Kidney & Blood Pressure Research

Kidney Blood Press Res 2017;42:327-337
DOI: 10.1159/000477609
Published online: June 07, 2017
Accepted: March 27, 2017

Original Paper

Filter Size Not the Anticoagulation Method is the Decisive Factor in Continuous Renal Replacement Therapy Circuit Survival

Monika Miklaszewska[a] Przemysław Korohoda[b] Katarzyna Zachwieja[a]
Krzysztof Kobylarz[c] Constantinos J. Stefanidis[d] Alina Sobczak[e] Dorota Drożdż[a]

[a]Department of Pediatric Nephrology and Hypertension, Jagiellonian University Medical College, Kraków, Poland; [b]AGH University of Science and Technology, Faculty of Computer Science, Electronics and Telecommunications, Department of Electronics, Kraków, Poland; [c]Department of Anesthesiology and Intensive Care, Institute of Pediatrics, Jagiellonian University Medical College, Kraków, Poland; [d]Department of Pediatric Nephrology "A. and P. Kyriakou" Children's Hospital, Athens, Greece; [e]Department of Pediatrics, Faculty of Medicine, Jagiellonian University, Kraków, Poland

Key Words
CRRT • PICU • Anticoagulation • Circuit • Filter • Clotting

Abstract
Background/Aim: As continuous renal replacement therapy (CRRT) has emerged as a standard therapy in pediatric intensive care units (PICU), many related issues that may have an impact on circuit survival have gained in importance. Objective of the study was an evaluation of factors associated with circuit survival, including anticoagulation (ACG). ***Methods:*** Retrospective study that included 40 patients, who in total received 7636 hours of CRRT during 150 sessions (84 filters, 4260 hours with heparin anticoagulation (Hep-ACG); 66 filters, 3376 hours with regional citrate anticoagulation (RCA)). ***Results:*** The Kaplan-Meier analysis of the total circuit survival time depending on the type of ACG did not demonstrate a significant difference between Hep-ACG and RCA. The percentage of clotted filters was significantly higher in case of smaller filters (HF20: 58.8%; ST60:29.5%; ST100: 15.8%), and their lifetime was significantly lower regardless of ACG (the mean and median lifetime for HF20: 38.7/27.0 h; for ST60: 54.1/72.0 h., for ST100: 62.1/72.0 h, respectively). ***Conclusions:*** Irrespectively of filter size, filter clotting occurs within the first 24 hours after the initiation of CRRT. Most commonly, clotting affects small filters, and their lifetime is significantly shorter as compared to larger filters regardless of the type of the ACG.

Monika Miklaszewska MD. PhD.
Department of Pediatric Nephrology and Hypertension, Jagiellonian University Medical College, Wielicka St. 265, 30-663 Kraków (Poland)
Tel. +48-606262484, Fax +48-126590663, E-Mail mmiklasz@wp.pl; mmilasz@mp.pl

Introduction

Owing to technical improvements over the past two decades, in many developed countries continuous renal replacement therapy (CRRT) has become the most preferred technique in managing critically ill children treated in pediatric intensive care units (PICUs) for acute kidney injury (AKI) and multi organ failure (MOF) [1].

As this technique has emerged as a standard, extracorporeal, supportive therapy, many CRRT-related issues that may potentially have an impact on the mortality in this patient population or on circuit survival have gained in importance [2]. One of these factors is the modality of the employed anticoagulation (ACG). Anticoagulation of the extracorporeal blood is necessary to maintain the patency of the circuit [3].

Currently, heparin anticoagulation (Hep-ACG), and regional citrate anticoagulation (RCA) remain the most commonly reported CRRT ACG methods in children. In recent years, Hep-ACG has been the most commonly used as the ACG modality [4]. Although heparin has the advantages of low cost, easy monitoring and simple reversal, it may increase the risk of life-threatening complications, such as bleeding or heparin-induced thrombocytopenia type II [5].

For a couple of years, RCA lacking systemic anticoagulation, which is an optimal option, especially in patients with a high bleeding risk [6, 7], offered an attractive alternative to Hep-ACG [8, 9]. Although citrate is primarily used for extracorporeal anticoagulation, it also has an effect on energy supply, membrane-induced inflammation and indirectly on parathyroid hormone secretion. As citrate acts by chelating calcium and consequently inhibiting the clotting cascade, its infusion may lead to hypocalcemia, metabolic alkalosis and citrate toxicity [10].

As the efficacy of CRRT therapies is directly related to the running time of the circuit and the most common complication is early clotting of the filter, hence it is important to use the best modality of ACG in those therapies. The ideal anticoagulant should act selectively in the circuit with minimal effects on patient homeostasis, be safe, available, consistently delivered, easily monitored, and reversible, and it should provide prolonged filter lifetime and high cost-effectiveness [11, 12].

Despite considerable technological advances, there still remains space for significant improvement both in the patient outcomes and in the outcomes of circuit survival, as frequent circuit changes increase not only the nursing workload, blood loss and economic costs, but also compromise achievement of the filtration rate goals [13].

The main objective of the present study was an evaluation of the factors (comprising filter sizes and pressures characterizing the CRRT procedure) associated with circuit survival time, including the modality of the employed anticoagulation.

Material and Methods

The present report describes an analytical, retrospective, single-center, chart-review study that included all 40 patients having been admitted to PICU in a tertiary pediatric center between January 2009 and June 2016 and required CRRT. In total, the analyzed patients received 7636 hours of CRRT during 150 CRRT sessions (on Hep-ACG: 84 filters, 4260 hours of CRRT, on RCA: 66 filters, 3376 hours of CRRT).

The investigation was approved by the local Bioethical Committee (L.Dz.OIL/KBL/4/2017). The detailed characteristics of the studied population is included in Table 1.

A Prismaflex dialysis machine (Gambro, Spain) was used for CRRT in all patients. Dual lumen catheters between 7 F and 13 F were individually adapted to the child's morphology and body weight according to literature recommendations, using the same criteria for patients treated with citrate (RCA) and heparin anticoagulation (Hep-ACG) [11, 14]. Hollow-fiber filters were used depending on the body weight of the patient according to the manufacturer's guidelines [15].

