH.[1] Data concerning timing of start of CVVH were retrieved; this included plasma creatinine, urea, potassium, pH, diuresis in the 24 h before start CVVH expressed as mL/h and as mL/kg body weight and AKI stage according to the AKI network classification at initiation of CVVH.[24] Also recorded were the following CVVH characteristics: the mode of CVVH (pre- or postdilution), blood flow, substitution flow, ultrafiltration flow, type of substitution fluid and of anticoagulation, filter life of all filters used, the hours of actually performed CVVH, downtime, prescribed and delivered dose. Downtime was defined as the interval that CVVH was prescribed but not applied as a result of circuit clotting or as a result of transport to radiology or operating room. The prescribed dose was defined as the ultrafiltration volume (substitution volume + net ultrafiltrate) delivered per kg preadmission body weight per hour for the total duration of CVVH. For predilution, the ultrafiltration flow per hour (Quf) was adjusted by the following formula:

$$\frac{[Qb \times 60 \times (1\text{-}Hct)]}{[(Qb \times 60 \times (1\text{-}Hct)) + Qs]} \times Quf,$$

where Qb = blood flow, mL per minute and Qs = substitution flow, mL per hour and Hct = hematocrit.

The delivered dose was calculated, by adjusting prescribed dose for downtime. The initial episode of CVVH was defined by the interval upon the first 48 h delay in clinically indicated reinstitution of CVVH treatment. The need for CVVH was considered abated when a patient had an unchanged or decreasing plasma creatinine during 48 hours after discontinuation of CVVH. The mean of data concerning filter life, down time, flow rates and dose were calculated for each patient per episode and for all episodes together, as well as the percentage use of predilution CVVH, heparin and the different substitution fluids. Azotemic control was determined by evaluating the baseline, highest and lowest (and their difference, reported as changes) levels of plasma creatinine and urea during CVVH.

Statistical analysis. A power analysis was not performed for this retrospective analysis, but we estimated a mortality rate of 50% for the population in the study interval. The data were often non-normally distributed (Kolmogorov-Smirnov test $P<0.05$) and values are therefore summarized as median±interquartile range (IQR). The Mann-Whitney U test was used for continuous variables. For categorical data, the Fisher's exact test was used. A receiver operating

characteristic (ROC) curve was made and the area under the curve (AUC) assessed to find the CVVH dose with the highest combined sensitivity and specificity for predicting mortality. We performed multiple logistic regression using backward elimination to assess the independent value of delivered dose to predict 28-day mortality, including variables reaching statistical significance in univariate analyses ($P<0.05$). The odds ratio and its 95% confidence interval (CI) were calculated. The Hosmer-Lemeshow test was done to assess goodness-of-fit of the model. Similarly, we performed multiple proportional hazards (Cox) regression analysis for survival time and calculated hazard ratios (95% CI). We did not include filter time, a major determinant of delivered dose, but included changes in creatinine to adjust for azotemic control and body weight in these models. The Spearman correlation coefficient r_s was used to describe relations. Exact P values are given, if >0.005, and considered statistically significant if <0.05.

Results

Patient and sepsis characteristics. In the study period, 199 patients were treated by CVVH and 97 were identified as having sepsis. There were 54 (56%) survivors and 43 (44%) non-survivors until day 28 in the ICU or hospital (n=1). Six patients died after day 28, yielding 55% hospital mortality, and 3 of them died after discharge from the ICU. There were 9 survivors who left the ICU, in 1 patient at day 32 after start of CVVH, and needed intermittent hemodialysis thereafter. The baseline characteristics are outlined in Table 2. The non-survivors had a higher body weight and BMI and more organ failures than survivors. There were no differences in sepsis-defining variables between groups (Table 3).

CVVH. The timing of initiation of CVVH was similar as judged from baseline azotemia, potassium levels and pH (Table 4). At the start, the non-survivors had less residual diuresis, however. We report variables for the total CVVH treatment and its first episode, since only 9 survivors and 2 non-survivors had a second episode of CVVH (Table 5). In only 2 patients the total time on CVVH, including down time, exceeded 28 days. In non-survivors, lactate-buffered substitution fluid was used less and bicarbonate-buffered fluid was used more often. As compared to non-survivors, survivors had a longer filter life, longer duration of CVVH, and higher prescribed and delivered dose. Delivered dose related to filter life ($r_s=0.27$, $P=0.01$). The AUC of the ROC curve for prediction of 28-day mortality by delivered dose was 0.65 ($P=0.01$) and the optimum cut off of the dose was 19.7 mL/kg/h. Fig. 1 shows that above and below this dose, survival duration differed. Survivors had a greater decrease in plasma creatinine level than

the non-survivors (Table 4). The plasma urea attained was also lower in survivors. The change in creatinine and urea related to the dose of CVVH multiplied by its duration: r_s=0.33-0.48, P<0.005.

