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HOW AND WHEN DO WE USE CONTINUOUS RENAL REPLACEMENT THERAPY FOR ACUTE KIDNEY INJURY IN SERBIA? – THE MULTICENTRIC SURVEY

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Abstract

**Background / Aim.** Absence of clear guidance in the definition, diagnostics and indications for renal replacement treatment (RRT) is present. The aim of this survey is creating a unique strategy for diagnostics and treatment of acute kidney injury (AKI) based on the current clinical practice. **Methods.**

**Results.** We have conducted a multicentric web-survey among nephrologists (46.8%) and other physicians in Serbia. The sample consisted of 119 participants, 78.9% out of which filled out the survey forms correctly, and were, therefore, included in the analysis. Most of them responded that the nephrologist indicates (76.8%) and prescribes (74.5%) of continuous renal replacement therapy (CRRT). The application of KDIGO 2 criterion for „early” start of CRRT used 74.5% of the respondents, and 91.5% of them started „late” initiation of CRRT in the presence of complications associated with AKI or poor response to conservative treatment. Regarding clinical experience of the respondents, 74.5% of them marked „early” start of CRRT within 12 hours whereas 56.4% of them considered the start of CRRT after 48h as „late”. The most commonly used modality was continuous venous hemodiafiltration (37.6%). Most participants used heparin as anticoagulant (95.7%) with average life span of filters less than 24 hours (71.3%) and 25 ml/kg/h efficiency target dialysis effluent dose (45.2%) during CRRT. The most common complications of CRRT were hypotension (55.3%) and catheter-related infections (29.8%). **Conclusion.** „Early” start of CRRT is considered favorite by the majority of the participants. According to the obtained data, standardization of the strategy in the diagnostics and treatment of AKI is necessary.

**Key words:** acute kidney injury, continuous renal replacement therapy, survey.
Apsrakt

Uvod / Cilj. Nedostaju jasne smernice u definiciji, dijagnostici i indikacijama za lečenje metodama zamene funkcije bubrega (ZFB). Cilj ovog istraživanja je koncipiranje jedinstvene strategije za dijagnostiku i lečenje akutnog oštećenja bubrega (AOB) na osnovu trenutne kliničke prakse. Metode.

Rezultati. Sproveli smo multicentričnu anketu među nefrolozima (46.8%) i lekarima drugih specijalnosti u Srbiji. Uzorak je činilo 119 učesnika od kojih su 94 (78.9%) korektno popunili anketu i bili uključeni u analizu. Većina je odgovorila da nefrolog indikuje (76.8%) i piše preskripciju (74.5%) kontinurane zamene funkcije bubrega (KZFB). Kriterijum KDIGO 2 koristi 74.5% ispitanika u „ranom” početku KZFB, a 91.5% „kasno” počinju KZFB kod komplikacija povezanih sa AOB ili slabijeg odgovora na konzervativnu terapiju. U odnosu na kliničko iskustvo ispitanika, 74.5% smatra da bi „rani” početak KZFB trebalo da bude unutar 12h, a 56.4% je odgovorilo da je preko 48h „kasni” početak. Najčešće je korišćena kontinuirana veno-venska hemodijafiltracija (37.6%). Najzastupljenija doza dijaliznog efluenta je bila 25 ml/kg/h (45.2%), preovladava sistemska antikoagulacija heparinom (95.7%) sa prosečnim trajanjem filtra manje od 24h (71.3%). Najčešće komplikacije KZFB su hipotenzija (55.3%) i infekcija povezana sa prisustvom katetera 29.8%. Zaključak. Većina ispitanika prednost daje „ranom” početku KZFB. Prema dobijenim podacima, neophodna je standardizacija strategije u dijagnostici i lečenju AOB.

Ključne reči: kontinurana zamena funkcije bubrega, rani/kasni početak KZFB.