In all Hep-ACG cases, the predilutional continuous venovenous hemodiafiltration was employed and unfractionated heparin was used. In the Hep-ACG protocol, a heparin bolus was administered during the connection along with a subsequent continuous heparin infusion to achieve a postfilter activated clotting

Table 1. Clinical characteristics of children treated with Hep-ACG and RCA. Pressors, diuretics and hypotensive index medications were calculated by adding the number of days of drug administration in a given patient and dividing the resultant sum by the number of days of PICU hospitalization of the same patient

Variable; Mean [SD]/ Median [IQR]	Hep-ACG (n=32; 80%)	RCA (n=8; 20%)	p/pW*	Total
Survivals/Deceased	11/21	5/3	NS*	16/24
Males/Females	17/15	6/2	NS*	23/17
Number of days in PICU	14.5 [10.9]/12.0 [16.0]	37.0 [21.9]/39.5 [37.5]	0.000	19.0 [16.2]/16.5 [19.0]
Day of CRRT start	5.2 [5.3]/2.0 [8.0]	4.4 [8.0]/1.0 [2.0]	NS*	5.0 [5.8]/2.0 [7.5]
Number of CRRT sessions	25 (29.8%) /	29 (43.9%) /	NS	54 (36%)/96 (64%)
clotted (%)/non-clotted (%)	59 (70.2%); 84 (56%)	37 (56.1%); 66 (44%)		150
Age (months)	121.9 [68.3]/ 137.5 [128.5]	96.0 [72.6]/ 96.5 [124.5]	NS	116.7 [69.1]/ 131.0 [130.0]
Body mass (kg)	34.8 [20.7]/29.5 [31.5]	35.2 [24.3]/32.5 [45.0]	NS	34.8 [21.1]/31.5 [33.0]
Primary diagnosis:Onco-Hematology	20	5	NS*	25
Primary diagnosis: Sepsis	3	0	NS*	3
Primary diagnosis: Burn	2	0	NS*	2
Primary diagnosis: Cardiology	1	0	NS*	1
Primary diagnosis: Nephrology	6	3	NS*	6
CRRT – MOF: patients*	24	4	NS*	28
CRRT– AKI and FO: patients **	8	4	NS*	12
Number of patients on mechanical ventilation at CRRT initiation (%)	27 (84,4%)	5 (62.5%)	NS*	32 (80%)
% of days of mechanical ventilation	78.8 [37.2]/100.0 [30.0]	53.8 [46.8]/65.0 [100.0]	NS*	73.8 [40.0]/100.0 [47.5]
Pressors' index during PICU stay	1.0 [0.7]/1.0 [1.2]	0.4 [0.5]/0.2 [0.6]	0.024	0.9 [0.7]/0.9 [1.2]
Diuretics' index during PICU stay	0.66 [0.47]/0.75 [0.85]	0.52 [0.40]/0.55 [0.46]	NS	0.63 [0.45]/0.69 [0.83]
Index of hypotensive medications	0.31 [0.54]/0.00 [0.55]	1.15 [1.04]/1.15 [1.83]	0.005*	0.48 [0.74]/0.00 [0.74]
CRP (mg/l) at CRRT initiation	189.2 [143.6]/ 188.7 [228.5]	119.4 [124.2]/ 71.1 [160.3]	NS	175.2 [141.3]/ 164.5 [222.8]
Total protein (g/l) at CRRT initiation	51.0 [11.3]/51.5 [14.1]	51.7 [11.3]/55.4 [12.3]	NS	51.2 [11.2]/52.2 [14.1]
Albumin (g/l) at CRRT initiation	26.4 [6.3]/26.0 [7.8]	30.1 [8.5]/31.5 [11.5]	NS	27.1 [6.8]/27.6 [9.8]
eGFR [ml/min/1.73m^2 at CRRT initiation	38.3 [23.8]/34.8 [27.7]	36.5 [24.7]/27.4 [35.9]	NS	37.9 [23.7]/33.2 [29.8]
Urea (mmol/l) at CRRT initiation	24.6 [14.6]/24.7 [24.9]	19.3 [6.7]/18.1 [10.4]	NS	23.5 [13.5]/21.7 [20.1]
UO (ml/kg/h) at CRRT initiation	0.78 [0.76]/0.45 [1.25]	1.09 [1.29]/0.70 [1.20]	NS	0.84 [0.88]/0.50 [1.20]
FO% at CRRT initiation	40.3 [35.8]/27.5 [35.8]	25.9 [14.2]/29.8 [24.3]	NS	37.4 [33.0]/27.8 [31.3]

* Main reason of CRRT implementation – MOF: patients' number; ** Main reason of CRRT implementation – AKI and FO: patients' number. UO - Urine output, FO% - fluid overload

time (ACT) between 180 and 240 seconds. The ACT value was checked on average every 2 hours within the first 12 hours of CRRT and then every 4-6 hours.

The RCA procedure was conducted according to the recommendations of Tolwani et al. [9, 16] and Prismaflex Operations Manual guidelines. An initial citrate concentration of 3.0 mmol/L was used for a target postfilter ionized calcium of 0.25 to 0.50 mmol/L. The citrate effect was neutralized using a continuous calcium infusion of 10% (or 5% in children weighting <15 kg) calcium gluconate to maintain ionized calcium blood levels between 0.9 and 1.2 mmol/L [15]. Samples were taken every hour for the first 4 hours and every 6-8 hours afterwards. Total calcium levels were also checked at least once daily. Citrate accumulation was avoided by monitoring the patient's pH status and maintaining the total calcium/ionic calcium index (CaT/CaI) at ≤ 2.5.

In case of the CRRT solutions, for Hep-ACG - Hemosol or PrismaSol 2 (Gambro) as dialysate and Phoxilium or PrismaSol 2 (Gambro) as predilutional substitute were used, whereas for RCA - citrate solution Prismocitrate 18/0 (Gambro) was administered on pre-blood pump (PBP), dialysate normo - carbonate solution PrismOcal B22 (Gambro) was used as calcium-free dialysis solution; and low-flow postfilter infusion of PrismaSol 2 (Gambro) or Phoxillum was employed as postdilutional substitute to avoid deaeration chamber for return line clotting.

In both techniques, dialysate and substitution flow rates were programmed initially to achieve the dialysis dose of at least 35 ml/kg/hour, and then were adjusted to the patient needs. None of the filters were used longer than 72 hours. Blood flow rates (BFR) were determined by the patient body weight and according by the accesses pressures [15].

