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Feasibility of a protocol to wean patients from continuous renal replacement therapy: A retrospective pilot observation

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ABSTRACT

Purpose: To evaluate the feasibility of a protocol-based algorithm to wean acute kidney injury (AKI) patients from continuous renal replacement therapy (CRRT).
Methods: The protocol was introduced on one of two similarly equipped ICUs, while on the other (reference) ICU, CRRT discontinuation was based on clinical judgement. Patients were allocated to either ICU and were subjected to physician- or protocol-directed weaning, respectively. According to the algorithm, periodical withdrawal trials (WTs) were mandatory. Interventions were recommended (administration of diuretics, fluid, vasopressors, inotropes, or human albumin) to achieve specific goals (sufficient urine output, balanced fluid status, adequate renal perfusion pressure, optimal oxygen delivery, normoalbuminemia). Clearly stated criteria defined when to abort a WT and to resume RRT for one cycle, followed by another WT.
Results: Urine output and $S_{cv}O_2$ during WTs were higher with protocol-directed weaning, as well as the amount of administered fluids. WT abort ratio was 48% with a tendency to prolonged WT duration, compared to 64% in the reference patients. No relevant adverse side effects were observed.
Conclusion: Our data show the feasibility of a structured approach to wean AKI patients from RRT that bundles established interventions and brings the weaning into the physician's focus.

1. Introduction

Incidence of acute kidney injury (AKI) requiring renal replacement therapy (RRT) in critically ill patients has almost doubled over the last years [1]. AKI is defined as an acute, though reversible deterioration of renal function. The need for RRT is associated with an increased risk of developing future chronic renal failure (CRF) [2]. Interestingly, RRT itself forms a risk factor for increased mortality, independent of disease severity [3]. Moreover, it consumes substantial financial and human resources, making RRT a major public health concern [4,5]. Thus, particular efforts should be made to achieve recovery of renal function and to be able to discontinue RRT.

While there exist generally accepted criteria for when to initiate RRT in AKI, published by the KDIGO (Kidney Disease: Improving Global Outcomes), the intensivist is given no such recommendations for its cessation during convalescence of AKI. In the KDIGO guidelines, it is just stated to "*… discontinue RRT when it is no longer required* […] *because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs* […] *(Not Graded)*" [6]. This means to solely rely on clinical 'gut feeling' to determine that point of adequately recovered kidney function. Obviously, this lack of standardization often results in vain withdrawal procedures.

In respiratory medicine, it was demonstrated that weaning from mechanical ventilation is optimized by the use of protocol-directed strategies and algorithms [7]. They reduce duration of mechanical ventilation as well as length of stay in the ICU independent from the individual approach and are therefore mandatory for structural quality [8].

However, although numerous single factors have been identified that may predict successful discontinuation of RRT [9-14], no structured approach for this purpose has been presented to date. For the first time, we propose a protocol-based algorithm that bundles elements that are of crucial importance for successful weaning from RRT. Its feasibility has been evaluated on a German university hospital anesthesiological ICU.

2. Methods

2.1. Setting, patient cohort, RRT

The protocol-based algorithm to wean patients from RRT was introduced on one of two specialized anesthesiological ICUs of the University Hospital Bonn in August 2014 in order to improve structural quality of patient care. These two units (ICU1, ICU2) are located in the premises of a neurological rehabilitation center. Patients are transferred there

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from other surgical ICUs of the university hospital when they have passed the acute postoperative or posttraumatic period but do require further intensive care treatment due to prolonged organ dysfunction. The patient population is given in Table 1. Patients are mostly mechanically ventilated, frequently via tracheostomy tube. These two specialized ICUs are similar with regard to training level of medical staff as well as equipment, providing all standard therapeutic intensive care options of a maximum care hospital (excluding ECMO therapy and intermittent RRT). Allocation to either ICU1 or ICU2 during transfer from another ICU is made on the basis of available treatment places.

Since intermittent RRT is not available on these two ICUs, solely continuous renal replacement therapy (CRRT) was performed in the form of post-dilution continuous veno-venous hemodiafiltration (CVVHDF) via a high-flow double-lumen dialysis catheter inserted into the femoral, jugular, or subclavian vein. A Multifiltrate™ dialysis apparatus, equipped with an Ultraflux™ AV1000S filter, was used (Fresenius Medical Care, Bad Homburg, Germany). Regional citrate anticoagulation (RCA) was applied whenever possible, whereas systemic anticoagulation with heparin or argatroban and an activated Partial Thromboplastin Time (aPTT) of around 35 s was used in case of relevant citrate accumulation. According to the local standard, dialysis dosage should be around 35 ml/kg bodyweight (BW)*hr. The ratio between dialysate flow and blood flow rate (usually 20:1) and the flow rate of the substitution solution were adjusted according to the manufacturer's recommendations. Systemic and post-filter calcium levels, pH, plasma bicarbonate, and aPTT were monitored regularly, and citrate and calcium administration, blood flow rate, or systemic anticoagulation, respectively, were adjusted accordingly. Patients undergoing CRRT should receive amino acid (AA) substitution amounting to 1.5–1.8 g/kg BW*d according to the local nutrition standard.