Introduction

Acute kidney injury (AKI) has a particularly high incidence in admissions to the Intensive Care Unit (ICU), with reports of an incidence range from 16.0%-36.0% and a three- to five-fold increase of in-hospital mortality (compared to those without AKI). Despite the evolution of the guidelines for diagnosing AKI, we are still largely indebted to serum creatinine, as well as
urinary output, to determine the stage of AKI. Thus, while the unification of
criteria for AKI is useful for furthering clinical research, it still permits only
a relatively late diagnosis. In any case, these biomarkers (as well as others
undergoing clinical research) are still too innovative to clinical practice and
in many low- and middle-income countries and lower resource areas of
high-income countries are too expensive for widespread utilization. In
general, outcomes for AKI are poor, with one systemic review of over 300
cohort studies revealing an overall mortality of 23.9% among adult AKI
patients (1). With AKI not requiring dialysis and AKI requiring dialysis both
rising, it remains unclear whether this is due to changes in International
Classification of Diseases coding, changes in AKI definition, awareness of
AKI, or clinical practice (2). As no specific pharmacological therapy is
effective in AKI patients, their care is limited to supportive management in
which continuous renal replacement therapy (CRRT) plays a central role (3).
Although there are many aspects of CRRT that are still under debate, its life-
saving potential in severe cases of AKI cannot be questioned (4).
The primary objective of this research is to help outlining future clinical
work to improve the treatment outcome and reduce complications.

Methods
The questionnaire was distributed among physicians of different specialties.
Nephrologists, anesthetists, intensivists, cardiologists and internists mostly
from tertiary and secondary health care institutions were invited to
participate voluntarily and anonymously. The questionnaire was drawn up in
accordance with the standard clinical practice (1). The 40-question survey
form included 4 parts: 1) information on the type of specialty, type of
institution and length of service of the physician 2) information on AKI
definition and classification, indications and contraindications of CRRT,
optimal start (regarding time, biomarkers, biochemical parameters) and
termination of CRRT treatment 3) information on the choice of vascular
approach, type of modality, dose administered, and anticoagulation, 4)
information on complications of CRRT, renal function recovery, dialysis
dependence, and mortality. All the data regarding statistical analysis were
compiled from hardcopy sources and processed by using a Microsoft Excel database/ datasheet. All the data are presented either as a percentage or as absolute numbers of the questionnaires.

**Results**

Out of the 119 survey participants, 78.9% fully completed the survey form.

1) According to the reported answers, 46.8% of the participants are nephrologists, 39.4% are specialists in anesthesiology, reanimatology and intensive care and 13.8% are internists of other branches of internal medicine and other physicians (Figure 1). 72.3% of them are employed in tertiary care institutions, 23.4% are secondary health care workers and 4.3% work in other institutions. 40.4% have more than 20 years of service, 16.0% have 5-10 years of service, 13.9% have more than 10 years of service and 1.5% have less than 5 years of service.