The collected data pertained to the patients, vascular accesses, filter and circuit characteristics, as well as modality and dose of the employed anticoagulation. The parameters of the CRRT procedure (filter pressure, trans-membrane pressure - TMP, access pressure) were recorded every 2 hours. Due to a large number of native results (4200 results for each parameter) and considerable differentiation in the number of the results among individual filters, to meet the needs of further statistical analysis, a decision was made

to calculate the mean value for each filter, which was obtained following discarding the results with extreme values. The basic dose of CRRT was calculated daily, by average blood, dialysate, supplement and citrate (in case of RCA) flow rates.

For ACT values, heparin doses, calcium compensation percent and citrate doses - all recorded values were included into the statistical analysis.

Prior to the study, 175 CRRT sessions were qualified. However, ultimately the analysis was performed for 150 filters selected when other than clotting causes of premature discontinuation of the procedure (patient decease -14, scheduled diagnostic or therapeutic procedures-11 cases) were excluded from the analysis, whereas cases of scheduled discontinuation of the procedure, when the patient ceased to require further treatment, continued to be included.

Statistical methods

Particular groups of data were described by means of mean values, standard deviation (SD), median values and interquantile range (IQR). The comparison of data groups was performed by the t-Student test when the Gaussian distribution was confirmed by the Kolmogorov-Smirnov test (KS), with the threshold value assumed to be $p>0.1$ (pt). Otherwise, the Wilcoxon rank-sum test was employed (pW). The group sizes were compared using the chi-square test, where Yates correction was used for predicted frequencies below 5. To determine the predictive value and cut-off point for the selected parameters, the analysis of ROC curves was performed, arriving at the following values: Area Under ROC (AUROC), cut-off value based on the Youden index, sensitivity, specificity, Likelihood Ratio (LR), Positive Predictive Value (PPV) and Negative Predictive Value (NPV). The effect of the selected parameters on the cumulative probability of filter survival was analyzed employing the Kaplan-Meier curves and the Mantel-Cox test, while Cox multivariable regression with determination of the Hazard Ratio (HR) was performed in comparing the effect of filter size and type of the applied anticoagulant upon filter lifetime. In all the tests with the exception of KS, the significance threshold was assumed as 0.05. The STATISTICA (version 12, StatSoft, Tulsa, OK, USA) and MATLAB (version 2015a, Mathworks, Natick, MA, USA) packages were used for all computations and to create the graphs.

Results

As it follows from the data presented in Table 1, in total, the analysis was performed for 7636 hours of CRRT, including 4260 hours of filter operation on Hep-ACG and 3376 hours of filter operation on RCA. In total, filter clotting occurred in 36% of the filters, including 29.8% Hep-ACG filters and 43.9% RCA filters. No significant difference was observed between the number of filters on Hep-ACG vs. RCA subpopulations, what indicates that the studied filter populations were mutually equivalent and representative. In the studied population, no difference was noted in mortality rates between the groups where Hep-ACG and the RCA was employed. Similarly, no differences were found in the majority of the analyzed clinical parameters describing the investigated patient population. The only significant difference involved the number of days at PICU (children treated employing the RCA method were hospitalized for a longer period) and the pressors and hypotensive medications indices.

The number of hours of CRRT sessions employing HF20 filters was 1976, ST60: 3300, and ST100: 2360. Already at the stage of the preliminary analysis, it was demonstrated that in case of smaller filters, significantly higher dialysis doses were employed, higher blood flow rates were seen, while filter survival was significantly lower. The longest survival time was demonstrated by large filters (Table 2).

As it follows from the data presented in Table 3, clotted filters – regardless of their size - were characterized by higher filter pressure values, higher TMPs values and lower values of access pressure (what may be associated with a poorer quality of vascular access). On the other hand, no significant differences were noted in the parameters of the employed anticoagulation, both in the case of Hep-ACG and RCA, with the exception of HF20 filters, where a significantly higher heparin dose was noted at the beginning of the session (bolus), as well as a higher citrate dose in clotted filters and ST60 filters, where the mean ACT values were significantly higher in case of clotted filters. In case of the smallest filters, the circuits

Table 2. General characteristics of all the studied filters. The variables are described as mean values [SD]/ median values [IQR].(P1: HF20 vs. ST60; P2: HF20 vs. ST100; P3: ST60 vs. ST100), BFR - blood fow rate

Variable	HF20 (n=51)	ST60 (n=61)	ST100 (n=38)	P1 pt/pW*	P2 pt/pW*	P3 pt/pW*	Total (n=150)
Body mass (kg)	9.5 [2.7]/ 10.0 [3.8]	35.7 [18.7]/ 35.0 [31.9]	59.0 [13.4]/ 60.5 [20.0]	0.000*	0.000*	0.000*	33.7 [23.5]/ 25.0 [44.0]
Circuit survival time (h)	38.7 [25.3]/ 27.0 [52.8]	54.1 [23.6]/ 72.0 [34.2]	62.1 [19.7]/ 72.0 [3.0]	0.002*	0.000*	0.035*	50.9 [25.0]/ 69.0 [48.0]
CRRT dose (ml/kg/h)	89.8 [24.7]/ 87.1 [17.8]	52.3 [17.7]/ 47.8 [26.6]	47.9 [12.3]/ 48.0 [17.3]	0.000*	0.000*	NS	62.7 [26.3]/ 56.0 [34.0]
BFR (ml/kg/min)	4.0 [1.1]/ 3.5 [0.5]	2.3 [0.8]/ 2.1 [1.5]	1.9 [0.5]/ 2.0 [0.9]	0.000*	0.000*	0.027*	2.7 [1.2]/ 2.4 [1.8]

Table 3. Detailed filter characteristics: 1 - CRRT session discontinuation due to filter clotting; 2-scheduled CRRT session discontinuation. The variables are presented as mean values [SD]/median values [IQR]. Negative access pressure is described in the table by an absolute value, TMP - trans membrane pressure, BFR - blood flow rate