Since the algorithm bundles established measures and recommendations that are likely to be substantial for successful weaning from RRT without making any interventions on random basis, it was introduced to improve treatment quality. Evaluation of feasibility was performed by retrospective analysis of the patient charts. Thus, prior ethics approval was waived. As of date of introduction, all consecutive patients with already initiated RRT due to prior AKI transferred to the ICU1 were subjected to algorithm-based weaning. In contrast, patients that developed RRT-requiring AKI during treatment on this unit or those with preexisting chronic kidney disease requiring dialysis were not. This was done in order to avoid possible influence on the initiation of RRT and to solely evaluate the feasibility of the protocol during the weaning process. Protocol-based weaning was performed until the patient either was discharged from ICU1 or was considered being successfully weaned which was defined as no need for further RRT for at least 5 days.

6 months following introduction of the algorithm, its feasibility was evaluated by retrospective analysis of the patient charts and protocols. A cohort of consecutive patients from the similarly equipped reference unit ICU2 was used to identify possible harmful side effects. These patients met the same inclusion criteria (only those transferred from another ICU with already established RRT due to prior AKI, no preexisting chronic kidney disease requiring dialysis). On this other ward (ICU2), discontinuation of CRRT was done physician-directed, based on clinical judgement and without formal guidelines or any other fixed criteria. Data from these reference patients were retrospectively analyzed for the period between admittance to the ICU2 and discharge or when the patient was considered being successfully weaned (no need for further RRT for at least 5 days).

Table 1
Patient characteristics.

Parameter	Physician-directed	Protocol-directed	*p* value
Number of patients	15	15	
Entity:			
Abdominal surgery (n)	2	4	
Cardiothoracic surgery (n)	7	5	
Orthopedic / Trauma surgery (n)	1	1	
Neurosurgery (n)	1	2	
Post-ARDS / -ECMO therapy (n)	4	3	
Baseline characteristics:			
SAPS II at first admission to ICU	40 (26–55)	42 (28–70)	0.61
SAPS II at inclusion	41 (16–54)	34 (29–49)	0.20
Age at admission (years)	72 (43–80)	62 (34–77)	**0.01**
Body mass index (kg/m^2)	29 (22–63)	26 (11–36)	0.06
Male sex (n)	11	10	
Serum creatinine at admission (mg/dl)	1.5 (0.8–5.1)	2.0 (1.0–5.0)	0.1
Serum urea at admission (mg/dl)	54 (34–148)	92 (35–268)	0.16
GFR at admission (ml/min)	47 (20–70)	34 (20–70)	0.22
Medical history:			
Hypertension (n)	12	9	
Diabetes (n)	8	5	
Preexisting statin therapy (n)	8	3	
Preexisting chronic kidney disease (n)	0	0	
ICU therapy, CRRT:			
Percentage time on mech. Vent.	75 (0−100)	100 (0–100)	0.81
Number of RBC transfusions	5 (0−23)	3 (0–17)	0.75
Length of observation period (hrs)	336 (144–1224)	240 (72–1248)	0.23
Total duration of CRRT (hrs)	123 (0–754)	97 (0–877)	0.48

Values are given as total numbers or as median (with range), respectively. Significance of differences between conservative and protocol-based treatment regimen was tested using Mann-Whitey *U* test. P values <.05 are given in bold numbers.
ARDS = Acute Respiratory Distress Syndrome, ECMO = Extracorporeal Membrane Oxygenation, SAPS II = Simplified Acute Physiology Score II, GFR = Glomerular Filtration Rate, CRRT = Continuous Renal Replacement Therapy, RBC = Red Blood Cell Concentrate.

