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NEW EXPERIENCES WITH THE THERAPY OF ACUTE KIDNEY INJURY

Kes P., Bašić Jukić N.

Department of Dialysis, Zagreb University Hospital Centre, Zagreb, Croatia

A b s t r a c t: Acute kidney injury (AKI) is encountered in a variety of settings (e.g., hospitalized and outpatient, non-intensive and intensive care unit patients, pediatric, adult, and elderly), with varied clinical manifestations ranging from a minimal elevation of serum creatinine (SCr) to anuric renal failure and/or multi organ failure (MOF), and a wide variation in causes, risk factors and comorbiditis. There is no hard and fast rule as to when renal replacement therapy (RRT) should be initiated, but is clearly not sensible to wait until an obvious uremic complication arises. Modern practice is to initiate RRT sooner rather than later, for example, when the SCr concentration reaches 500–700 μmol/L, perhaps even earlier, unless there is clear evidence that renal function is about to recover. The choice of the treatment will depend on the clinical practice, technical resources, and well-trained nurses of a given department, than on precise clinical indication. The ideal RRT should mimic the functions and physiological mechanisms of the native organ, ensuring qualitative and quantitative blood purification, be free of complications, have good clinical tolerance and restore and maintain homeostasis, thus favouring organ recovery. Now available RRT options /peritoneal dialysis (PD), 2. intermittent hemodialysis (IHD), 3. continuous therapies (CRRT), and 4. hybrid therapies/, differ in the method of delivery, efficiency, and their clinical tolerability. AKI without MOF is less complex, can be managed outside intensive care unit and the same RRT techniques used for the treatment of chronic renal failure may be applied. AKI associated with MOF is a more complex condition and requires more flexible RRT. Acute PD remains a viable option for the treatment of selected patients with AKI, particularly pediatric population, and those who are hemodynamically compromised, have severe coagulation abnormalities, difficulty in obtaining blood access, removal of high molecular weight toxins (> 10 kD), and clinically significant hypothermia and hyperthermia. Patients that are hemodynamically stable can be managed with IHD techniques. Maintaining hemodynamic stability is probably one of the most important aspects

of dialysis technique as well as one of the most difficult challenges. With CRRT, the continuous regulation of volume homeostasis could lessen the hourly rate of required UF, thereby improving hemodynamic stability compared with IHD. Clinical data suggest that CRRT should be strongly considered for patients with severe hyperphosphatemia, elevated intracranial pressure, cerebral edema complicating acute liver failure, sepsis or septic shock, might be a useful component of therapy for lithium intoxication, and because of continuous nature of process prevents the post-dialytic "rebound" elevation of plasma concentration of uremic toxins typically seen with IHD. Hybrid therapies using a variety of machines are safe and convenient, providing excellent control of electrolytes and fluid balance, and offers several advantages over CRRT, including less cumbersome technique, patient mobility, and decreased requirements for anticoagulation, while providing similar hemodynamic stability and volume control. Currently, it has been found no difference in mortality or renal recovery between hybrid RRT, CRRT or IHD for critically ill patients with AKI. However, future investigations should collect detailed information on long-term costs and the relative likelihood of renal recovery associated with dialysis modality.

Key words: Acute kidney injury, renal replacement therapy, peritoneal dialysis, intermittent hemodialysis, continuous therapies.

Acute renal failure (ARF), classically defined as an abrupt decrease in kidney function that leads to accumulation of nitrogenous wastes such as serum creatinine (SCr) and blood urea nitrogen, is a common clinical problem with increasing incidence, serious consequences, unsatisfactory therapeutic options, and an enormous financial burden to society [1, 2]. ARF may be classified as pre-renal (functional response of structurally normal kidneys to hypoperfusion), post-renal (urinary tract obstruction), and intrinsic renal (involving structural damage to the renal parenchyma), which has emerged as the most common and serious subtype in hospitalized patients and can be associated pathologically with acute tubular necrosis (ATN). Despite decades of basic and clinical research and important technical advances in clinical treatment and dialysis, the prognosis for patients with intrinsic ARF remains poor, with a mortality rate of 40% to 80% in the intensive care setting. A variety of factors contribute to the lack of success. ARF is encountered in a variety of settings (e.g., hospitalized and outpatient, non-intensive and intensive care unit patients, paediatric, adult, and elderly), with varied clinical manifestations ranging from a minimal elevation of SCr to anuric ARF and/or multi organ failure (MOF), and a wide variation in causes, risk factors and comorbidities.