Variable	HF20-1 30 (58.8%)	HF20-2 21 (41.2%)	P1 pt/pW*	ST60-1 18 (29.5%)	ST60-2 43 (70.5%)	P2 pt/pW*	ST100-1 6 (15.8%)	ST100-2 32 (84.2%)	P3 pt/pW*
HepACG/RCA	7/23	8/13	NS	13/5	33/10	NS	5/1	18/14	NS
Patient body mass (kg)	8.5[1.9]/ 10.0[3.8]	10.5[2.9]/ 10.0[1.5]	0.030*	33.8[21.3]/ 25.0[41.3]	35.9[18.2]/ 42.0[31.8]	NS	64.0[6.9]/ 65.0[10.0]	58.3[14.0/ 60.5[20.0]	NS
Filters survival time (h)	22.5[14.0]/ 19.5[14.0]	62.0[18.9]/ 72.0 [4.5]	0.000*	21.2[12.7]/ 20.0[13.0]	67.8[8.6]/ 72.0[3.0]	0.000*	23.8[13.5]/ 25.0[21.0]	69.3[9.8]/ 72.0[0.0]	0.000*
Filter pressure (mmHg)	102.8[21.6]/ 104.0[29.7]	75.8[13.6]/ 72.5[19.3]	0.000	131.8[31.5]/ 126.5[33.0]	86.4[21.6]/ 84.6[36.2]	0.000	151.5[24.7]/ 148.5[38.3]	101.7[28.2]/ 97.7[37.8]	0.000
TMP (mmHg)	111.5[65.9]/ 83.1[92.4]	62.2[24.0]/ 54.5[36.4]	0.001	121.9[70.0]/ 97.9[47.3]	87.1[31.5]/ 79.2[43.0]	0.004	143.1[20.4]/ 138.9[20.9]	100.3[23.4]/ 94.5[40.7]	0.000
Access	63.4[35.0]/ 56.1[36.3]	37.9[11.5]/ 35.6[9.9]	0.001	65.5[30.3]/ 67.7[36.3]	41.2[18.2]/ 40.5[22.1]	0.000	102.4[41.2]/ 120.6[58.3]	44.1[16.8]/ 43.2[17.1]	0.000
ACT (sec.)	128.6[13.4]/ 122.6[20.8]	117.9[18.1]/ 125.2[28.3]	NS	184.8[62.3]/ 171.5[86.8]	144.2[33.1]/ 134.8[40.0]	0.017*	120.7[19.8]/ 110.3[24.3]	136.5[34.4]/ 135.1[52.4]	NS
Heparin bolus at the session start (mg/kg)	0.39[0.13]/ 0.40[0.07]	0.22[0.16]/ 0.18[0.17]	0.044*	0.22[0.10]/ 0.20[0.05]	0.23[0.12]/ 0.20[0.08]	NS*	0.11[0.02]/ 0.10[0.01]	0.07[0.07]/ 0.07[0.10]	NS*
Heparin dose (mg/kg/h)	0.17[0.23]/ 0.05[0.14]	0.11[0.05]/ 0.11[0.08]	NS	0.14[0.07]/ 0.10[0.11]	0.17[0.07]/ 0.16[0.09]	NS	0.10[0.03]/ 0.09[0.05]	0.08[0.08]/ 0.04[0.12]	NS*
Calcium compensation (%)	68.0[11.9]/ 70.0[17.3]	55.6[20.4]/ 57.9[35.0]	0.025	62.2[22.6]/ 65.0[30.6]	78.2[18.9]/ 80.0[22.9]	NS	80.0[0.0]/ 80.0[0.0]	76.0[15.4]/ 78.3[20.0]	NS*
Citrate dose (mmol/l)	3.19[0.15]/ 3.10[0.20]	3.04[0.19]/ 3.07[0.22]	0.008	3.11[0.13]/ 3.20[0.19]	3.15[0.16]/ 3.13 [0.24]	NS	2.80[0.0]/ 2.80[0.0]	3.04[0.33]/ 3.05[0.33]	NS*
CRRT dose (ml/kg/h)	94.8[24.2]/ 89.7[18.5]	83.2[24.9]/ 79.4[21.0]	NS*	55.7[17.0]/ 54.6[29.8]	51.3[18.2]/ 46.5[24.7]	NS*	46.8[8.2]/ 45.6[16.4]	48.1[12.9]/ 48.0[16.8]	NS
BFR (ml/kg/min)	4.0[1.1]/ 3.5[0.5]	4.1[1.3]/ 3.5[0.5]	NS*	2.3[0.9]/ 2.0[1.1]	2.3[0.8]/ 2.4[1.5]	NS*	1.7[0.4]/ 1.6[0.8]	2.0[0.5]/ 2.0[0.8]	NS*

employed in treating children with lower body mass were demonstrated to significantly more frequently be clotted. However, no differences were observed in dialysis doses between the groups of filters that were and were not clotted. The mean and median CaT/CaI ratio for RCA in the current study indicating citrate accumulation was 2.11 [SD:0.27]and 2.10 [IQR:0.28] mmol/l, respectively, which was within normal limits.

As it follows from the analysis of the sole sub-population of 54 filters that were clotted, clotting most commonly affected small as compared to larger filters (HF20 vs. ST60: pt=0.001; HF20 vs. ST100: pW=0.018); while there were no significant differences in clotting frequency between ST60 vs. ST100 filters; no difference was also noted in the time needed by particular filters to become clotted. The significantly longest ACT time was maintained in case of ST60 filters (ST60 vs. HF20: pt=0.032 and ST60 vs. ST100: pt=0.041). On the other hand, the highest doses of heparin administered at the beginning of the procedure as boluses per one kilogram of body mass were given to the smallest children (HF20 vs. ST100: pW=0.016; HF20 vs. ST100: pW=0.015; ST60 vs. ST100: pW=0.005). In case of RCA, no significant differences were noted between clotted filters in ACG parameters.

Data presented in Table 4 and Fig. 1 indicate that no significant differences were noted in the total filter running time depending on the type of the ACG employed. Citrate flow in the RCA technique – in case of HF20 filters – was associated with a higher dose of dialysis supplied and a significantly higher TMP, but the differences did not affect the survival time of the circuits. In case of HF20 and ST60 filters, RCA was selected for patients with higher body mass.