Table 2. Patient characteristics according to day 28 outcome.

	Survivors n=54	Non-survivors n=43	P
Age, year	68 ± 28	70 ± 19	0.49
Gender, male/female	34 (63)/20 (37)	29 (67)/14 (33)	0.67
Weight, kg	75 ± 13	80 ± 20	0.01
Body mass index, kg/m^2	24.2 ± 4.6	26.2 ± 5.3	0.01
Co-morbidity			
Hypertension	23 (43)	16 (37)	0.68
Diabetes mellitus	14 (26)	9 (21)	0.36
CRF	9 (17)	6 (14)	0.78
CAD	6 (11)	3 (7)	0.73
COPD	3 (6)	3 (7)	1.00
Other	14 (26)	17 (40)	0.21
APACHE II	26.5 ± 6.0	28.0 ± 11.0	0.13
Elective admission to ICU	19 (35)	23 (54)	0.10
Reason of admission to ICU			
Respiratory insufficiency	30 (55)	33 (77)	0.04
Septic shock	27 (50)	23 (54)	0.84
Gastro-intestinal surgery	7 (13)	2 (5)	0.29
Cardiac surgery	3 (6)	3 (7)	1.00
Aortic repair	4 (7)	3 (7)	1.00
Congestive heart failure	4 (7)	5 (12)	0.50
Mechanical ventilation within 24 h	49 (91)	42 (98)	0.16
Vasopressors within 24 h	39 (72)	35 (81)	0.34
Lactate within 24 h, mmol/L	2.7 ± 2.4	3.2 ± 5.1	0.08
SOFA within 24 h	10.0 ± 4.0	12.0 ± 4.0	<0.005
Length of stay in hospital, d	23.5 ± 27.0	9.0 ± 17.0	<0.005

Median ± interquartile range or number (percentage) of patients, where appropriate. CRF: chronic renal failure; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; APACHE: acute physiology and chronic health evaluation; ICU: intensive care unit; SOFA: sequential organ failure assessment.

Table 3. Sepsis characteristics according to day 28 outcome.

	Survivors n=54	Non-survivors n=43	P
ICU-acquired sepsis	15 (28)	7 (16)	0.46
Temperature, °C	36.0 ± 3.2	36.1 ± 3.6	0.63
Heart rate, bpm	113 ± 30	108 ± 31	0.96
Respiratory rate, bpm	24.5 ± 6.2	25.0 ± 6.0	0.81
Leukocytes, 10^9/L	16.9 ± 14.2	16.5 ± 11.2	0.72
Focus			
Lung	18 (33)	17 (40)	0.53
Gastro-intestinal tract	10 (19)	6 (14)	0.55
Urinary tract	7 (13)	2 (5)	0.16
Soft tissue and bone	8 (15)	7 (16)	0.85
Miscellaneous	5 (9)	4 (9)	0.99
Unknown	6 (11)	7 (16)	0.46
Microorganism			
Gram-positive cocci	27 (50)	20 (47)	0.65
Gram-negative cocci	1 (2)	1 (2)	0.87
Gram-negative rods	19 (34)	9 (21)	0.13
Yeasts	8 (15)	3 (7)	0.21
Fungi	0	2 (5)	0.11
Anaerobes	7 (13)	3 (7)	0.34
Miscellaneous	7 (13)	3 (7)	0.33
Bacteremia	19 (35)	20 (47)	0.26

Median ± interquartile range or numbers (percentage), where appropriate. ICU: intensive care unit.