Over 20 definitions for ARF have been used in published studies, ranging from subtle increases in SCr to alterations in urine output (UOP) and dialysis requirement. Similarly, clinical trials have used varying criteria for diagnosing ARF and ascertaining outcomes from the treatment. Recent evidence suggests that ARF is often under-recognized, and even small alterations in serum

SCr are associated with severe consequences [2, 3]. In an attempt to standardize the definition and reflect the entire spectrum of the condition, the term acute kidney injury (AKI) has been proposed [4]. AKI refers to a complex disorder that comprises multiple causative factors and occurs in a variety of settings with varied clinical manifestations that range from a minimal but sustained elevation in SCr to anuric renal failure. From the clinical viewpoint AKI is frequently multi-factorial, with concomitant ischaemic, nephrotoxic, and septic components and with overlapping pathogenetic mechanisms.

Definition, diagnostic criteria and staging for AKI

Diagnostic criteria are used to establish the presence of a disease, whereas staging criteria define the severity of the disease process at any given time. The Acute Kidney Injury Network (AKIN) workgroup defined AKI as an abrupt (within 48 h) reduction in kidney function as manifest by an increase in SCr of either ≥ 25 μmol/L or a relative increase of ≥ 50%, or reduction in UOP to < 0.5 mL/kg per h for > 6h [5]. The goal of the staging system is to allow classification that supports accurate identification and prognostication and inform diagnostic or therapeutic interventions. The staging system proposed is a highly sensitive interim staging system and based on recent data indicating that a small change in SCr influences outcomes [2, 3, 6]. Only one criterion (SCr or UOP) has to be fulfilled to qualify for a stage (Table 1).

Table 1 – Табела 1

Classification and staging system for acute kidney injury
Класификација и стадиуми на акутното бубрежно оштетување

Stage	SCr criteria	UOP criteria
1	Increase in SCr to ≥ 25 μmol/l or increase to ≥ 150 to 200% from baseline	< 0.5 ml/kg *per* h for > 6 h
2	Increase in SCr to > 200 to 300% from baseline	< 0.5 ml/kg *per* h for > 12 h
3	Increase in SCr to > 300% from baseline (or SCr ≥ 353.6 μmol/l with an acute rise of at least 44.3 μmol/l)	< 0.3 ml/kg *per* h × 24 h or anuria × 12 h

Relatively few studies have examined the association between smaller changes in SCr and outcomes [2, 7, 8, 9]. Smith *et al.* [7] explored this issue in elderly individuals who were hospitalized with congestive heart failure, for whom small changes in SCr concentration have been associated with increased mortality and extended length of stay (LOS) in hospital (> 10 days). Recently, Lassnigg *et al.* [8] showed a two-fold increase in the risk of death for patients who experienced no change or a small increase (< 44.2 μmol/L) in SCr 48 h after cardiothoracic surgery compared with patients who experienced a small decline in SCr during the same time frame. In a similar population, Loef *et al.* [9] showed an association between a 25% increase in SCr during the first postoperative week and short- and long-term (> 8 year) mortality. Chertow *et al.* [2] described a progressive rise in hospital mortality associated with increases in SCr in a cohort of 19,982 adults who were admitted to an urban academic medical centre during an 8-month period. The presence and degree of ARI were assessed using absolute and relative increases from baseline to peak SCr concentration during hospitalization. Large increases in SCr concentration were relatively rare (*e.g.*, ≥ 176.8 μmol/L in 1% of the patients), whereas more modest increases in SCr were common (*e.g.*, ≥ 44.2 μmol/L in 13% of the patients). Modest changes in SCr were significantly associated with mortality, LOS, and costs, even after adjustment for age, gender, severity of illness, and chronic kidney disease. For example, an increase in SCr ≥ 44.2 μmol/L was associated with a 6.5-fold increase in the odds of death, a 3.5-day increase in LOS, and nearly $7,500 in excess hospital costs. Moreover, outcomes were related directly to the severity of AKI, whether characterized by nominal or percentage changes in SCr [2].