Table 4. CRRT parameters depending on the employed ACG modality. The variables are presented as mean values [SD]/median values [IQR], BFR - blood flow rate

Variable	HF20Hep 15 (29.4%)	HF20RCA 36 (70.6%)	P2 pt/pW*	ST60Hep 46 (75.4%)	ST60 RCA 15 (24.6%)	P3 pt/pW*	ST100Hep 23 (60.5%)	ST100 RCA 15 (39.5%)	P4 pt/pW*
Patient body mass (kg)	8.3 [2.2]/ 10.0 [3.9]	10.0 [2.7]/ 10.0 [0.0]	0.021*	29.4 [14.0]/ 25.0 [27.0]	55.8 [17.8]/ 61.0 [16.0]	0.000*	60.2 [12.4]/ 60.0 [20.0]	57.3[14.8]/ 61.0 [19.0]	NS*
Number of clotted filters (%)	7 (46.7%)	23 (63.9%)	NS	13 (28.3%)	5 (30.0%)	NS	5 (21.7%)	1 (6.7%)	NS
Filter survival-time (h)	33.3 [23.8]/ 24.0 [38.8]	41.0 [25.9]/ 41.0 [55.0]	NS*	53.1 [23.8]/ 69.0 [38.0]	57.0 [23.5]/ 72.0 [31.0]	NS*	57.2 [23.3]/ 72.0 [35.0]	69.7 [8.2]/ 72.0 [0]	NS*
Filter pressure - (mmHg)	85.6[24.0]/ 74.7[31.1]	93.2 [22.1]/ 92.4 [33.3]	NS	94.2 [32.3]/ 90.9 [42.8]	106.9[25.0]/ 104.4 [40.1]	NS	118.9 [35.7]/ 117.9 [44.9]	93.0 [18.9]/ 88.2 [21.1]	0.006
TMP (mmHg)	62.8[39.6]/ 48.4[25.2]	103.0[59.9]/ 80.1[84.2]	0.001*	83.8 [42.1]/ 78.3 [34.7]	132.4 [37.6]/ 131.5 [41.0]	0.000*	104.1 [27.8]/ 94.5 [37.3]	108.4 [26.6]/ 107.1 [47.7]	NS
Access (mmHg)	54.7 [33.5]/ 48.6[23.7]	50.8[28.2]/ 41.1[30.4]	NS*	45.1 [24.9]/ 42.3 [25.2]	53.0 [19.9]/ 53.6 [23.4]	NS	59.3 [34.4]/ 49.5 [34.7]	40.8 [11.8]/ 39.6 [10.8]	0.036*
CRRT dose (ml/kg/h)	69.3 [14.5]/ 74.0[19.8]	99.3[22.7]/ 91.3[37.1]	0.000*	53.4 [16.4]/ 48.1 [27.9]	48.7 [21.3]/ 40.3 [29.2]	NS	46.3 [12.3]/ 48.0 [15.7]	50.3 [12.2]/ 48.3 [18.6]	NS
BFR (ml/kg/min)	4.3 [1.4]/ 4.0 [1.7]	3.9 [1.0]/ 3.5 [0.5]	NS*	2.4 [0.8]/ 2.4 [1.4]	1.9 [0.8]/ 1.6 [1.0]	0.008	2.0 [0.5]/ 2.1 [1.1]	1.9 [0.4]/ 1.9 [0.6]	NS*

While assessing the Kaplan-Meier survival curves plotted for the 150 filters for the observation time of 0 to 72 hours and for the observation time of 0 to 36 hours (including the 36-th hour), no significant difference was noted in filter survival values depending on the ACG employed. On the other hand, for the observation time of after 36 to 72 hours of filter operation, there was detected a significant difference in filter survival time in favor of filters with Hep-ACG (the Mantel-Cox test: p=0.004; HR=11.2, p=0.022). Thus, after 36 hours of the circuit operation, the probability of clotting of RCA filters became more than 11-fold higher as compared to Hep-ACG filters. But when the filters were divided into groups according to their size, no differences were noted in survival time between the compared ACG methods, what indicates that differences in filter survival time depend on filter size rather than the employed ACG method.

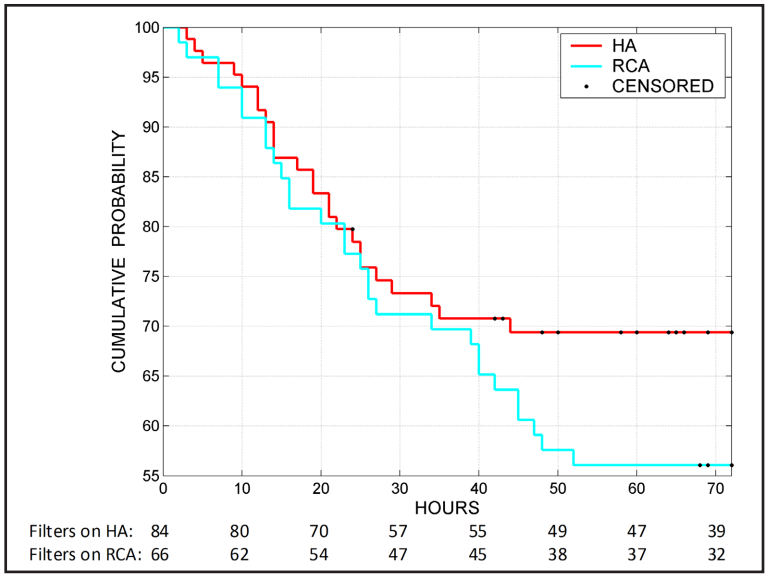

Fig. 1. Kaplan-Meier circuit lifetime survival analysis (n=150). The survival curves were compared with the Mantel-Cox test (NS).

Irrespectively of the type of ACG employed, significant differences were demonstrated in each case in the percentage of filter survival when comparing HF20 vs. ST100 filters. A comparison of survival percentage between HF20 vs. ST60 filters showed significant differences for all the three time points in all the filters, while in the case of Hep-ACG, a significantly lower number of HF20 filters survived 48 and 60 hours, and in case of RCA - 60 and 72 hours of the circuit operation. Differences in percentage of survival between ST60 vs. ST100 filters were non-significant, with the exception of 72 hours in the analysis involving all the filters (Table 5).