2.2. Protocol-based weaning approach

The weaning approach consists of two elements:

2.2.1. Algorithm (Fig. 1):

In the absence of clearly stated abort criteria, every patient on CRRT due to prior AKI transferred to the ICU1 from one of the other surgical ICUs of the hospital is subjected to a withdrawal trial (WT) at admittance. A WT is supported by the administration of furosemide and crystalloid infusion solution, and diuresis is evaluated over the following 12 h. When the patient remains anuretic or meets specific abort criteria, one cycle of CRRT is performed. The duration of one cycle is defined by the time by which the filter expires (72 h) or by any other premature malfunction (e.g., clotting of the filter system) requiring an exchange. During the cycle, diuretics are paused, no ultrafiltration is applied via the CRRT device in the absence of clinically relevant hypervolemia and with sufficient spontaneous diuresis (≥0.5 ml/kg BW*hr), and dialysis dosage and AA substitution are adjusted as described above. After one CRRT cycle, another WT is performed.

During the WT, urine output is supported with continuous infusion of furosemide (step 1) and additionally hydrochlorothiazide (step 2) only in case of oliguria (diuresis <0.5 ml/kg BW*hr) and relevant fluid overload. Otherwise, spontaneous diuresis volume is substituted by crystalloid infusion solution to maintain urine output.

Key element of the algorithm is to respect the goal parameters during a WT. Diuresis should be at least 0.5 ml/kg BW*hr, and the patient's fluid status should be balanced. If the mean arterial blood pressure (MAP) is below 65 mmHg, vasopressors should be administered, and if the central venous oxygen saturation ($S_{cv}O_2$) is below 70%, inotropes, fluid, or (according to recent transfusion guidelines) red blood cell concentrates (RBC) should be used. In the case of low serum albumin, this should likewise be substituted. As long as no abort criterion is met, hyperphosphatemia as well as hyperkalemia are treated conservatively.