Consensus criteria for the definition and staging of AKI have been developed on the basis of changes in SCr and UOP. Although these criteria correlate with mortality risk and will facilitate uniformity of definitions in clinical trials, there is still a need for sensitive and specific biomarkers of kidney injury. Cystatin C, a low molecular weight protein produced at a constant rate by all nucleated cells, correlates with GFR and is not significantly affected by gender, race, muscle mass, and age. Increases in serum levels of cystatin C may be detected one to 2 days earlier than comparable changes in SCr [10]. Several clinical studies have suggested that urine N-acetyl-β-D-glucosaminidase (NAGL), a biomarker of renal tubular injury, may serve as an early marker of AKI [11, 12, 13]. The relationship between NGAL and human ischaemia-reperfusion injury is illustrated in a study of allograft kidney biopsy samples obtained within the first hour of vascular anastomosis after transplantation of 13 deceased-donor and 12 living-donor kidney allografts [11]. In a clinical trial of 71 children who underwent open heart surgery, urinary NGAL increased within 2 hours of cardiopulmonary bypass to a level > 50 μg/L in 100% patients who had an increase in SCr of 50% and in only 2% of patients who did not meet the definition of AKI [12]. IL–18 also has been considered as a candidate biomarker for renal

tubular injury. It has been evaluated after paediatric cardiac surgery. Urinary IL-18 increased 4 to 6 hours after cardiopulmonary bypass, peaked with > 25-fold increases over baseline at 12 hours, and remained up to 48 hours after operation in patients who developed AKI, but did not significantly increase in children without AKI [13]. Further progress in the development and clinical validation of biomarkers for early diagnosis of renal injury may permit early targeted interventions to reverse or ameliorate tubular injury in AKI.

When should renal replacement therapy be started?

Mandatory indications for the urgent instigation of life-saving renal replacement therapy (RRT) are: (a) severe refractory hyperkalaemia; (b) intractable fluid overload causing pulmonary oedema; (c); acidosis producing circulatory compromise and (d) overt uraemia manifesting as encephalopathy, pericarditis, or uraemic bleeding. It is more common, however, to see a state in which a patient's renal function gradually declines over a period of a few days whilst they are in hospital. In this circumstance, there is no hard and fast rule as to when RRT should be initiated. It is clearly not sensible to wait until an obvious uraemic complication arises. Modern practice is to initiate RRT sooner rather than later, for example, when the SCr concentration reaches 500–700 μmol/L, perhaps even earlier, unless there is clear evidence that renal function is about to recover. There are, however, no controlled trials relevant to modern practice that can be used to justify the initiation of RRT at one specific SCr concentration rather than another.

Institution and monitoring of renal replacement therapy

Any treatment should be easy to apply, rapid to institute, and simple to monitor. The choice of the treatment will depend on the clinical practice, technical resources, and well-trained nurses of a given department, rather than on precise clinical indication. A proficient and accountable team, experienced in various dialysis modalities with a quality assurance education programme would be ideal. If this is not possible, the best combination of simple and easy treatment schedules, which are functional and efficient with no significant increases in personnel demand or labour intensity, must suffice.