2) The most common AKI classification responses are: RIFLE-Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease criteria - 59.6% in total, followed by KDIGO - Kidney Disease Improving Global Outcomes criteria - 30.9%. Regarding the use of diuretics in oliguric patients, 43.6% of the participants confirmed administering high doses of furosemide (≥250 mg/day), 48.9% use low doses of furosemide (≤250 mg/day), whereas 7.0% of the participants do not use diuretics. The respondents had an almost equal distribution of responses in the prevalence of patients requiring CRRT (<5.0% - 28.7% of the respondents; 5.0-10.0% - 22.3%; 11.0%-20% -16.0%; 21.0%-30% -18.1% and more than 30.0% - 14.9% of the respondents). The majority of participants (74.5%) use the KDIGO 2 criterion when deciding on „early” CRRT initiation, and 91.5% start „late” CRRT for AKI complications (oliguria/anuria, elevated creatinine, hyperkalaemia, metabolic acidosis and/or refractory hypervolaemia) or a lower response to conservative therapy. In addition to the above criteria, regarding the clinical experience of the subjects, 46.8% thought that the „early” onset of CRRT should be within 6h (Figure 2), whereas 22.3% said that the „late” onset was > 24 hours, a similar percentage of respondents (21.3%) thought it was from 24-48 hours, and the majority (56.4%) thought the „late” onset of CRRT was
> 48 hours. The prediction for the onset of RRT could be increased by functional tests (Furosemide stress test), considered relevant by most of the participants (63.8%). Regarding the use of biomarkers as predictors of onset of RRT, 43.6% of these indicated cystatin C in urine, 36.2% referred to Neutrophil gelatinase-associated lipocalin in urine and 20.3% indicated a combination of urine tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor (IGF) binding protein 7, whereas 3.2% were related to other biomarkers (Figure 3). As high as 77.7% stated that the severity and course of the disease were the determining factors for initiation of RRT, but that the decision was also influenced by the availability (apparatus, equipment, staff), the day of the week as well as the time of the day, the response to diuretic therapy and comorbidities (Figure 4). Relative contraindications for the onset of CRRT in 56.4% of the responses were advanced malignant disease (except for multiple myeloma), followed by hypotension without vasopressor response (35.1%), older age, as well as other reasons in 4.3% of the cases. CRRT is indicated in 76.6% of the cases by a nephrologist, in 12.8% of the cases by a nephrologist in consultation with a specialist of anesthesiology, reanimatology and intensive care, and in 7.4% specialists employed in ICU/semi-intensive care. A similar percentage was reported for the CRRT prescription (a nephrologist 74.5%; a nephrologist in consultation with an anesthesia, reanimatology and intensive care specialist 16%; a specialist employed at the intensive care unit 8.5% and an internist of another branch of internal medicine 1.1%). 37.2% of the participants reported less than 6h from the time the indication was given until the CRRT treatment began (Figure 5). Most of the respondents (51.1%) discontinued CRRT if diuresis > 450 ml/day, 35.1% if creatinine clearance > 20ml/min while the others remain neutral.

3) In most institutions (87.2%) a specialist employed in ICU/semi-intensive unit places a dialysis catheter, whereas in others it is done by a nephrologists in consultation with a specialist of anesthesia, reanimatology and intensive care. Catheter is mostly inserted by using Seldinger blind technique (69.1% cases). The most often choice was the left/right internal jugular vein
followed by US assessment in 12.8%, femoral in 5.3%, subclavian 3.2% and the jugular internal vein in obese and the femoral vein in non-obese in 1.1% of the cases. CRRT/hybrid modalities are used in 48.9% of the cases, with the continuous veno-venous hemodiafiltration (CVVHDF) 49.5% being most commonly used (Figure 6). The choice of modality depends on the clinical indication (38.7%), the decision of the nephrologist (34.4%), availability of modalities, logistics, personnel (20.4%) and other factors (6.5%). The most common target dose of CRRT is 25 ml/kg/h (45.2%), followed by 35 ml/kg/h (40.9%), 45 ml/kg/h (5.4%), and other values (8.6%). Systemic heparin-anticoagulation is prevalent 95.7%, followed by regional anticoagulation (citrate) 3.2%, and another anticoagulation in 1.1% of the cases. The average filter life is in most respondents less than 24 hours (71.3%). Adsorptive membranes in the treatment of sepsis in AKI are used by 60.6%, the most prevalent being Emic-2 in 50.6% of the cases (Figure 7).