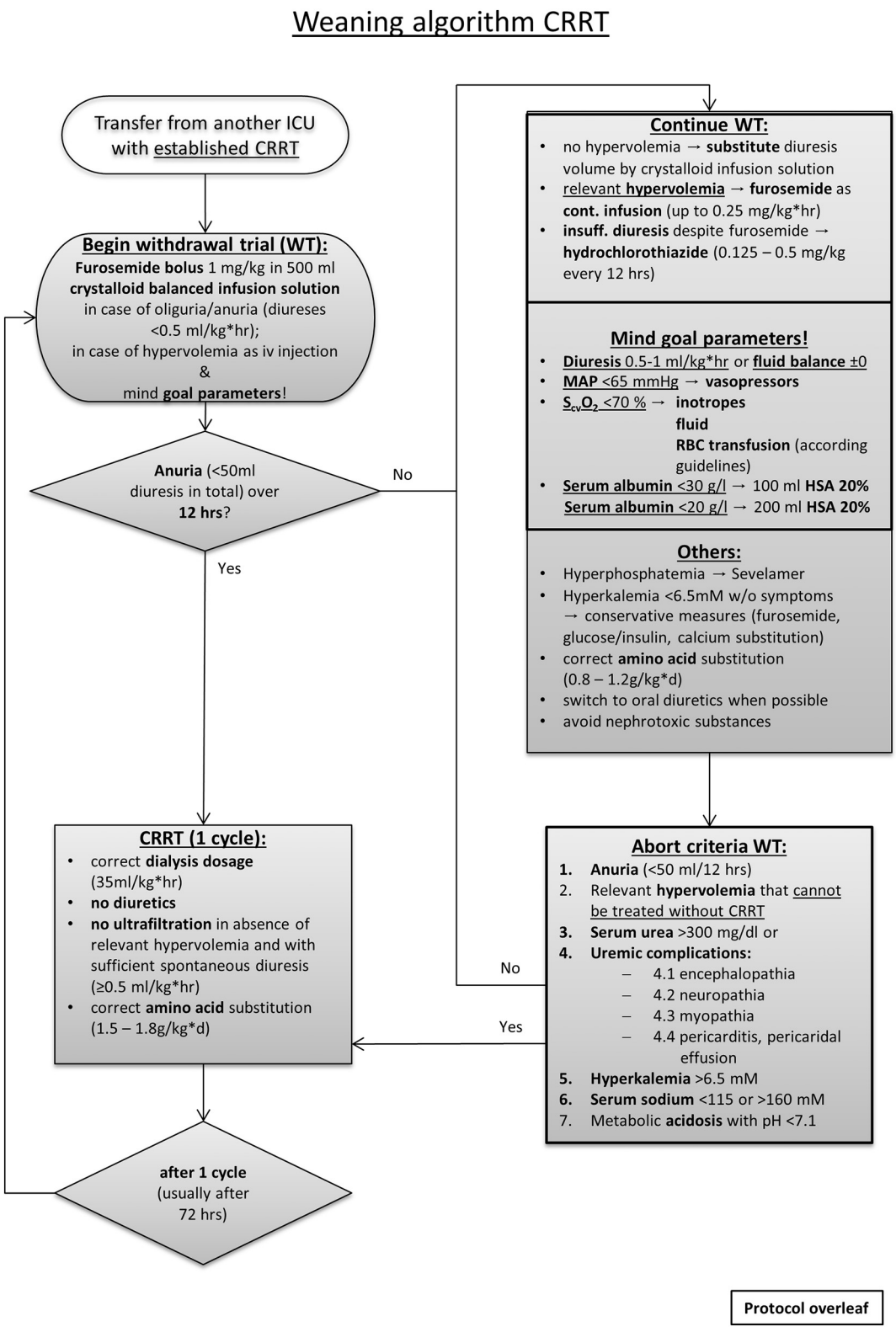

Fig. 1. CRRT weaning algorithm. CRRT = Continuous Renal Replacement Therapy, WT = Withdrawal Trial, MAP = Mean Arterial Pressure, $S_{cv}O_2$ = Central Venous Oxygen Saturation, RBC = Red Blood Cell Concentrate.

AA substitution should be between 0.8 and 1.2 g/kg BW*d during the WT. In general, nephrotoxic substances should be limited to the necessary minimum.

Clearly stated criteria are given for when to abort the WT and to re-initiate RRT. This is done in case of anuria over ≥12 h or in the presence of clinically relevant fluid overload that demands RRT. The same applies to uremia with serum urea >300 mg/dl or below this limit when uremic complications occur. Last, electrolyte or metabolic disorders with critical serum potassium or sodium values or pH derangement lead to abortion of the WT.

Weaning protocol CRRT

Patient name and birthdate	Date				✓ ≙ „Yes" (within the last 6 hrs) — ≙ „No" (within the last 6 hrs)
	14.00	20.00	2.00	8.00	
Withdrawal trial (WT)?					
Sufficient diuresis (≥0.5 ml/kg BW*hr)?					
Diuresis volume substituted?					
Furosemide currently administered [mg/hr]					
Hydrochlorothiazide [mg]					(cummulative dosage during the last 6 hrs)
Goal parameters:					
MAP >65 mmHg?					
$S_{cv}O_2$ >70 %?					
Serum albumin >30 g/l?					
Vasopressors/inotropes administered?					
Fluid/RBCs administered?					
Albumin substituted?					
AA substitution adjusted (0.8 - 1.2 g/kg BW*d)?					
Checked WT abort criteria?					
CRRT?					
Sufficient diuresis (≥0.5 ml/kg BW*hr)?					
Correct dialysis dosage (≥35 ml/kg BW*hr)?					
Current ultrafiltration flow rate [ml/hr]					
Diuretics paused?					
AA substitution adjusted (1.5 - 1.8 g/kg BW*d)?					

Algorithm overleaf

Fig. 2. Daily bedside protocol. CRRT = Continuous Renal Replacement Therapy, WT = Withdrawal Trial, MAP = Mean Arterial Pressure, $S_{cv}O_2$ = Central Venous Oxygen Saturation, RBC = Red Blood Cell Concentrate, AA = Amino Acid.

2.2.2. Protocol (Fig. 2):

A daily bedside protocol sheet has to be filled in as long as the patient is not considered to be weaned from RRT. Every 6 h, urine output or ultrafiltration rate as well as the amount of currently administered diuretics, respectively, is recorded, depending on whether a WT or a CRRT cycle is performed. MAP, $S_{cv}O_2$, albumin level, the consideration of the WT abort criteria as well as the pivotal elements of the WT (substitution of spontaneous diuresis volume, administration of vasopressors/inotropes, fluid/RBCs, albumin, and AAs) or the CRRT periods (correct dialysis dosage and AA substitution, discontinuation of diuretics), respectively, have to be ticked off against a checklist (all referred to as 'vigilance goals').

2.3. Data collection and description

In general, data were extracted from patient charts and not from the filled-in protocols. They were retrospectively collected and analyzed for patients on the ICU1 (protocol-directed weaning) and ICU2 (physician-directed weaning). Percentage achievement of the vigilance goal parameters in both cohorts refers to time spans of 6 h, since during algorithm-based weaning, this is the respective query interval. All data were transferred into MS Excel (Microsoft Corp., Redmond, USA). Statistical analysis was performed using IBM SPSS 24 (Armonk, NY, USA). Frequencies are given as absolute numbers, and continuous variables are described as median with range. Significance of differences between the two cohorts is tested using the non-parametric Mann-Whitney *U* test. *P* values <.05 were considered statistically significant. The datasets generated and analyzed are available from the corresponding author on reasonable request.

