Discontinuation of continuous renal replacement therapy: A *post hoc* analysis of a prospective multicenter observational study*

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Objectives: **To describe current practice for the discontinuation of continuous renal replacement therapy in a multinational setting and to identify variables associated with successful discontinuation. The approach to discontinue continuous renal replacement therapy may affect patient outcomes. However, there is lack of information on how and under what conditions continuous renal replacement therapy is discontinued.**

Design: Post hoc **analysis of a prospective observational study.**

Setting: **Fifty-four intensive care units in 23 countries.**

Patients: **Five hundred twenty-nine patients (52.6%) who survived initial therapy among 1006 patients treated with continuous renal replacement therapy.**

Interventions: **None.**

Measurements and Main Results: **Three hundred thirteen patients were removed successfully from continuous renal replacement therapy and did not require any renal replacement therapy for at least 7 days and were classified as the "success" group and the rest (216 patients) were classified as the "repeat-RRT" (renal replacement therapy) group. Patients in the "success" group had lower hospital mortality (28.5% vs. 42.7%, $p < .0001$) compared with patients in the "repeat-RRT" group. They also had lower creatinine and urea concentrations and a higher urine output at the time of stopping continuous renal replacement therapy. Multivariate logistic regression analysis for successful discontinuation of continuous renal replacement therapy identified urine output (during the 24 hrs before stopping continuous renal replacement therapy: odds ratio, 1.078 per 100 mL/day increase) and creatinine (odds ratio, 0.996 per μmol/L increase) as significant predictors of successful cessation. The area under the receiver operating characteristic curve to predict successful discontinuation of continuous renal replacement therapy was 0.808 for urine output and 0.635 for creatinine. The predictive ability of urine output was negatively affected by the use of diuretics (area under the receiver operating characteristic curve, 0.671 with diuretics and 0.845 without diuretics).**

Conclusions: **We report on the current practice of discontinuing continuous renal replacement therapy in a multinational setting. Urine output at the time of initial cessation of continuous renal replacement therapy was the most important predictor of successful discontinuation, especially if occurring without the administration of diuretics. (Crit Care Med 2009; 37:2576–2582)**

Key Words: acute renal failure; critical illness; continuous renal replacement therapy; epidemiology; hemofiltration; intensive care

Approximately 6% of critically ill patients develop severe acute kidney injury (AKI) and 4% are treated with renal replacement therapy (RRT) (1). Because of hemodynamic stability and steady solute control, continuous RRT (CRRT) is often the preferred choice over intermittent RRT (IRRT) in the intensive care unit (ICU) (2–4).

Although both CRRT and mechanical ventilation are common organ support therapies in the ICU, there is a gap between the two therapies in terms of amount and quality of evidence. For mechanical ventilation, there are multiple international epidemiologic studies (5–7), multicenter randomized trials (8–10), and several international consensus guidelines (11–13). For CRRT, on the other hand, there has been only one international epidemiologic study (1) and one consensus set of guidelines (14), although the number of multicenter randomized trials is increasing (15, 16). Therefore, when conducting CRRT, physicians currently have to make decisions about patient care with limited information. In particular, there are negligible data about the process of discontinuation of CRRT. This lack of evidence is different from the field of mechanical ventilation, where many studies dealing with the process of "weaning" from mechanical ventilation have been conducted (17–19).

The BEST Kidney (Beginning and Ending Supportive Therapy for the Kid-

***See also p. 2664.**

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ney) study is a multicentered, multinational, prospective, epidemiologic study for AKI. Its aims are to understand multiple aspects of AKI at an international level (1, 20–24). As part of the BEST kidney study, we sought to investigate the current practice of CRRT discontinuation in a multinational multicenter setting and to identify which factors present at the time of discontinuation may assist physicians in predicting successful cessation of CRRT.