4) The most common complications of CRRT are hypotension 55.3% and catheter-associated infection 29.8%, followed by electrolyte imbalance 8.5%, bleeding 2.1% and other complications (4.3%). The incidence of catheter-related infections (1-3/1000 catheter days) was reported by 43.6% of the participants, (4-6/1000 catheter days) by 37.2% and (<6/1000 catheter days) by 19.1%. In patients who required CRRT, 41.9% of the respondents stated that 5-20% of the patients recover their renal function by the period of 3 months. 35.1% reported that 5-20% of the patients had died, 47.9% said that the same percentage of patients lacked some of the stages of chronic renal failure and 44.7% reported that 6-10% of the patients remained dialysis dependent. Over the past year, 33% reported that 21-40% of the patients had „early” onset CRRT recovery in renal function and 46.8% said that less than 5.0% of the patients had died, as opposed to „late” CRRT onset which reported an increase in renal function <5.0% out of 44.7% of the participants, whereas 40.4% reported death in 5.0%-20% of the patients (Table 1).
Discussion

The lack of clear guidelines in the definition, diagnosis and treatment of AKI, as well as the fact that standard biochemical and clinical parameters as well as new biomarkers did not optimize treatment outcomes, indicates the need for further research. The main objective of this multicentric research is to summarize CRRT clinical practice information for one year in order to gain insight into the most important issues, especially treatment timing and to guide clinicians in their daily work.

Mostly nephrologists, followed by specialists in anesthesiology, reanimatology and intensive care and physicians with other specialties, of whom 40.4% have work experience of over 20 years and most of them are employed in tertiary care institutions, participated in our questionnaire.

According to the results, slightly more than half of the participants still use the RIFLE criteria to define the AKI, while in terms of representation, the following use the KDIGO criteria, which is different from the results published last year, in which the KDIGO criteria are dominant (5). The higher prevalence of the RIFLE classification has been reported in previous studies, and in our sample it can be explained by the participation of non-nephrological specialty respondents and possibly by a high percentage of physicians with many years of experience who are somewhat skeptical about accepting novelties (6,7).

Our subjects use almost equally high (≥250 mg/day) and low doses of Furosemide (≤250 mg/day) in the conservative treatment of AKI, and a relatively equal representation in the range of up to 30.0% of AKI patients requiring CRRT is reported. These results are different from last year's study in which it was stated that most use high doses in oligurian patients and that 13.0% of patients require CRRT (5). In our institutions, most respondents stated that they use the KDIGO 2 criterion for „early” start of CRRT, and for already present complications associated with AKI or poor response to conservative therapy, participants start CRRT „late”. Compared to comprehensive clinical work so far, almost 50.0% believe that the timeline for „early” start of CRRT should be within 12 hours, which corresponds to
the KDIGO 2 criterion, and slightly more than 50.0% believe that over 48 hours is „late” start. These early start CRRT results rule out urgent indications and leave time for patient monitoring and clinical evaluation for late start. However, Thakar VC and colleagues reported in their survey that 53.0% of respondents felt that there was no benefit from early-start CRRT, moreover 35.0% of respondents believed that the risk of early CRRT outweighed the benefit. However, 46.0% of respondents indicated that they often initiate „early” CRRT in patients with AKI in ICU. Most influential parameters in determining dialysis initiation were complications of AKI, such as hyperkalemia and hypoxemia due to volume overload, whereas the degree of severity of kidney injury or markers of azotemia played a less important role in the early dialysis decision (8). In their work, Clark and associates have shown that potassium levels and pulmonary edema are the most common indicators of early CRRT (9). The aforementioned surveys were conducted in 2012, when different biochemical and clinical parameters were used in deciding to initiate CRRT. By defining the KDIGO guidelines in the same year in the AKI classification, the use of the same was made possible in the following years, and the above mentioned surveys are not comparable with ours. Most believe that the Furosemide Stress Test, Cystatin C, and NGAL in the urine could increase the prediction for the start of CRRT. Our centers have no experience in using biomarkers other than Cystatin C, and this may be the reason why only 20.3% of respondents said that (TIMP-2)•(IGFBP7) and other biomarkers would be good predictors. In a previous survey, 60.0% of participants indicated that they were implementing new biomarkers in their practice and research (9). It is interesting to note that 77.7% still consider the severity and course of the disease to be the deciding factors for the start of CRRT, which indicates the importance of the „clinical scenario” as the most important part of the strategy in the treatment of AKI and also meets the current „watchful waiting” recommendations. However, the responses of the rest of the participants stating comorbidities, response to diuretic therapy, and availability (appliances, equipment, staff), day of the week, and time of day
are not negligible. It should be noted that none of the subjects indicated a
decisive factor for the start of CRRT, but 4.3% indicated that older age was
a relative contraindication for start of CRRT. Just over 50.0% of participants
cited advanced malignancy (except for multiple myeloma), and about a third
reported hypotension with no response to vasopressors as relative
contraindications for start of CRRT. So far, many studies have been
conducted towards the decision to initiate treatment, and there are few data
about who are the patients with a very low probability of surviving where
the used CRRT would be a source of inadequate information, as it would
probably suggest that CRRT itself increases the risk of poor outcomes. The
complexity of the clinician's decision-making in comprehensive
consideration of the indications, prognosis and outcome of the disease is
sometimes hampered by subjectivity relative to the preferences of the patient
or family, so CRRT is applied, although it is unlikely to modify the
outcome. Therefore, the future consensus of the decision to start CRRT
should include irrelative contraindications. Most participants stated that the
nephrologist indicates the start and writes the CRRT prescription. Please
note that in our region, due to the distance of CRRT institutions and some
without employed nephrologists, training was conducted by nephrologists in
previous years and consultative cooperation continued. About 50.0% of the
respondents believe that from the diagnosis to the indication for RRT it takes
up to 6 hours and from the indication to the beginning of RRT around 6 h,
although a quarter of them stated that the stated time depends on the
availability of the apparatus, logistics and staff.