3. Results

Charts from 30 patients (15 consecutive patients on either ICU) were retrospectively analyzed. Basic characteristics of patients are shown in Table 1.

3.1. Algorithm-based WT periods are longer and result in increased urine output during CRRT withdrawal

15 patients were weaned according to the algorithm on 207 ICU days in total, and 159 daily bedside protocols had been filled in (77%). 23 WTs had been performed in total, 11 of which had been terminated because the abort criteria had been fulfilled (48%): 3 due to persistent anuria, 2 due to clinically relevant hypervolemia, 3 due to uremic side effects (encephalopathy), and 3 due to high serum potassium or metabolic acidosis. On the reference ICU, 36 WTs had been performed during the same period, 23 of which had been aborted (64%): 11 due to persistent anuria, 2 due to clinically relevant fluid overload, and 1 due to uremic side effects. In 9 cases, the reason for aborting the WT was not to be identified retrospectively. Details on the WT periods are given in Table 2. Although not significant, the data suggest that WT periods were longer when the algorithm-based approach was used (median averaged duration of WT periods 159 h), compared to physician-directed weaning (102h). This also applies when WT duration was normalized to the total observation time. With regard to the patients' shortest WT period, this was 102 h in median in the protocol-based cohort, compared to 25 h in the cohort with the standard procedure. Diuresis volume was significantly higher when using the weaning algorithm. Accordingly, since the protocol demands substituting the urine output, the amount of infused crystalloid fluids was likewise higher than on the reference ICU. The same applied for the substitution of human albumin solution. There were no differences in given diuretics or vasopressors and inotropes. However, target $S_{cv}O_2$ was reached in >90% of the WT periods in the protocol cohort, compared to 41% in the reference patients.

Table 2
Withdrawal trial periods.

Parameter	Physician-directed	Protocol-directed	*p* value
Total number of WTs per patient	2 (0–7)	1 (0–7)	0.17
Percentage of total observation time	59 (0–100)	78 (0–100)	0.46
Mean WT duration (hrs)	102 (7–186)	159 (55–189)	0.19
Shortest WT (hrs)	25 (0–186)	102 (0–189)	0.14
Longest WT (hrs)	176 (0−210)	180 (0–189)	0.59
Vigilance goals:			
Diuresis volume (ml/kg*hr)	1.21 (0–1.77)	1.66 (0.42–2.91)	0.02
MAP >65 mmHg? (%)	100 (100−100)	100 (100–100)	1.00
$S_{cv}O_2$ > 70%? (%)	41 (0–100)	93 (28–100)	**0.003**
Serum albumin >30 g/l? (%)	0 (0–61)	0 (0–97)	0.41
Diuresis volume substituted? (%)	59 (23−100)	62 (35–100)	0.49
AA substitution adjusted? (%)	59 (0–100)	80 (0–100)	0.4
Interventions:			
Mean furosemide dsg. (mg/kg*hr)	0.05 (0.02–0.18)	0.1 (0.01–0.46)	0.06
Mean torasemide dsg. (mg/kg*hr)	0 (0–0.01)	0 (0–0.01)	0.98
Mean HCTZ dsg. (mg/kg*hr)	0 (0–0.02)	0.01 (0–0.03)	0.28
Mean NE dsg. (μg/kg*min)	0.003 (0–0.23)	0.003 (0–0.22)	0.69
Mean vasopressin dsg. (IU/kg*hr)	0 (0–0)	0 (0–0.01)	0.96
Mean dobutamine dsg. (μg/kg*min)	0 (0–2.76)	0 (0–2.52)	0.76
Mean crystalloid inf. Vol. (ml/kg*hr)	1.5 (0.8–3)	1.7 (1.4–5.6)	**0.04**
Mean albumin dsg. (mg/kg*hr)	2.1 (0–12.5)	6.1 (0–25.4)	**0.04**

Values are given as median (with range) of the individual averaged values. Data in percent describe the fraction of WTs with the respective vigilance goal being achieved. Significance of differences between conservative and protocol-based treatment regimen was tested using Mann-Whitey *U* test. P values <.05 are given in bold numbers.
WTs = Withdrawal Trials, MAP = Mean Arterial Pressure, $S_{cv}O_2$ = Centralvenous Oxygen Saturation, AA = Amino Acid, dsg. = dosage, HCTZ = Hydrochlorothiazide, NE = Norepinephrine.