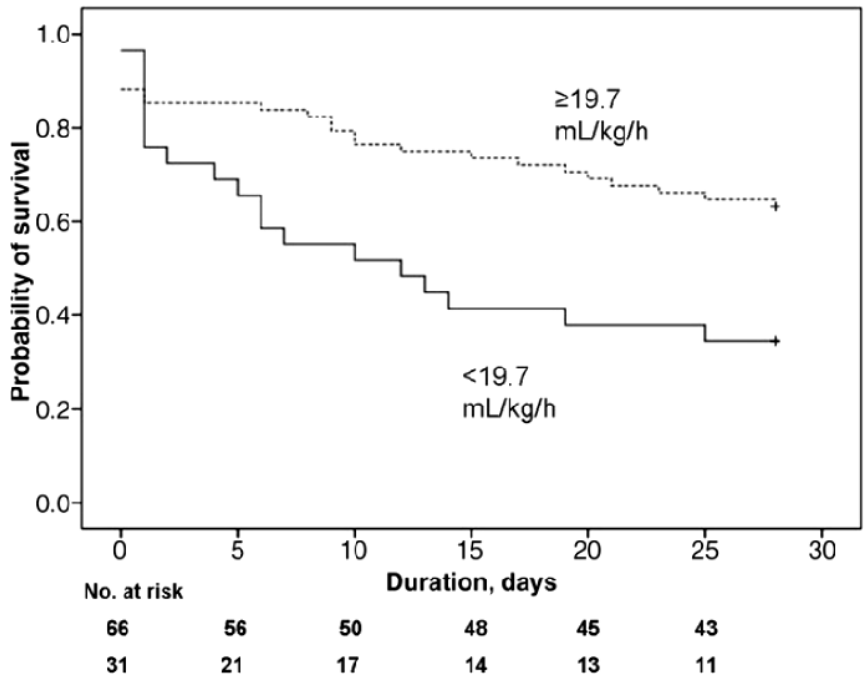

Fig. 1. Survival probabilities according to dose of continuous venovenous hemofiltration in septic patients with acute kidney injury: continuous line: delivered dose <19.7 mL/kg/h, dashed line: delivered dose ≥19.7 mL/kg/h. Log rank test: P=0.006.

Table 4. Metabolic control according to day 28 outcome.

	Survivors n=54	Non-survivors n=43	P
Within 24 h prior to start CVVH			
Diuresis, mL/h	17 ± 31	7 ± 12	0.01
Diuresis, ml/kg	0.24 ± 0.39	0.09 ± 0.16	0.144
pH	7.23 ± 0.13	7.20 ± 0.15	0.35
Bicarbonate, mmol/L	15.4 ± 4.6	16.2 ± 5.0	0.27
Potassium, mmol/L	4.6 ± 1.0	4.7 ± 1.2	0.89
Creatinine, µmol/L	261 ± 197	230 ± 114	0.12
Urea, mmol/L	19.1 ± 13.7	21.8 ± 16.3	0.17
AKI stage	3 ± 0	3 ± 0	0.082
During CVVH			
Highest creatinine, µmol/L	270 ± 119	226 ± 88	0.06
Lowest creatinine, µmol/L	132 ± 71	148 ± 78	0.14
Change in creatinine, µmol/L	172 ± 200	69 ± 101	0.01
Highest urea, mmol/L	21.0 ± 14.8	24.6 ± 16.2	0.19
Lowest urea, mmol/L	9.1 ± 5.7	11.5 ± 7.6	0.02
Change in urea, mmol/L	12.2 ± 9.7	7.0 ± 13.6	0.58

Median ± interquartile range. CVVH: continuous venovenous hemofiltration. AKI: acute kidney injury.

Table 5. Characteristics of continuous venovenous hemofiltration according to day 28 outcome.

	Survivors n=54	Non-survivors n=43	P
Time intervals, days			
Diagnosis sepsis and start CVVH	1 ± 1	1 ± 2	0.56
ICU admission and start CVVH	1 ± 1	1 ± 2	0.82
SOFA, at day of start CVVH	12.0 ± 3.0	14.0 ± 4.0	<0.005
First CVVH episode			
Duration, h	104 ± 121	47 ± 142	0.01
Number of filters	3 ± 4	3 ± 7	0.61
Mean filter life, h	34 ± 26	20 ± 22	<0.005
Mean down time, h	1.6 ± 2.0	1.9 ± 1.8	0.88
Mean blood flow, mL/min	180 ± 0	180 ± 0	0.16
Mean substitution flow, mL/h	2008 ± 309	2109 ± 400	0.10
Mean ultrafiltration flow, mL/h	2119 ± 340	2160 ± 401	0.67
Percentage on:			
predilution	100 ± 4	100 ± 0	0.54
heparin	53 ± 100	0 ± 67	0.06
citrate	0 ± 64	6 ± 100	0.02
bicarbonate	0 ± 25	24 ± 100	0.38
lactate	50 ± 100	0 ± 27	<0.005
Mean prescribed dose, mL/kg/h	23.9 ± 5.3	22.9 ± 6.0	0.05
Mean delivered dose, mL/kg/h	22.7 ± 5.2	20.0 ± 6.2	0.01
Total CVVH episode			
Duration, h	119 ± 169	47 ± 193	0.003
Number of filters	3.5 ± 5.0	3.0 ± 8.0	0.38
Mean filter life, h	34 ± 26	20 ± 22	<0.005
Mean down time, h	1.3 ± 1.9	1.1 ± 2.3	0.12
Mean blood flow, mL/min	180 ± 0	180 ± 0	0.05
Mean substitution flow, mL/h	2120 ± 388	2019 ± 400	0.62
Mean ultrafiltration flow, mL/h	2150 ± 332	2141 ± 401	0.80
Percentage on:			
predilution	100 ± 18	100 ± 0	0.51
heparin	51 ± 83	0 ± 67	0.04
citrate	13 ± 59	20 ± 100	0.46
bicarbonate	0 ± 25	6 ± 89	0.03
lactate	50 ± 100	0 ± 50	<0.005
Mean prescribed dose, mL/kg/h	23.8 ± 4.7	22.9 ± 5.6	0.05
Mean delivered dose, mL/kg/h	22.7 ± 6.0	20.0 ± 6.0	0.01