In most of our centers, the specialist employed in the ICU places a dialysis
catheter, predominantly by the blind Seldinger technique, most commonly in
the left/right internal jugular vein. About half of the respondents use CRRT
in their institutions and all modalities (CRRT/hybrid), and the most
commonly used modality is CVVHDF. Although there is an upward trend in
extracorporeal methods, the results indicate an under-representation of
CRRT (5-7). Most participants indicated that the choice of CRRT modality
depends on the clinical indication and the decision of the nephrologist. The
most commonly used target dose of CRRT is 25 ml/kg/h, systemic anticoagulation with heparin (95.7%) with an average filter life of less than 24 hours (71.3%) is prevalent. Last year's study reported similar results, except in the use of anticoagulation (mostly unfractionated heparin followed by citrate, low molecular weight heparin, and regional anticoagulant therapy) (5). Overberger and associates stated that in their study CRRT was also the most commonly used modality of therapy as well as the applied dialysis effluent dose of 25 ml/kg/h (10). In another earlier study, over 90.0% of subjects used CRRT, however, the most commonly prescribed dose was 35 mL/kg/h (8). In our study, adsorptive membranes are used by 60.6% of subjects to treat sepsis in AKI (Emic-2-50.6% were the most prevalent).

The most common complications of CRRT are hypotension 55.3% followed by catheter-related infection with an incidence of 1-6/1000 catheter days reported by most subjects similar to the results of certain previous studies (11-13). In our patients who required CRRT, the majority of respondents stated that up to 20.0% of patients had renal function recovery by 3 months, and that in the same percentage some patients have some stage of chronic renal failure/dialysis dependency/death in the first year. Those that survive the initially high mortality rate associated with dialysis-requiring AKI, mostly become independent of renal replacement therapy (RRT) within a year, but some of them do go on to develop chronic kidney disease and even progress to end-stage renal disease (14).