3.2. The algorithm has no apparent influence on CRRT periods

One important element of our algorithm is, in addition to support the WTs, to improve the quality of treatment during periods of CRRT in order to increase weaning success. In the two analyzed cohorts, no apparent influence of the protocol-based approach on recorded parameters during CRRT periods could be identified (Table 3). Although these

Table 3
Renal replacement therapy periods.

Parameter	Physician-directed	Protocol-directed	*p* value
Total number of RRTPs	1 (0–7)	1 (0–6)	0.23
Percentage of total observation time	40 (0–100)	30 (0–100)	0.49
Mean RRTP duration (hrs)	104 (55–341)	109 (41–271)	0.86
Shortest RRTP (hrs)	66 (0–329)	64 (0–271)	0.79
Longest RRTP (hrs)	83 (0–384)	70 (0–287)	0.42
Vigilance goals:			
Ultrafiltration (UF) rate (ml/kg*hr)	1.7 (0.9–2.5)	1.4 (0.1–2.9)	0.44
Dialysis dosage (ml/kg*hr)	22 (16–32)	27 (20–49)	0.23
Diuretics discontinued? (%)	96 (59–100)	97 (0–100)	0.97
AA substitution adjusted? (%)	44 (0–100)	69 (0–100)	0.48

Values are given as median (with range) of the individual averaged values. Data in percent describe the fraction of RRTPs with the respective vigilance goal being achieved. Significance of differences between conservative and protocol-based treatment regimen was tested using Mann-Whitey U test.
RRTP = Renal Replacement Therapy Period, AA = Amino Acid.

periods seemed to be shorter in general when the algorithm was used, this was not significant.

3.3. Global indicators of renal performance and oxygen delivery during protocol-based CRRT weaning

Global indicators of renal damage and performance are given in Table 4. While median serum creatinine (SCr) and urea were not altered when using the algorithm in comparison to the standard treatment, the liberal abort criterion for elevated serum urea during WT periods (>300 mg/dl) resulted in tolerating maximum averaged levels of up to 219 mg/dl (124 mg/dl in reference cohort). Serum lactate was low in both patient cohorts, and minimum hemoglobin values were likewise not different. The minimum $S_{cv}O_2$ was significantly lower in the reference patients than in the ones weaned according to the algorithm, suggesting optimization of global oxygen delivery.

On both units, 12 of the 15 patients were successfully weaned from RRT during the observation period. The others were transferred to another intensive or intermediate care unit still requiring RRT. Median duration from admittance to one of the two ICUs and thereby entering the weaning process until successful weaning from RRT was 1.5 (0–46) days with the protocol-directed and 5 (0–44) days with physician-directed weaning (not significant). None of the patients died during the observation period.

4. Discussion

RRT, once initiated, often receives little attention during everyday ICU life. Withdrawal trials are often aborted much too early due to underestimation of the patient's capability to recover renal function. Since the duration of RRT is directly and independently related to the patient's morbidity and mortality [3,15], we need to think about how to improve weaning from RRT.

There is a substantial body of evidence that protocol-based approaches help weaning patients from e.g., opioids, immunosuppression, ECMO therapy or, most prominent, from mechanical ventilation [7,16-18]. Protocol-based weaning from the respirator follows two main principles: '*Weaning begins with the intubation.*' and '*Start and continue weaning unless there is a good reason not to.*'. This may sound somewhat general, and it explains why algorithms in general increase weaning success, but no specific protocol has been shown to be superior to another [19].

These principles also form the basis of our algorithm for the weaning of patients from RRT due to AKI and are realized by the following three cornerstones:

4.1. Bring the weaning into focus

Withdrawal trials in predefined intervals are mandatory unless clearly stated abort criteria are met. If the WT fails (i.e., meeting at least one abort criterion), only one cycle of RRT is performed, immediately followed by another WT. This is to prevent the CRRT device from being reinstalled over and over again after filter expiration. Regular screening in predefined intervals increases attention for the process of weaning and is, e.g., in the form of a daily wean screen, a key element of protocols to wean patients from respirator [20,21].

Only patients already on RRT were subjected to weaning at admittance to the wards. This does, however, mean that specific entry criteria for protocol-based weaning, such as e.g., hemodynamic or pulmonary stability, will have to be established if this approach is transferred to other institutions.