Biocompatibility, doses of dialysis, and adequacy of treatment

The treatment should cause the least interaction of the materials with blood. To improve the biocompatibility of the dialysis system, pyrogen-free

dialysate and sterile replacement solutions are strongly recommended. The dialysis membranes for extracorporeal RRT are also important. Biocompatibility of the haemodialysis membrane refers to the degree to which blood exposure to a membrane activates complement and neutrophils; more complement activation signifies less biocompatibility, and may cause a systemic inflamematory response. Cellulosic membranes may stimulate monocyte activation with release of cytokines and chemical mediators possibly causing a delay in the recovery from acute tubular injury. Synthetic membranes have the advantage of producing little or no inflammatory effect [14] and may reduce the concentration of several inflammatory mediators by filtration/adsorption. Two major studies found that use of biocompatible membranes improved these outcomes in AKI, but each study suffered from methodologic flaws [15]. Use of a biocompatible dialyzer that also has higher permeability than the bioincompatible dialyzer may have influenced the outcome in one study [15]. Potentially serious protocol problems such as lack of randomization, centre-specific practice variations, un-blinded interim analysis and publication by one centre, and failure to perform an intention-to-treat analysis may have influenced the outcome in the other major "positive" biocompatibility trial [16]. Several subsequent studies have failed to confirm the benefits of biocompatibility in AKI, but have lacked the statistical power to definitively exclude any effect. In the recent trial 180 patients with ARF were randomized to intermittent haemodialysis (IHD) with a bioincompatible (cuprophane, n = 90) or biocompatible (polymethylmethacrylate [PMMA], n = 90) membrane [17]. The main outcome measure was survival for 14 days after the end of treatment. Forty-four patients (58%) assigned cuprophane membranes survived as did 50 patients assigned PMMA (60%). There was still no difference in mortality between the two groups when the analysis was adjusted for age and APACHE II score, or stratified according to the presence or absence of oliguria. The study size of this trial was larger than in the two earlier positive investigations, but the power was still inadequate to detect a 25% mortality difference related to membrane biocompatibility [18], if such existed. In the light of a number of conflicting studies, the clinical relevance of this aspect of the acute dialysis prescription remains unproven, despite the fact that this strategy has already become standard in many centres [19]. The haemofilter membranes used for CRRT are among the most biocompatible, so it is important that future studies comparing the effects of IHD and CRRT use identical haemofilters in both groups, to eliminate any potential differential impact of this variable.

We currently do not have evidence-based recommendations regarding the optimal dialysis dose in AKI. Until further data is available, a reasonable recommendation offered by the Acute Dialysis Quality Initiative is to deliver a dose of IHD in the acute setting that is at least equal to what is considered acceptable in the chronic end-stage renal disease (ESRD) population. This is a

Kt/V > 1.2 per treatment if IHD is provided three times per week. Alternatively, one can attempt to deliver a Kt/V > 1.0 per treatment on a dialysis schedule of at least six days a week. Paganini *et al*. [20] demonstrated by retrospective analysis of a prospectively gathered database that the delivered dialysis dose was predictive of mortality in critically ill AKI patients treated with RRT if they had moderate-range severity of illness, but mortality of the most and least severely ill patients was independent of the dialysis dose [20]. Pending results of future prospective studies of the impact of dialysis dose on the outcome in the AKI population, a common-sense approach dictates provision of a dialysis prescription and delivered dose at least consistent with adequate therapy of chronic renal failure patients. Future interventions should include use of anticoagulation whenever possible, placement of catheters with optimal blood flow rates, and prescription of an increased dialysis dose for larger patients.