MATERIALS AND METHODS

This study was conducted by 54 centers in 23 countries from September 2000 to December 2001 (Appendix). The study protocol was reviewed by the Ethics Committees or Investigational Review Boards of each participating site. Because of the anonymous and noninterventional fashion of this study, Ethical Committees in most centers waived the need for informed consent. Where Ethics Committees or Investigational Review Boards required informed consent, we obtained formal written consent. All patients who were treated with CRRT for AKI in one of the participating ICUs during the observational period were considered. From this population, we excluded patients <12 yrs (several units treated older children in their ICU), patients with any dialysis treatment before admission to the ICU, and patients with end-stage renal failure on chronic dialysis.

We developed a case report form for the purpose of the study, and demographic and clinical information was obtained prospectively at study inclusion (1). Additionally, when CRRT was stopped, the following physiologic and laboratory variables were collected: mean arterial pressure, central venous pressure, urine output and diuretics use in 24 hrs before stopping CRRT, need for mechanical ventilation and vasopressors, creatinine, urea, potassium, Pa_{O_2}/F_{IO_2} ratio, pH, lactate, and mode of CRRT. Reasons why CRRT was stopped were identified from a group of several possible choices (increased urine output, improved metabolic/electrolyte state, improved fluid overload state, decreased urea/creatinine, stable hemodynamics). More than one reason could be selected in each case. The date and time of stopping CRRT were collected and duration from starting CRRT to stopping CRRT was calculated (first CRRT period). Finally, ICU outcomes and hospital outcomes were recorded.

We collected data by means of an electronically prepared Excel-based data collection tool. This was made available to participating centers with instructions. All centers were asked to complete data entry and e-mail the data to the central office. On arrival, all data were screened in detail by a dedicated intensive care specialist for any missing information, logical errors, insufficient detail, or any other queries. Any queries generated an immediate e-mail inquiry with planned resolution within 48 hrs.

Data Analysis

To analyze predictive variables for successful discontinuation of CRRT, only patients whose CRRT was stopped were included. Patients who died while they were on CRRT, patients whose treatment was withdrawn, and patients who were transferred to another hospital while still on CRRT were excluded for the analysis. Remaining patients were then divided into two groups according to their RRT requirement within 7 days after the initial discontinuation of CRRT. Patients were placed in the "success" group if they were free from RRT at 7 days after the discontinuation and the rest were in the "repeat-RRT" group. Demographics and variables at discontinuation for these two groups were compared, using the Mann-Whitney *U* test and the Fisher's exact test. To further analyze relevant factors for successful discontinuation of CRRT, we conducted a multivariate logistic regression analysis with successful discontinuation of CRRT as the dependent variable. All variables presented in Table 1 (demographics of patients and variables at starting CRRT) and Table 2 (patient characteristics at discontinuation of CRRT) were included as dependent variables. Backward stepwise elimination process was used to remove variables if multivariate $p > .05$. Finally, the prediction ability of urine output and serum creatinine concentration for successful discontinuation of CRRT was assessed with the area under the receiver operating characteristic (ROC) curve method (25). We used a commercially available statistical package (StatView, Abacus Concepts, Berkeley, CA). Data are presented as median and interquartile ranges (25th to 75th percentiles) or percentages. A $p < .05$ was considered statistically significant.

RESULTS

There were 1006 patients who received CRRT during the study period. Among these patients, 330 died while on CRRT, 12 were transferred to another hospital while on CRRT, and 135 had CRRT withdrawn. These patients were ex-

Table 1. Demographics of study patients and variables at starting continuous renal replacement therapy