4.2. Optimize and reevaluate conditions for successful weaning

Diuretics are commonly used to prevent or treat AKI by pushing diuresis. However, despite theoretical benefits due to the reduction of renal oxygen consumption [22], several randomized controlled trials (RCTs) have shown that furosemide in AKI is ineffective or may be even detrimental [23,24]. On the other hand, urine output at the beginning of a WT was shown to be predictive for a successful discontinuation, regardless whether diuretics were used or not [9-12,14]. Moreover, in AKI, fluid overload is associated with an increased mortality and the use of diuretics to achieve a balanced fluid status results in improved outcome and is therefore recommended by the European Society of Intensive Care Medicine (ESICM) [10,25,26]. According to our algorithm, WTs are started with a bolus of furosemide and crystalloid infusion solution. Urine output then is maintained by substituting diuresis volume. The use of diuretics is restricted to fluid overload and only permitted during WTs to keep cumulative dosages as low as possible and to avoid hypotension. Goals are a sufficient diuresis as well as a balanced fluid status. In our small cohort, the protocol-based approach had no influence on the administration of diuretics. However, urine output during WTs was significantly increased, as well as crystalloid infusion volume, suggesting that diuresis was maintained by administering fluid, as intended by the algorithm. In addition, WT abortion due to persistent anuria occurred not as frequent as on the reference ICU. However, future studies should address the question how intensive use of diuretics influences the long-term outcome of AKI and post-AKI patients.

Second goal is to keep MAP above 65 mmHg to maintain sufficient renal blood flow, assuming that autoregulation may be impaired in critically ill patients. This arbitrary value is likewise oriented towards the ESICM recommendations [26]. There is some evidence for a critical role of hypotension for the development and progression of AKI [27,28]. A recent retrospective analysis on AKI patients requiring RRT revealed that a MAP below a threshold of 64 mmHg was independently associated with a poor outcome [29]. Individually determined target values may become more significant in future [27]. This is furthermore underlined by the fact that an acutely increased MAP is likewise associated with failing RRT withdrawal [11].

Several studies have demonstrated an association of lowered $S_{cv}O_2$ values with organ failure [30,31]. Thus, $S_{cv}O_2$ is to be kept above 70% according to our protocol, either by administering inotropes, fluid or, according to recent hemotherapy guidelines, RBC transfusion. The algorithm did not influence the number of transfused RBC units. However, target $S_{cv}O_2$ was significantly more often achieved with protocol-

Table 4
Renal damage and performance, overall oxygen delivery.

Parameter	Physician-directed	Protocol-directed	*p* value
Noxious agents			
CA examinations per day (n)	0.02 (0–0.13)	0 (0–0.22)	0.26
Mean aminoglycoside dsg. (mg/kg*d)	0 (0–4.2)	0 (0–3.2)	0.58
Mean vancomycin dsg. (mg/kg*d)	1.7 (0–16.1)	0 (0–19.7)	0.36
Renal performance			
Max. serum creatinine (fold from bl)	2.2 (0.5–5.9)	1.3 (0.6–3.9)	0.17
Mean serum creatinine (mg/dl)	1.9 (0.7–3.4)	1.6 (0.9–3.9)	0.66
Mean serum creatinine (fold from bl)	1.2 (0.3–3.3)	0.8 (0.3–2.2)	0.13
Max. serum urea (fold from bl)	2.1 (0.5–5.6)	1.5 (0.7–4.0)	0.49
Mean serum urea (mg/dl)	83 (37–124)	86 (33–219)	0.42
Mean serum urea (fold from bl)	1.4 (0.3–2.3)	0.9 (0.3–2.7)	0.69
Oxygenation			
Minimum $S_{cv}O_2$ (%)	54 (47–75)	66 (53–75)	**0.004**
Maximum serum lactate (mmol/l)	1.9 (1.2–4.7)	2.1 (1.2–9.9)	0.20
Minimum hemoglobin (g/dl)	6.8 (5.5–8.6)	7.2 (6.0–8.7)	0.34

Values are given as median (with range) of the individual averaged values. Significance of differences between conservative and protocol-based treatment regimen was tested using Mann-Whitey U test. P values <.05 are given in bold numbers.
CA = Constrast Agent, dsg. = dosage, bl = baseline value, $S_{cv}O_2$ = Centralvenous Oxygen Saturation.

based weaning, and individual lowest values were significantly above the ones in the reference cohort, most likely due to increased crystalloid infusion volume.

Hypoalbuminemia is independently related to AKI development and progression and to failing RRT withdrawal [11,32]. A recent RCT revealed that substituting human albumin solution in patients with hypoalbuminemia (defined by a liberal threshold value of 40 g/l) increases urine output and decreases incidence of AKI following cardiac surgery [33]. In our cohort, increased urine output, together with significantly higher dosages of administered albumin solution, may be indicative of improved renal recovery due to albumin substitution.