Median ± interquartile range. CVVH: continuous venovenous hemofiltration; ICU: intensive care unit; SOFA: sequential organ failure assessment.

Multivariate analyses. Multiple logistic regression using backward selection was done to identify a set of variables independently associated with mortality up to day 28 (Table 6). The use of lactate-buffered substitution fluid and the delivered dose were inversely associated with mortality, independently of SOFA at start of CVVH and the decrease in plasma creatinine

levels. The Hosmer-Lemeshow test (X^2 1.7, df8, P=0.99) indicated that the model calibrated well. A similar model was obtained after exclusion of patients with chronic renal failure (n=15). According to the logistic regression model of Table 6, we calculated a risk of 28 day-mortality of median 35% at a delivered CVVH dose of 20 mL/kg/h or higher (in 62 patients) vs. a risk of 54% at lower dose (P<0.005), and a risk of median 12% at a dose exceeding 30 mL/kg/h (in 10 patients) vs. a risk of 48% at lower dose (P<0.005), consistent with an absolute risk reduction of 23%. In a Cox regression analysis, survival duration (up to day 28 after start of CVVH) was also independently predicted by delivered dose (Table 6). Body weight and decrease in plasma creatinine did not significantly contribute to this prediction.

Table 6. Multivariate analysis (logistic and cox regression) for prediction of mortality and time to death until day 28.

	Odds ratio (95% CI)	P	Hazard ratio (95% CI)	P
Delivered dose, mL/kg/h	0.85 (0.75-0.95)	<0.005	0.90 (0.83-0.97)	0.01
Use of lactate-buffered fluid	0.98 (0.97-0.99)	<0.005	0.99 (0.98-0.99)	0.01
SOFA at start CVVH	1.26 (1.03-1.55)	0.02	1.16 (1.04-1.31)	0.01
Change in creatinine, μmol/L	na	0.26	na	0.16

CI: confidence interval; SOFA: sequential organ failure assessment; CVVH: continuous venovenous hemofiltration; na, not applicable.

Discussion

Our retrospective single-center study suggests that in critically ill, septic patients with AKI, delivered CVVH dose is a linear determinant of outcome, independently of disease severity, timing and mode of administration and azotemic control by CVVH.

The mortality rate of our septic AKI patients in need of CVVH of 44% at day 28 and 55% in the hospital roughly agrees with the literature.[1,2,4,5,19] Our observations support dosing of CVVH per kg (prehospital) body weight, since a low dose predicted mortality, independently of concomitant organ failure. The difference in dose between outcome groups was achieved by a higher body weight in non-survivors than in survivors, subjected, as per our clinical protocol, to the same rate of fluid substitution, as observed by others before.[5] Outcome groups were otherwise comparable at baseline except for more organ failure in ultimate non-survivors. We cannot exclude that the difference in dose was mainly determined by the difference in body weight and that the latter was contributing to outcome rather than the dose, even if insufficiently adjusted to body weight. However, some other CVVH characteristics were also predictive, such as a low filter life, and overweight may not increase ICU mortality.[25] So, patients with high body weight are indeed at risk for underdosing. Prescribed and delivered doses may differ