	All Patients	Success	Repeat-RRT	*p*
Number of patients	1006	313	216	
Age, yrs	66 (51–74)	66 (48–74)	64 (50–72)	.69
Male, %	65.8	69.6	67.6	.63
Chronic kidney disease, %	28.1	26.5	39.8	.0017
Surgery, %	45.3	47.3	43.5	.42
SAPS II	48 (39–62)	47 (38–57)	47 (38–58)	.83
Hosp-CRRT, days	5 (1–12)	3 (1–9)	4 (1–12)	.37
Contributing factors to AKI, %				
Sepsis/septic shock	50.2	43.4	48.6	.25
Major surgery	37.6	39.9	38.4	.79
Low cardiac output	26.1	25.4	19.4	.12
Hypovolemia	20.0	20.6	22.2	.67
Drug induced	17.5	16.4	20.4	.25
Hepato-renal syndrome	7.3	6.1	7.9	.48
Obstructive uropathy	2.0	2.6	2.8	>.99
Others	11.4	7.7	8.3	.87
Mechanical ventilation	84.1	77.1	80.5	.39
Vasopressors/inotropes	78.8	76.5	63.3%	.0012
Creatinine, μmol/L	292 (192–427)	300 (190–428)	366 (265–508)	<.0001
Urea (mmol/L)	23 (15–34)	22 (15–32)	27 (18–38)	.0026
Urine output, mL/6 hrs	100 (23–280)	160 (50–390)	100 (29–253)	.0009
Furosemide, mg/6 hrs	60 (0–200)	60 (0–240)	40 (0–180)	.018
Mode of CRRT, %				
CAVHD	0.1	0	0	—
CVVH	52.8	61.3	48.6	.0043
CVVHD	13.1	7.7	13.4	.039
CVVHDF	34.0	31.0	38.0	.11
Intensity, L/hr	2.0 (1.3–2.1)	2.0 (1.4–2.3)	2.0 (1.4–2.1)	.17

RRT, renal replacement therapy; SAPS II, Simplified Acute Physiology Score II; CRRT, continuous renal replacement therapy; Hosp-CRRT, duration between hospital admission and start of CRRT; AKI, acute kidney injury; CAVHD, continuous arteriovenous hemodialysis; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration.

Table 2. Variables at discontinuation of continuous renal replacement therapy

Variables	Success	Repeat-RRT	p
Number of patients	313	216	
MAP, mm Hg	84 (75–95)	85 (75–98)	.46
CVP, mm Hg	10 (8–13)	10 (7–13)	.79
Vasopressors/inotropes	45.5%	29.5%	.0003
Lactate, mmol/L	1.6 (1.0–2.5)	1.4 (0.9–2.3)	.23
pH	7.43 (7.39–7.48)	7.42 (7.37–7.47)	.023
Po_2/Fio_2 ratio, torr	274 (215–337)	267 (195–347)	.55
Mechanical ventilation	62.1%	53.8%	.068
Creatinine, μmol/L	151 (102–229)	199 (141–290)	<.0001
Urea, mmol/L	13 (9–18)	15 (11–21)	.0015
Potassium	4.0 (3.7–4.4)	4.1 (3.7–4.4)	.37
Urine output, mL/day	1500 (627–2500)	180 (22–767)	<.0001
Diuretics use	44.9%	24.9%	<.0001
Furosemide, mg/day	0 (0–240)	0 (0–0)	.0001
Other diuretics	4.3%	2.4%	.33
First CRRT period, days	5 (3–9)	8 (4–15)	<.0001
Reasons to stop CRRT, %			
Urine output increased	63.2	19.9	<.0001
Metabolic state improved	49.2	39.8	.039
Fluid overload improved	36.2	31.3	.26
Urea/creatinine decreased	59.0	47.4	.012
Hemodynamically stable	42.7	51.7	.049

RRT, renal replacement therapy; MAP, mean arterial pressure; CVP, central venous pressure; CRRT, continuous renal replacement therapy.

Table 3. Outcomes of study patients

Outcomes	All Patients	Success	Repeat-RRT	p
Number of patients	1006	313	216	
ICU LOS, days	12 (5–23)	14 (8–27)	21 (11–34)	.0002
ICU outcome, %				<.0001
Alive off RRT	32.1	82.7	25.7	
Alive on RRT	12.6	0.6	50.9	
Died	55.3	16.7	23.4	
Hospital LOS, days	23 (11–46)	33 (19– 61)	42 (25–77)	.0055
Hospital outcome, %				<.0001
Alive off RRT	30.7	70.8	38.9	
Alive on RRT	5.1	0.6	18.5	
Died	64.2	28.5	42.7	

RRT, renal replacement therapy; ICU, intensive care unit; LOS, length of stay.