In 2017, Mendu et al. already proposed a decision-making algorithm to manage and standardize the therapy of patients developing AKI that can be compared to ours and which they call SCAMP (Standardized Clinical Assessment and Management Plan) [34]. However, unlike our approach, their algorithm rather focuses on when to begin RRT. Regular WTs are not mandatory. Most importantly, the algorithm lacks all the specific goal parameters that are key elements of our protocol to optimize the quality both of WT as well as of CRRT periods. Consequently, the authors found "… *no differences in outcomes* […] *for discontinuing RRT*" when using their algorithm. The lack of key goals also applies to a simple diagram that was presented by Klouche et al. in 2018 [35].

While our flowchart-like algorithm integrates all those respective key goals and gives recommendations on how to achieve them, the daily bedside protocol is used to increase the personnel's vigilance. The treating physician is periodically prompted to reevaluate and -adjust the therapy, to intervene if the goals are missed, and to check if criteria to abort a WT are met. It has been shown that protocols are useful instruments to improve physician adherence to structured therapy algorithms [36].

4.3. Continue weaning unless there is a good reason not to

Clearly stated criteria for when to abort a withdrawal trial are crucial in every weaning protocol [21]. We defined seven criteria, each of which, if fulfilled, results in resuming CRRT. They are mostly based on the KDIGO criteria, recommending to urgently initiate RRT "… *when life-threatening changes in fluid, electrolyte, and acid-base balance exist*" [6]. While threshold values for serum potassium, sodium, and pH as well as clinically relevant fluid overload seem reasonable criteria to abort a WT, a serum urea cut-off value of >300 mg/dl might appear somewhat liberal. According to our experience, weaning from RRT very often fails as WTs are aborted too early, triggered by a sole increase in serum urea without any associated uremic symptoms. Isolated elevation in serum urea represents no indication for RRT and is not outcome-related in AKI patients [37-40]. Thus, no upper limit of serum urea absolutely requiring RRT can be defined. However, it is consensus that uremic complications such as e.g., encephalopathy or pericardial effusions constitute an indication to urgently initiate or resume RRT in AKI patients [38,40].

Several authors have identified and evaluated parameters to predict successful weaning from CRRT. For example, Viallet et al. showed that a daily urinary creatinine excretion ≥5.2 mmol was associated with successful discontinuation of RRT in 84% of AKI patients [41]. In accordance with that, Shealey et al. could demonstrate that a 24-h creatinine clearance above 15 ml/min predicted successful termination of CRRT [42]. In addition, more sophisticated markers such as serum neutrophil gelatinase-associated lipocalin (NGAL) were recently likewise shown to be of value for the prediction of RRT weaning success [43]. In our algorithm, defined clinical and laboratory parameters are used to increase likelihood of weaning success (goal parameters) or to avert harm from the patient (abort criteria). Possibly, in a next step, the inclusion of parameters with predictive character could further increase the clinical usefulness of such protocol. This would have to be evaluated in subsequent studies.

In our small cohort, the clear definition of abort criteria probably helped reducing the WT abort ratio compared to the reference ICU. This was likely due to prolongation of the WT periods. Most often, persisting anuria triggered termination, however, probably due to an overall increased urine output, this was not as frequent in the protocol- than in the physician-directed cohort. According to the abort criteria, maximum accepted serum urea levels exceeded those in the reference cohort. Strikingly, in the latter one, the reason to abort a WT was implausible in retrospect in a substantial number of cases, questioning the absolute necessity of termination.

5. Conclusions

We are the first to develop a structured approach to wean AKI patients from RRT that bundles established interventions and aims to bring the weaning into the physician's focus. We conclude that the implementation of our protocol into the clinical routine is feasible. We experienced no relevant adverse side effects of the algorithm, compared to a conservative physician-directed strategy. This report has its limitations. It lacks the consideration of implementation of intermittent RRT due to the unavailability on the respective ICUs. Furthermore, due to a very small cohort and a restricted follow-up period, it can only be viewed as hypothesis-generating. An influence on patient outcome cannot be estimated and management of patients during their acute postoperative or posttraumatic period or of those with preexisting chronic kidney disease requiring dialysis or with prolonged or even persistent AKI is not covered by our observation. This reduces the generalizability of the results significantly. If, as our data suggest, this approach might have a positive effect on the duration of the weaning process, will have to be evaluated in a larger prospective and randomized trial.

Declarations of interest

None.

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