The data included in Table 6 confirm the absence of a difference in the percentage of filter clotting depending on their size within a given ACG method, with the exception of a

Table 5. Percentage of filters that survived 48, 60 and 72 hours of the circuit operation; **results obtained with Yates correction due to small frequencies; (P1: HF20 vs. ST60; P2: HF20 vs. ST100; P3: ST60 vs.ST100)

Hep-ACG	48 h	60 h	72 h	RCA	48 h	60 h	72 h	Hep-ACG and RCA	48 h	60 h	72 h
HF20 (n=15)	4 (26.7%)	4 (26.7%)	3 (20%)	HF20 (n=36)	15 (41.7%)	13 (36.1%)	9 (25%)	HF20 (n=51)	19 (37.3%)	17 (33.3%)	12 (23.5%)
ST60 (n=46)	31 (67.4%)	27 (58.7%)	21 (45.7%)	ST60 (n=15)	10 (66.7%)	10 (66.7%)	10 (66.7%)	ST60 (n=61)	41 (67.2%)	37 (60.7%)	31 (50.8%)
ST100 (n=23)	16 (69.6%)	16 (69.6%)	15 (65.2%)	ST100 (n=15)	14 (93.3%)	14 (93.3%)	13 (86.7%)	ST100 (n=38)	30 (79%)	30 (79%)	28 (73.7%)
P1	0.006	0.031	NS	P1	NS	0.046	0.005	P1	0.002	0.004	0.003
P2	0.010	0.010	0.006	P2	0.000	0.000	0.000	P2	0.000	0.000	0.000
P3	NS	NS	NS	P3	NS **	NS**	NS **	P3	NS	NS	0.024

Table 6. Filter survival time when other than clotting causes of early procedure discontinuation were excluded.**Results obtained with Yates correction due to small frequencies. (P1: HF20 vs. ST60; P2: HF20 vs. ST100; P3: ST60 vs.ST100)

Variable	HF20 Hep	ST60 Hep	ST100 Hep	P1:	P2:	P3:
Mean[SD]/Median[IQR]	15 (29.4%)	46(75.4%)	23 (60.5%)	(pt/pW*)	(pt/pW*)	(pt/pW*)
Number of clotted filters	7/15 (46.7%)	13/46 (28.3%)	5/23(21.7%)	NS	NS	NS
Filter survival time (h)	33.3[23.8]/24[38.8]	53.2[23.8]/69[38]	57.2[23.3]/72[35]	0.020*	0.005*	NS*
Variable Mean[SD]/Median[IQR]	HF20 RCA 36(70.6%)	ST60 RCA 15(24.6%)	ST100 RCA 15 (39.5%)	P1:	P2:	P3:
Number of clotted filters	23/36(63.9%)	5/15 (33.3%)	1/15(6.7%)	NS	0.013	NS**
Filter survival time (h)	41[25.9]/41[55.0]	57[23.5]/72[31.0]	69.7[8.2]/72[0.0]	0.022*	0.000*	NS*

significant difference for RCA between HF20 vs. ST100. No differences were also noted either in the percentage of filter survival or in the time of their operation as depending on the employed ACG modality within particular filter size groups. On the other hand, smaller filters were demonstrated to operate shorter as compared to larger filters employed within the same type of ACG.

The process of data analysis also included Cox multivariable regression addressing filter survival (the analysis was performed at 12 hours), which showed that in no case was the type of the employed ACG of importance with respect to its affecting filter survival time. On the other hand, filter size proved to be of significance. When a comparison was made between HF20 vs. ST60, the risk of clotting increased 2.36-fold every 12 hours (95%CI: 1.21-4.61; p=0.012), while when comparing HF20 vs. ST100, the said risk increased 5.64-fold (95%CI: 2.65-14.06; p=0.000).

Table 7 presents data on the values of selected parameters describing filter pressure in particular types of filters. From these data, the values of cut-off points for filter pressure can be inferred, together with the value of the likelihood ratio, which shows how many times the risk of filter clotting is increased as compared to a filter that will not clot, with the test predictive value being good or very good (presented AUROCs values were at least 80%). In view of the fact that in case of ST100 filters, only one RCA filter was clotted, calculation of the AUROCs value was not possible.

Table 7. Prognostic capacity of mean ROCs values for selected filters (mmHg), for circuit clotting depending on the applied ACG modality; AUROC - area under the receiver operating characteristic curve; LR -likelihood ratio; PPV -positive predictive value; NPV - negative predictive value

	AUROCs /Cut Off/Sensitivity / Specificity / LR / PPV /NPV
Filter type - HF20	
Filter pressure (Hep-ACG)	91.4% / 85.8 / 90% / 85.7% / 6.3 / 90% / 85.7%
Filter pressure (RCA)	80.4% / 96.8 / 92.9% / 60.9% / 2.4 / 59.1% / 93.3%
Filter type - ST60	
Filter pressure (Hep-ACG)	89.7% / 105.6 / 84.1% / 84.6% / 5.5 / 94.9% / 61.1%
Filter pressure (RCA)	93.8% / 126.5 / 92.3% / 80% / 4.6 / 92.3% / 80%
Filter type - ST100	
Filter pressure (Hep-ACG)	90.9% / 133.2 / 81.8%/ 80% / 4.1/ 94.7% /60%

Discussion

Prolonged circuit survival is very important, as early filter clotting may have several negative effects, including a decreased efficacy of treatment, increased blood loss, hemodynamic instability and increased costs [12]. On the other hand, the circuit life span is affected by many factors, such as the patient's clinical condition, coagulation status, the position and patency of the vascular access, the choice of anticoagulant, the modality of CRRT and filtration fraction [17].

In the studied population, there were no cases of severe side effects associated with the applied modality of ACG. Treatment was generally well tolerated in all the patients, and the flow rate adaptability to the patient needs was highly acceptable.

The principal objective of the study was the assessment of factors affecting filter survival and the supplied dialysis dose depending on the employed anticoagulation method. In the current literature, there are divergent results about the superiority of the applied modality of ACG (Hep-ACG vs. RCA) in terms of circuit survival [12]. There are randomized and observational studies proving that RCA significantly extends CRRT circuit lifetime as compared to heparin [11-13, 18] and studies showing no significant differences between those two modalities of ACG [19, 20].

Unfractionated heparin - due to its pharmacokinetics and reversibility - has been widely used for CRRT ACG for decades [14]. According to the literature, heparin is an effective ACG in CRRT therapy with a mean dose of 11.1-20 U/kg/h and a post-filter ACT being maintained between 180 and 240 sec. [11, 19]. The heparin doses employed in the present study were similar to the values reported in the literature [19] and did not affect the percentage of filter clotting, regardless of their size. With the exception of ST60 filters, no significant differences were observed in the ACT time in clotted and non-clotted filters (Table 3).