Choice of renal replacement therapy

W.J. Kolff was the physician who performed the first successful HD for AKI, in Kampen, Holland, on 11. September 1945. [21]. This first successful RRT for a patient with ARF was described as follows: *"A 67-year-old woman is admitted to the surgical service with a high fever, a painful and distended abdomen, jaundice, and almost complete anuria. A urinalysis revealed dark red-brown urine notable for albuminuria, erythrocytes, leukocytes, and casts. The patient was treated with antibiotics, but continued to have oligoanuria. On the eighth day of hospitalization, the following laboratory tests were obtained: serum potassium 13.7 mEq/l and BUN 396 mg/dl. At this time the patient was noted to be encephalopathic with deteriorating clinical condition. Renal replacement therapy was initiated using a rotating drum. The initial dialysis treatment lasted 690 minutes (i.e. 11.5 hours), blood flow was 116 ml/min and urea reduction rate 69% (i.e. pre- and post-treatment urea serum concentrations were 396 and 121 mg/dl). The calculated urea clearance was 87 ml/min and Kt/V 1.40. After the initial dialysis treatment, the patient went on to become nonoliguric, followed by gradual recovery of urea clearance. She survived her acute illness, left the hospital, and at 7 months posthospitalization was doing quite well* [21]*."* W.J. Kolff described a RRT that has only recently become established as a treatment for severely ill patients with renal failure in the ICU– prolonged dialysis with low blood and dialysate flow rates (sustained low-efficiency dialysis; SLED). Since that time, RRTs have undergone enormous technical improvement. There are now many available options divided into 4 groups: 1. peritoneal dialysis (PD), 2. IHD, 3. continuous therapies (CRRT), and 4. hybrid therapies (SLED). The ideal RRT should mimic the functions and physiological mechanisms of the native organ, ensuring qualitative and quantitative blood purification, be free of complications, have good clinical tolerance and

restore and maintain homeostasis, thus favouring organ recovery (Table 2). These 4 groups of RRT differ in the method of delivery, efficiency, and their clinical tolerability. There is wide variability worldwide in the methods used for the treatment of AKI. The reasons for this variation include local practice and organization (nephrologist-or intensivist-based management), the centre's experience of the various techniques, and health resources. Technical support and adequate training of personnel is essential for the performance of each substitutive treatment. Some techniques require less investment in terms of equipment and personnel and may therefore be preferred in spite of their limited efficacy. There are also certain clinical situations in which only a particular therapy is indicated (e.g., CRRT in critically ill patients with cardiovascular instability) [22]. Distinguishing whether AKI is a result of single organ dysfunction or part of MOF is a key factor. These two groups of subjects differ substantially and should be treated differently. AKI without MOF is less complex, can be managed outside ICU and the same RRT techniques used for the treatment of chronic renal failure may be applied. AKI associated with MOF is a more complex condition and requires more flexible RRT [23].

Table 2 – Табела 2

Technical and clinical requirements for an optimal renal replacement therapy in acute renal injury

Технички и клинички потреби за изведување на оптимална бубрежно заместителна терапија кај акутното бубрежно оштетување

Rapid and easy institution with simple treatment monitoring
Efficiency and efficacy which satisfies therapy prescription
Volume control without causing cardiovascular instability
Allows fluid administration/nutrition maintaining normal volume of circulating plasma
Maintains stable acid–base balance
High biocompatibility with minimal interaction with blood
Clinical tolerance
No deleterious effects on renal function or duration of acute renal failure
Easy and predictable adjustment of drug dosing
Inexpensive

Peritoneal dialysis

Acute PD remains a viable option for the treatment of selected patients with ARI, particularly the paediatric population, and those who are haemodynamically compromised, have severe coagulation abnormalities, difficulty in ob-

taining blood access, removal of high molecular weight toxins (> 10 kD), and clinically significant hypothermia and hyperthermia.

There are very few absolute contraindications for acute PD, most of the following conditions are only relative contraindications to this modality: 1. recent abdominal and/or cardiothoracic surgery, 2. diaphragmatic peritoneal-pleural connections, 3. severe respiratory failure, 4. extremely high catabolism, 5. life-threatening hyperkalaemia, 6. severe volume overload in a patient not on a ventilator, 7. low peritoneal clearances, 8. severe gastroesophageal reflux disease, 8. fecal or fungal peritonitis, 9. abdominal wall cellulites, and 10. AKI in pregnancy.