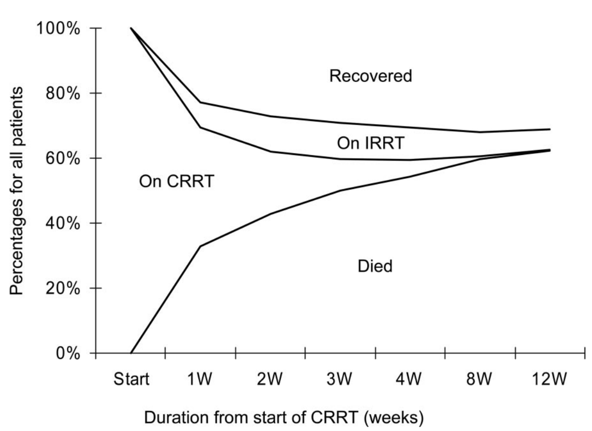

Figure 1. Outcome of patients treated with continuous renal replacement therapy (*CRRT*). *IRRT*, intermittent renal replacement therapy.

cluded from further analysis. Among the remaining CRRT patients, 298 were removed successfully from CRRT and did not require RRT until hospital discharge. Fifteen patients were free from RRT until 7 days after the initial discontinuation of CRRT but required RRT again before hospital discharge. These 313 patients were classified as the success group and the rest (216 patients) were classified as the repeat-RRT group. The demographics of patients in these two groups are shown in Table 1. Patients in the success group were less likely to have chronic kidney disease (CKD), had lower creatinine and urea, had higher urine volume, and were treated with continuous veno-venous hemofiltration more frequently compared with patients in the repeat-RRT group.

Table 2 shows variables at discontinuation of CRRT. Patients in the success group had lower creatinine and urea concentrations, higher urine output, and were on CRRT for a shorter period before the initial discontinuation compared with patients in the repeat-RRT group. They also had "urine output increased," "metabolic state improved," and "urea/creatinine decreased" as the most common reasons for stopping CRRT.

Patient outcomes are shown in Table 3. Hospital mortality for all patients was 64.2%, and 5.1% were still on RRT at hospital discharge. The outcome of these patients over time is shown in Figure 1. For example, 1 wk after starting CRRT, 32.8% had died, 36.6% were still on CRRT, 7.7% had switched to IRRT, and 22.9% had recovered renal function and were free from RRT. Figure 2 shows the outcome of patients who required prolonged RRT. For example, 4 wks after starting CRRT, there were 121 patients who were alive but still required RRT (CRRT or IRRT). The hospital mortality of these patients was 49.6%, and 16.5% of these patients were dialysis dependent at hospital discharge. Patients in the success group had lower ICU and hospital mortality and shorter ICU and hospital length of stay (Table 3).

The multivariable model for successful discontinuation of CRRT showed that the most significant variable was urine output (urine output in the 24 hrs before stopping CRRT: odds ratio, 1.078 per 100 mL/day, $p < .0001$; "urine output increased" as a reason to stop CRRT: odds ratio, 3.097, $p < 0.0001$). Decreased creatinine was also found be a significant factor (odds ratio, 0.996 per μmol/L change, $p = .0005$).

The area under the ROC curve to predict successful discontinuation of CRRT was 0.808 (0.768–0.844) for urine output and 0.635 (0.586–0.681) for creatinine. Figure 3 shows the impact of diuretics use on the predictive ability of urine output. The area under the ROC curve of urine output for successful discontinuation of CRRT was

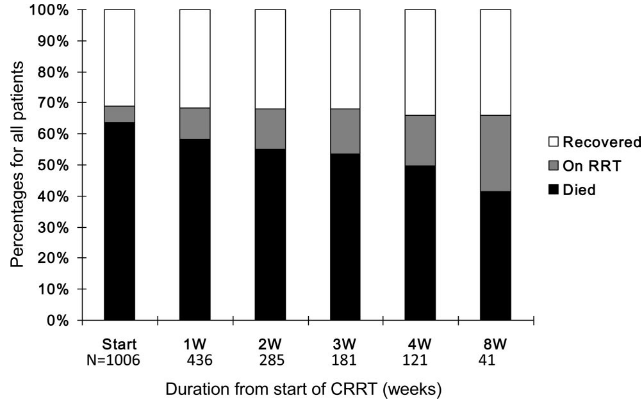

Figure 2. Outcome of patients who required prolonged renal replacement therapy (*RRT*). *CRRT*, continuous renal replacement therapy.