In the study on RCA by Fernández et al., the median citrate dose was 2.6 mmol/l, the median and maximum CaT/CaI index was 2.16 and 2.33, respectively [11]. In the present report, the mean values of citrate doses were higher than in the cited study and there were no significant differences between the filter types (Table 3). The CaT/CaI ratio was within normal limits. According to the literature, RCA is not only a safe and effective ACG modality for pediatric CRRT, but it also achieves longer circuit survivals than Hep-ACG; hence, the use of RCA may provide a substantial cost saving and it is an ideal option in a critically ill children after recent surgery or with coagulopathy, for whom systemic ACG is discouraged [11]. Supporting this conclusion in their study, Sołtysiak et al. [21] stated that the circuit lifetime was significantly higher in RCA than in Hep-ACG (58.04 h vs. 37.64 h) and early circuit clotting was observed in 11.63% of children receiving RCA and 34.15% of those receiving Hep-ACG. Similarly, in a study by Fernández et al. [11], the median RCA circuit survival was 48 hours, while in case of Hep-ACG - 31 hours and the difference was statistically significant. Nevertheless, in both the aforementioned studies, the authors considered all the studied filter types as a single homogenous group (HF20, ST60 filters [21], and HF20, ST60, ST100 filters [11]). However, in the study by Rico et al. [22], the authors not only proved that the

survival of filters was higher in the RCA (72 h) than in the Hep-ACG (18 h) group, but they also showed that the filter coagulation risk was significantly increased when heparin was used, regardless of filter size.

In the current literature, there are also contrary results that state that the mean circuit survival is no different between HepACG and RCA [19, 23]. In a study by Brophy et al. [19], the clotting rates were similar for Hep-ACG circuits (25%) and RCA circuits (27%) and the analysis showed that 69% of Hep-ACG and Cit-ACG circuits were functional at 60 hours.

Contrary to some of the above quoted studies ([11, 19, 21]), in the present report the investigated filters were divided according to their size and all the statistical analyses (Tables: 2-7) addressed a given filter size, what represents a fairly novel approach to the problem. Thanks to such a view, it was demonstrated that filter survival was significantly affected by its size rather than the type of ACG employed (Tables: 2,3,5). Anyhow, according to Rico et al. [22], filter size is irrelevant to filter survival time, but yet the authors only evaluated filters of 0.4 and 0.7 m^2 of size. In the current paper, a wider range of filter sizes including HF20 (0.2m^2), ST60 (0.6 m^2) and ST100 (0.9 m^2) were analyzed, which allowed for demonstrating the impact of a very small size of the filter (HF20) on circuits survival.

On the average, the filters underwent clotting between 21.2 and 23.8 hours of their operation and no significant differences were observed between particular filter types (Table 3). While evaluating filter survival time depending on the type of the employed ACG modality, no significant difference was demonstrated between Hep-ACG and RCA (Table: 4, 6). Only in the Kaplan-Meier analysis, when the time span exceeding 36 hours was taken into consideration, was the probability of the RCA filter clotting more than 11-fold higher as compared to the Hep-ACG filter (Fig.1). Nevertheless, in the same analysis, when the filters were divided according to their size, no differences were demonstrated in the survival time between the analyzed ACG modalities, what indicates that differences in filter survival time depend on their size rather than the employed ACG method.

The data examination also included Cox multivariable regression addressing filter survival, which also demonstrated that in none of the cases, the type of the employed ACG modality was of importance in the effect of filter survival time, while filter size turned out to be of significance. For HF20 filters, the risk of clotting increased more than twofold every 12 hours as compared to ST60 filters, and more than five-fold as compared to ST100 filters. Additionally, in the present paper, calculations were made of the cut-off points for the parameter of filter pressure for particular types of filters, achieving a good or very good predictive value of the test (Table 7).

Determining the optimal therapeutic dose for CRRT in critically ill children remains a challenge. CRRT doses should be determined according to the disease conditions, taking into consideration the metabolic state, fluid volume, and duration of dialysis [24]. Here, the employed ACG modality also exerts a significant impact. According to the current literature, the total mean dialysis dose and mean blood flow rate in children are 52 ml/kg/h [21] and 5.2 ml/kg/min [25], respectively. In a study by Fernández et al. [11], although the total CRRT dose was higher in the RCA as compared to the Hep-ACG group, the difference was not statistically significant (69 vs. 59 ml/kg/h). The present study demonstrated that in the case of the smallest filters (and thus in the youngest children), significantly higher dialysis doses were employed, as well as significantly higher blood flow rate values (Table 2). On the other hand, no differences were shown between clotted and non-clotted filters with respect to the prescribed dialysis dose (Table 3), although a significantly higher dialysis dose was noted in the population of HF20 filters in the RCA group as compared to ACG-Hep, what is associated with an additional citrate flow (Table 4). Attention was also drawn to significantly higher heparin doses administered at the beginning of the procedure as boluses given to the youngest children.

The authors are aware of the limitations of the present retrospective, single-center, observational study, with only 8 patients being treated with RCA. Nevertheless, no significant difference was observed between the number in the two analyzed filter populations (Hep-ACG vs. RCA), what indicates their being mutually equivalent; furthermore the study resulted from a detailed analysis of 7636 hours of operation of 150 filters, taking into consideration all

their most important parameters, including the percentage of clotted filters, time of circuit operation, filter pressure values, TMP values, parameters of heparin and citrate ACG and the dose of the supplied dialysis, and employing a novel approach consisting in dividing the filters into particular size-associated types. Moreover, the authors calculated cut-off points for filter pressure values, at which – when exceeded – the risk of circuit clotting is increased. In the opinion of the authors, having such data at one's disposal in clinical practice may prove to be highly helpful in monitoring CRRT procedures and in more active preventing circuit clotting, what should be reflected not only in higher efficacy and safety of the method, but also in its economic aspect.