It is unclear whether a preventive/early strategy of the initiation of RRT in order to avoid complications associated with AKI leads to better patient outcomes and the use of health services, or a more conservative strategy in which RRT is started as a response to the development of complications provides better results (15). About 50.0% of the respondents stated that least patients died with „early” start of RRT, as opposed to the „late” start of RRT, which was confirmed in our single-center retrospective study of 385 patients with acute kidney injury who were admitted between 2014 and 2017 (16).
About half of the physicians reported that patients with late dialysis start had the recovery of renal function in the lowest number, while one in three respondents said that 20.0%-40.0% of patients who started dialysis “early” recovered the renal function. Recent meta-analyzes are also remarkably clear, noting that increased mortality and recovery of renal function by early dialysis stems from lower quality data (i.e., high heterogeneity and / or higher risk of bias). Meanwhile, an analysis of high-quality pooled data shows no significant difference in mortality (17-22).

**Conclusion**

Most subjects consider the severity and course of the disease to be the determining factors for initiation of CRRT and favored the early start of CRRT - KDIGO criterion within 12 hours of diagnosis with increasing prediction of the Furosemide stress test. Although there is an increasing trend in the use of extracorporeal methods, our data indicate an underutilization of CRRT and a lack of citrate dialysis. Further research is needed to form a clinical model that, in addition to a functional test, would include one of the biomarkers or a combination of biomarkers in order to increase the prediction of initiation of CRRT treatment.

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Addition:

Part 1
**Figure 1:** Participants of multicentric web-survey: medical specialists

![Participants of multicentric web-survey](image)

Part 2

**Figure 2:** Timing of „early” CRRT initiation in AKI

![Timing of „early” CRRT](image)

**Figure 3:** Promising biomarkers for predictions of CRRT initiation in patients with AKI

![Biomarkers for prediction CRRT](image)
**Figure 4**: Factors influencing the decision to start CRRT

| The decision to start RRT | 0% | 20% | 40% | 60% | 80% | 100% |
|---------------------------|----|-----|-----|-----|-----|------|
| availability (devices...), day of week, time of day | 16.0 | | | | | |
| severity and course of the disease | | 77.7 | | | | |
| response to diuretic | 5.3 | | | | | |
| comorbidities | 1.1 | | | | | |
| age | 0 | | | | | |

**Figure 5**: „Timing“ from setting the indication to initiation of CRRT

| “Timing“ from setting indications to initiation of CRRT | 0% | 10% | 20% | 30% | 40% |
|--------------------------------------------------------|----|-----|-----|-----|-----|
| <6 hours | 37.2 | | | | |
| about 6 hours | 16.0 | | | | |
| 12 hours | 6.4 | | | | |
| >12 hours | 14.9 | | | | |

Part 3

**Figure 6**: Most commonly use modalities of CRRT
**Figure 7:** Adsorptive membranes in the treatment of septic patients with AKI

![Diagram showing adsorptive membranes](image)

### Part 4

**Outcomes AKI required RRT patients (Early vs Late start RRT)**

| Outcomes | Recovery one year | Mortality one year |
|----------|-------------------|-------------------|
| **Patients with AKI who required CRRT** |                    |                   |
| Early start CRRT | Participants (%) |                   |
| <5%       | 7.4%              | 46.8%             |
| 5%-20%    | 29.8%             | 31.9%             |
| 21%-40%   | 33.0%             | 10.6%             |
| 41%-60%   | 23.4%             | 9.6%              |
| >60%      | 6.4%              | 1.1%              |
| Late start CRRT | Participants (%) |                   |
| <5%       | 44.7%             | 19.1%             |
| 5%-20%    | 26.6%             | 40.4%             |
| 21%-40%   | 19.1%             | 21.3%             |
| 41%-60%   | 8.5%              | 10.6%             |
| >60%      | 1.1%              | 8.5%              |

Legend: AKI-acute kidney injury; CRRT-continuous renal replacement therapy
Abbreviations:
CRRT-Continuous renal replacement therapy
AKI-Acute kidney injury
KDIGO-Kidney Disease Improving Global Outcomes
RIFLE-Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease
CVVHDF-Continuous venovenous hemodiafiltration
CVVHD-Continuous venovenous hemodialysis
ICU-Intensive Care Unit

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