considerably when downtime is substantial. In our study, prescribed dose was about 15% higher than delivered dose, as reported before,[7] but outcome groups differed in both variables. Even though our median delivered doses were relatively low, the data suggest that at least 20 mL/kg/h should be prescribed in line with current recommendations.[15] Moreover, the difference between outcome groups in delivered dose was greater than in prescribed dose, partly because of a lower filter life in non-survivors, and we therefore cannot exclude that our policy of withholding heparin in patients with a hemorrhagic tendency was more often applied in non-survivors and thereby contributed to a lower filter survival. However, the use of heparin did not contribute to mortality prediction in the multivariable models. Furthermore, severe organ failure seems to be a major determinant of early filter clotting partly due to heparin resistance.[26] So, as filter life is a determinant of dose we cannot exclude that the difference in dose between survivors and non survivors was eventually determined by the difference in disease severity, though in our analysis the effect of dose on outcome was independent of the SOFA score. Finally, our study suggests that the mode of CVVH, pre- or postdilution, does not affect survival. However, lactate-buffered substitution fluids were not used in case of hyperlactatemia, thereby explaining less use in non-survivors with relatively higher lactate levels than in survivors.

The independent contribution of dose rather than of azotemic control to predict survival (time) suggests that, in septic AKI, dose-dependent survival is only partly determined by the latter, as judged from the course of plasma creatinine and urea levels and in line with the potential benefits, beyond azotemic control, of high-volume CVVH for septic AKI in observational studies.[5,7,20,21] These benefits may relate to clearance of pro-inflammatory mediators, cooling, and others. Nevertheless, the decrease in creatinine was greater and the urea level achieved was lower in survivors, because of higher dose and longer duration of CVVH, as our data suggest. The similarity of metabolic parameters at baseline for the groups suggests that outcome was independent of the timing of starting CVVH in our patients, even though urinary flow was lower and thus the risk for overhydration was greater in non-survivors, as described before.[1,4,12,14,27] Overhydration may have contributed to somewhat lower baseline creatinine levels in non-survivors, as noted before.[27] Our data nevertheless argue against early start of CVVH to improve azotemic control and outcome from sepsis-induced AKI, in line with negative prospective and inconclusive observational studies on these issues.[9-11,13,14] Finally, the lack of contribution of azotemic control on mortality may explain lack of survival benefit in prospective studies when intensity of intermittent hemodialysis was targeted on a low vs.

relatively high urea level, in septic AKI.[28] Conversely, an impact on survival of concomitant organ failure, independently of azotemia, is in line with other studies.[1-4,8,14]

Our retrospective study may carry the advantage over the large, prospective studies published sofar on the CVVH dose issue,[6,17,18] by reflecting a 'real life' situation and focusing on sepsis-induced AKI in need of CVVH. It also examines various characteristics of CVVH as a single mode in a single cohort. Obviously, our results should be interpreted cautiously and confirmed, if feasible, in a prospective randomized clinical trial. They nevertheless prompt us to change our own current practise. The trials on intensity of renal replacement therapy conducted sofar are hard to compare with each other, use different modes and endpoints and lack stratified randomisation for sepsis. Taken together in meta-analyses, they may be inconclusive on the dose issue.[15,16] On the other hand, our data agree with those obtained in the prospective randomized trial by Ronco et al.,[6] who observed a mortality in sepsis of 75% at a prescribed CVVH dose of 20 mL/kg/h and of 53% at a dose of 45 mL/kg/h. In our study, increasing a delivered dose of at least 20 to 30 mL/kg/h, which may conform with a 15% higher prescribed dose of about 23 and 35 mL/kg/h, respectively, would confer a survival benefit of about 23%, as our logistic regression model predicts.

In conclusion, our retrospective, single-center study suggests that CVVH dose is an independent predictor of outcome in sepsis-induced AKI in the critically ill in need of renal replacement therapy. A delivered dose < 20 ml/kg may be too low for septic AKI. This argues in favour of a prospective trial on delivered doses of CVVH in sepsis-induced AKI with 20 ml/kg as the lower limit. Our data also allow to estimate the effect for which a prospective study could be powered.

Acknowledgements

We thank the staff of the intensive care and nephrology departments for their care of patients.

Conflict of interest statement

The results presented in this paper have not been published previously in whole or in part, except in abstract form.