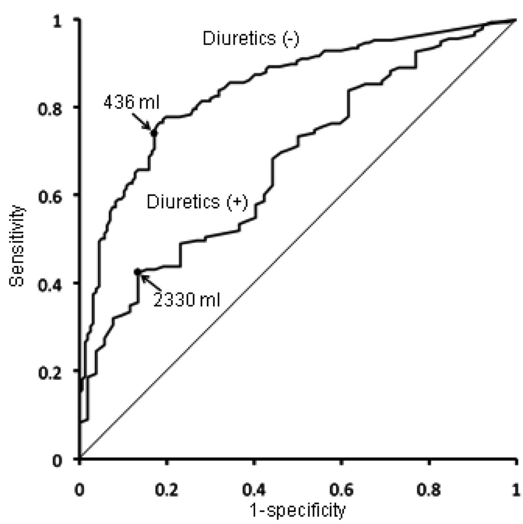

Figure 3. Impact of diuretics use on predictive ability of urine output. The area under the receiver operating characteristics curve of urine output for successful discontinuation of continuous renal replacement therapy was 0.671 (0.585–0.750) with diuretics and 0.845 (0.799–0.883) without diuretics. Urine output of 436 mL/day for patients without diuretics and of 2330 mL for those with diuretics had the highest accuracy.

0.671(0.585–0.750) with diuretics and 0.845 (0.799–0.883) without diuretics. In the latter ROC curve, a urine output of 436 mL/day without diuretics had the highest sensitivity and specificity. Therefore, the cutoff point of 400 mL/day was chosen to calculate the sensitivity, specificity, positive predictive value, negative predictive value and accuracy, which were 46.5%, 80.9%, 80.9%, 76.5%, and 78.6%, respectively. For patients receiving diuretics, a urine output of 2330 mL had the highest sensitivity and specificity and its positive predictive value (threshold of 2300 mL/day) was 87.9%.

DISCUSSION

In this study, for the first time, we assessed the worldwide practice for discontinuation of CRRT in the ICU. We found that approximately 50% of patients treated with CRRT in the ICU had their CRRT stopped, as decided by their attending physician. We also found that urine output at cessation of CRRT was the most important predictor of successful discontinuation of CRRT. However, its predictive ability was affected negatively by the administration of diuretics.

Patients whose CRRT was discontinued successfully had better outcome than patients who needed to be retreated with RRT. The success group had hospital mortality of 28.5%, significantly lower than the repeat-RRT group (42.7%) ($p < .0001$). Patients who require CRRT for AKI have been reported to have a mortality >60% (26). Our findings suggest that, once they recover renal function enough to be free from RRT, most patients survive to hospital discharge. When discontinuation of mechanical ventilation fails, patients often require immediate reintubation and/or prolonged mechanical ventilation. These have been reported to be significantly correlated with higher mortality and morbidity (27, 28). Our study shows that this is also the case for CRRT. It is uncertain whether failure of discontinuation of mechanical ventilation or need for CRRT is just a marker of severity of disease or whether failure itself causes harm to patients. A period without renal support might cause fluid overload, electrolyte abnormalities, and increased uremia. Therefore, it might be better to try to avoid a failed attempt at discontinuation of CRRT in the same way one should seek to avoid a failed extubation.

The only study previously reported in the literature for discontinuation of RRT was conducted by Wu et al (29). Among 304 patients treated with IRRT in their unit, 94 patients (30.9%) did not require RRT for >5 days and 64 of them were free from RRT for >30 days. The independent factors for restarting RRT within 30 days were: longer duration of RRT, higher Sequential Organ Failure Assessment score, oliguria (<100 mL in 8 hrs), and age >65 yrs. There are several differences between their study and ours: number of centers and patients included (94 patients in a single center vs. 529 patients in 54 centers), patient characteristics (postsurgical patients only vs. general ICU patients), mode of RRT (IRRT vs. CRRT), inclusion criteria (patients free from dialysis for >5 days vs. all patients whose CRRT was discontinued), and the definition of successful discontinuation (>30 days vs. >7 days).