Conclusions

In the present study, no significant difference was noted in filter survival time depending on the type of the employed anticoagulation; only when time interval beyond 36 hours was taken into consideration, the authors did demonstrate that the risk of RCA filter clotting was more than 11-fold higher as compared to Hep-ACG filters. Filter clotting, irrespectively of their size, most often occurs in the first 24 hours following CRRT initiation. Clotting the most frequently involves small filters (HF20), and the time of their operation is significantly shorter as compared to larger filters (ST60, ST100), irrespectively of the type of ACG employed. In case of HF20 filters, the risk of clotting increases more than two fold every 12 hours as compared to ST60 filters and more than five-fold as compared to ST100 filters.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

Acknowledgments

Publication was supported by the Faculty of Medicine of Jagiellonian University Medical College (Leading National Research Centre 2012–2017; KNOW 2012-2017).

References

1 Warady BA, Bunchman T: Dialysis therapy for children with acute renal failure: survey results. Pediatr Nephrol 2000;15:11-13.

2 Brierley J, Carcillo JA, Choong K, Cornell T, DeCaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas M-A, Duncan A, Evans B, Feldman J, Felmet K, Fisher G, Frankel L, Jeffries H, Greenwald B, Gutierrez J, Hall M, , Han YY, Hanson J, Hazelzet J, Hernan L, Kiff J, Kissoon N, Kon A, Irazusta J, Lin J, Lorts A, Mariscalco M, Mehta R, Nadel S, Nguyen T, Nicholson C, Peters M, Okhuysen-Cawley R, Poulton T, Relves M, Rodriguez A, Rozenfeld R, , Schnitzler E, Shanley T, Skache S, Skippen P, Torres A, von Dessauer B, Weingarten J, Yeh T, Zaritsky A, Stojadinovic B, Jerry Zimmerman J, Zuckerberg A: Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009;37:666-688.

3 Joannidis M, Oudemans-van Straaten HM: Clinical review: Patency of the circuit in continuous renal replacement therapy. Crit Care 2007;11:218.

4 Davenport A: What are the anticoagulation options for intermittent hemodialysis? Nat Rev Nephrol 2011;7:499-508.

5 Oudemans-van Straaten HM, Kellum JA, Bellomo R: Clinical review: anticoagulation for continuous renal replacement therapy--heparin or citrate? Crit Care 2011;15:202.

6 Wu MY, Hsu YH, Bai CH, Lin YF, Wu CH, Tam KW: Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2012;59:810-818.
7 Zappitelli M, Juarez M, Castillo L, Coss-Bu J, Goldstein SL: Continuous renal replacement therapy amino acid, trace metal and folate clearance in critically ill children. Intensive Care Med 2009;35:698-706.
8 Morabito S, Pistolesi V, Tritapepe L, Zeppilli L, Polistena F, Strampelli E, Pierucci A: Regional citrate anticoagulation in cardiac surgery patients at high risk of bleeding: a continuous venovenous hemofiltration protocol with a low concentration citrate solution. Crit Care 2012;16:R111.
9 Tolwani A, Wille KM: Advances in continuous renal replacement therapy: citrate anticoagulation update. Blood Purif 2012;34:88-93.
10 Lanckohr C, Hahnenkamp K, Boschin M: Continuous renal replacement therapy with regional citrate anticoagulation: do we really know the details? Curr Opin Anaesthesiol 2013;26:428-437.
11 Fernández SN, Santiago MJ, López-Herce J, García M, Del Castillo J, Alcaraz AJ, Bellón JM: Citrate Anticoagulation for CRRT in Children: Comparison with Heparin. Biomed Res Int 2014;2014:786301.
12 Zhang Z, Hongying N: Efficacy and safety of regional citrate anticoagulation in critically ill patients undergoing continuous renal replacement therapy. Intensive Care Med 2012;38:20-28.
13 Kleger GR , Fässler E: Can circuit lifetime be a quality indicator in continuous renal replacement therapy in the critically ill? Int J Artif Organs 2010;33:139-146.
14 Vinsonneau C, Launay EA, Blayau C, Darmon M, du Cheyron D, Gaillot T, Honore PM, Javouhey E, Krummel T, Lahoche A, Letacon S, Legrand M, Monchi M, Ridel C, Robert R, Schortgen F, Souweine B, Vaillant P, Velly L, Osman D, Van Vong L: Renal replacement therapy in adult and pediatric intensive care Recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD). Ann Intensive Care 2015;5:58-76.
15 Gambro Prismaflex Operations Manual. Sweden: Gambro Lundia AB. 2005-2011.
16 Tolwani, JA, Prendergast MB, Speer RR, Stofan BS, Wille KM: A practical citrate anticoagulation continuous venovenous hemodiafiltration protocol for metabolic control and high solute clearance. Clin J Am Soc Nephrol 2006;1:79-87.
17 Baldwin I:Factors affecting circuit patency and filter 'life'. Contrib Nephrol 2007;156:178-184.
18 Liu C, Mao Z, Kang H, Hu J, Zhou F: Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. Crit Care 2016;20:144-156.
19 Brophy PD, Somers MJG, Baum MA, Symons JM, McAfee N, Fortenberry JD, Rogers K, Barnett J, Blowey D, Baker C, Bunchman TE, Goldstein SL: Multi-centre evaluation of anticoagulation in patients receiving continuous renal replacement therapy (CRRT). Nephrol Dial Transplant 2005;20:1416-1421.
20 Park SJ, Shin JI: Overview of Pediatric Continuous Renal Replacement Therapy in Acute Kidney Injury. J Korean Soc Pediatr Nephrol 2011;15:107-115.
21 Soltysiak J, Warzywoda A, Kociński B, Ostalska-Nowicka D, Benedyk A, Silska-Dittmar M, Zachwieja J: Citrate anticoagulation for continuous renal replacement therapy in small children. Pediatr Nephrol 2014;29:469-475.
22 Prada Rico MP, Sarmiento JF, Rojas Velasquez AM, González Chaparro LS, Gastelbondo Amaya R, Mulett Hoyos H, Tibaduiza D, Quintero Gómez AM: Regional citrate anticoagulation for continuous renal replacement therapy in children. Pediatr Nephrol 2017;32:703-711.
23 Davis TK, Neumayr T, Geile K, Doctor A, Hmeil P: Citrate anticoagulation during continuous renal replacement therapy in pediatric critical care. Pediatr Crit Care Med 2014;15:471-485.
24 Sebestyen JF, Warady BA: Advances in pediatric renal replacement therapy. Adv Chronic Kidney Dis 2011;18:376-383.
25 Baldwin I: Is there a need for a nurse emergency team for continuous renal replacement therapy? Contrib Nephrol 2007;156:191-196.