References

1. De Mendonça A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000;26:915-921.
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C, for the beginning and ending supportive therapy for the kidney (BEST Kidney) investigators. Acute renal failure in critically ill patients. A multinational, multicenter study. JAMA 2005;294:813-818.
3. Hoste EAJ, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JMA, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol 2003;14:1022-1030.
4. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA; beginning and ending supportive therapy for the kidney (BEST kidney) investigators. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol 2007;2:431-439.
5. Honoré PM, Jamez J, Wauthier M, Lee PA, Dugernier T, Pirenne B, Hanique G, Matson JR. Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 2000;28:3581-3587.
6. Ronco C, Bellommo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000;356:26-30.
7. Piccinni P, Dan M, Barbacini SS, Carraro R, Lieta E, Marafon SS, Zamperettie N, Brendolan A, D'Intini V, Tetta C, Bellomo R, Ronco C. Early isovolaemic haemofiltration in oliguric patients with septic shock. Intensive Care Med 2006;32:80-86.
8. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten H, Ronco C, Kellum JA. Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. Intensive Care Med 2007;33:1563-1570.
9. Bouman CSC, Oudemans-van Straaten HM, Schultz MJ, Vroom MB. Hemofiltration in sepsis and systemic inflammatory response syndrome; the role of dosing and timing. J Crit Care 2007;22:1-12.
10. Liu KD, Himmelfarb J, Paganini E, Ikizler TA, Soroko SH, Mehta RL, Chertow GM. Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol 2006;1:915-919.
11. Palevsky PM. Clinical review: timing and dose of continuous renal replacement therapy in acute kidney injury. Crit Care 2007;11:232.
12. Gibney RTN, Bagshaw SM, Kutsogiannis DJ, Jonhston C. When should renal replacement therapy for acute kidney injury be initiated and discontinued? Blood Purif 2008;26:473-484.
13. Bagshaw SM, Uchinno S, Bellomo R, Morimmatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HM, Ronco C, Kellum JA, for the

beginning and ending supportive therapy for the kidney (BEST Kidney) investigators. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. J Crit Care 2009;24:129-140.

14. Ostermann M, Chang RWS. Correlation between parameters at initiation of renal replacement therapy and outcome in patients with acute kidney injury. Crit Care 2009;13:R175.
15. Van Wert R, Friedrich JO, Scales DC, Wald R, Adhikari NK; University of Toronto Acute Kidney Injury Research Group. High-dose renal replacement therapy for acute kidney injury: systematic review and meta-analysis. Crit Care Med 2010;38:1360-1369.
16. Jun M, Lambers-Heerspink HJ, Ninomiya T, Gallagher M, Bellomo R, Myburgh J, Finfer S, Palevsky PM, Kellum JA, Perkovic V, Cass A. Intensities of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2010; Apr 15 (Epub ahead of print).
17. The VA/NIH acute renal failure trial network. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7-20.
18. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009;361:1627-1638.
19. Vesconi S, Cruz DN, Fumagalli R, Kindgen-Milles D, Monti G, Marinho A, Mariano F, Formica M, Marchesi M, Robert R, Livigni S, Ronco C for the DOse REsponse Multicentre International collaborative Initiative (DO-RE-MI study group). Crit Care 2009;13:R57.
20. Cornejo R, Downey P, Castero R, Romero C, Regueira T, Vega J, Castillo L, Andresen M, Dougnac A, Bugedo G, Hernandez G. High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. Intensive Care Med 2006;32:713-722.
21. Schefold JC, Hasper D, Jörres A. Organ crosstalk in critically ill patients: hemofiltration and immunomodulation in sepsis. Blood Purif 2009;28:116-12.
22. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003;29:530-8.
23. Vervloet MG, Nurmohamed SA. How do I use citrate-based CVVH in predilution. Neth J Crit Care 2007;11:8-12.
24. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG et al. Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11(2):R31.
25. Sakr Y, Madl C, Filipescu D, Moreno R, Groeneveld J, Artigas A, Reinhart K, Vincent JL. Obesity is associated with increased morbidity but not mortality in critically ill patients. Intensive Care Med 2008;34:1999-2009.
26. Oudemans-van Straaten HM, Van Schilfgaarde M, Molenaar PJ, Wester JP, Leyte A. Hemostasis during low molecular weight heparin anticoagulation for continuous venovenous hemofiltration: a randomized cross-over trial comparing two hemofiltration rates. Crit Care. 2009;13(6):R193.

27. Cerdá J, Cerdá M, Kilcullen P, Prendergast J. In severe acute kidney injury, a higher serum creatinine is paradoxically associated with better patient survival. Nephrol Dial Transplant 2007;22:2781-2784.
28. Faulhaber-Walter R, Hafer C, Jahr N, Vahlbruch J, Hoy L, Haller H, Fliser D, Kielstein JT. The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit. Nephrol Dial Transplant 2009;24:2179-2186.