Despite these differences between the two studies, urine output at discontinuation of RRT was found to be an important predictor of successful discontinuation in both studies. Diuretics administration, however, negatively affected the predictive ability of urine output. This finding is not surprising because diuretics only increase urine output but not glomerular filtration rate. Nonetheless, if patients make >400 mL/day of urine without diuretics or >2300 mL/day with diuretics, they seem to have a >80% chance of successful discontinuation of CRRT. This finding is likely to be of practical utility to clinicians. However, it needs to be tested prospectively in future studies.

Creatinine at discontinuation of CRRT was also found to be a significant variable in our study. This finding is different from that in the study by Wu et al (29).

Table 4. Multivariate logistic regression analysis for successful discontinuation of continuous renal replacement therapy

	Odds Ratio (95% CI)	p
Urine output, 100 mL/day	1.078 (1.049–1.108)	<.0001
Urine output increased	3.097 (1.873–5.121)	<.0001
Creatinine, μmol/L	0.996 (0.994–0.998)	.0005
Chronic kidney disease	0.534 (0.338–0.844)	.0072
First CRRT period, days	0.969 (0.947–0.993)	.010

CI, confidence interval; CRRT, continuous renal replacement therapy.

This discrepancy might come from the small sample size of the study by Wu et al, as they found significant differences in urea and creatinine between successful weaning and failed weaning from RRT in their univariate analysis. Nevertheless, the predictive ability of creatinine seems to be small (area under the ROC curve <0.7). This is probably because creatinine is lowered by the therapy itself and its value is not related to renal recovery.

We have found that CKD is a strong negative predictor of successful discontinuation of CRRT (odds ratio, 0.534). Wu et al also found that the frequency of CKD was higher in the failed discontinuation group (56.7%) compared with the successful discontinuation group (42.4%), although this difference was not statistically significant ($p = .27$) possibly due to the small sample size. Also, urine output and creatinine level had a stronger association with successful discontinuation of CRRT compared with CKD (Table 4). This observation suggests that, although CKD is an important predictor of successful discontinuation of CRRT, acute variables are likely more important predictors.

Although there were several variables (Table 4) that predicted successful discontinuation of CRRT, only urine output and serum creatinine concentration were measured at the time CRRT was stopped. For mechanical ventilation, many techniques/parameters before extubation have been reported as useful in predicting successful weaning: vital capacity, negative inspiratory force, rapid shallow breathing index, spontaneous breathing trial, and cuff leak test (30). Further studies are needed to identify other parameters, which might assist in correctly predicting successful discontinuation of CRRT.

This study has several limitations. First, centers chose to participate in this study. It is likely, therefore, that there was a self-selection bias toward centers with a particular interest in AKI and its management. These centers might have managed more AKI patients, treated them more aggressively, made decisions for discontinuing CRRT in different ways and produced different outcomes compared with other institutions. Second, this is an observational study, not a randomized controlled trial. Physicians made decisions to discontinue CRRT according to clinical judgment, not standard predefined criteria. Some CRRT might have been electively switched to IRRT. However, data were collected in 23 countries and this is the first study assessing the current practice of discontinuation of CRRT in the world. As such, it provides the first available glimpse of global practice and outcomes. Finally, it remains unclear whether a better ability to predict successful cessation of CRRT can translate into improved patient-centered outcomes. Also, our findings for the prediction, especially the threshold of urine volume, have not been validated in another external data set. More work is needed to address these issues.

CONCLUSIONS

In summary, for the first time, we have reported the current practice of discontinuing CRRT in a multinational setting. We found that urine output at the time of initial cessation of CRRT was the most important predictor of successful discontinuation. Diuretics usage, however, negatively affected the predictive ability of urine output. Although a lower creatinine concentration was also related to successful discontinuation of CRRT, its predictive ability was low. Prospective studies are needed to test the success rate of an approach to discontinuation of CRRT based on the urine output cutoff identified in this study.

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APPENDIX. Participating Centers and Investigators

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