One of the important determinants of a successful acute PD procedure is a reliable peritoneal access, which can easily be obtained by inserting a semirigid acute catheter (can be placed easily at the bedside by a nephrologist), or a single-cuff Tenckhoff catheter (inserted by a surgical procedure). Acute PD can be performed intermittently or continuously (depending upon the desired amount of fluid and solute removal), and either manually or via an automated device. Manual PD is usually performed by nurses, since it requires constant supervision to ensure proper inflow, accurate dwell and drain times, the maintenance of a record of exchange and drain volumes, as well as the documentation of net ultrafiltration rate (UFR). The use of the automated device reduces the need for constant nursing supervision. The number of interruptions is significantly decreased since large volumes of solutions can be prepared at the beginning of the procedure [24]. Acute PD requires the use of pyrogen-free solutions infused into the peritoneal cavity and drained in a series of cycles. Diffusive removal of solutes is achieved by a concentration gradient between blood flowing in the peritoneal capillary network and dialysate. Convective removal of water and solutes is obtained by increasing dialysate osmolality, which represents the major component of peritoneal transmembrane pressure. There are large individual variations in peritoneal membrane characteristics. Intermittent peritoneal dialysis (IPD) consists of a series of rapid exchanges with complete drainage of fluid at the end of each cycle. Continuous equilibration peritoneal dialysis (CPD) utilizes long intraperitoneal dwell times in order to achieve a dialysate/plasma equilibration with reduced fluid usage. Equilibration for urea occurs at about a 4-hour dwell-time. In tidal peritoneal dialysis (TPD), one litre of solution is maintained in the peritoneal cavity while rapid one-litre exchanges are continuously performed. This schedule reduces the time in which the peritoneal cavity is empty [25]. While short exchanges are indicated for fast transporters to achieve less glucose reabsorption and higher UF rates, long dwell-times are indicated in normal to low transporters. A new modality has recently emerged called continuous flow peritoneal dialysis (CFPD) where a double lumen catheter allows PD fluid to circulate continuously and to achieve the highest levels of clearance possible in PD [24]. Such a form is still under evaluation and clinical results in acute patients are awaited.

IPD regimes can achieve remarkable clearance and UFR values, but large amounts of fluid are required, so continuous monitoring is mandatory. CPD requires much less dialysis solution, but its efficiency is rather low. TPD

offers a compromise although PD equipment is generally required for its performance. The final efficiency is obtained by the product (clearance × time) and it is expressed in litres of clearance per 24 hours [26]. In IPD, urea clearances up to 25 l/day can be achieved at an average dialysate flow rate of 5 l/h, while with other PD techniques lower clearances are generally achieved. Despite its low efficiency in most uncomplicated patients, PD can effectively control urea concentration because of its continuous action guaranteeing stable biochemistry and significant solute extraction. The unique permeability of the peritoneal membrane allows for remarkable clearances of larger molecules other than urea and has the capacity for the removal of peptides of up to 50,000 Da.

Complications of acute PD are numerous and potentially serious, but preventable, and include peritonitis, hyperglycaemia, substantial protein loss, disturbance of respiratory mechanics, and visceral perforation while inserting the catheter. The complications of PD and IHD for AKI have been compared in one centre study. The patients treated by IHD had a high incidence of severe hypotension and severe haemorrhage, acidosis, and vascular access clotting. PD patients had a high incidence of hyperglycaemia, asymptomatic peritonitis, and poor catheter drainage [27, 28] (Table 3).

Table 3 – Табела 3

Complications of dialysis in acute kidney injury
Компликации при дијализата на акутното бубрежно оштетување

	IHD	**PD**
No. (patients; dialyses)	34; 240	43; 65
Severe hypotension[1]	85/240 (35%)	8/65 (12%)
Severe haemorrhage[2]	15/34 (44%)	2/43 (5%)
Metabolic complications		
Hyperglicaemia		37/65 (57%)
Hypernatraemia		2/65 (3%)
Acidosis	9/34 (26%)	
Neurologic complications		
Seizures	1/34 (3%)	3/43 (7%)
Deterioration of consciousness		9/65 (14%)
Mechanical complications		
Mild bleeding		17/65 (26%)
Poor drainage, leaking		34/65 (52%)
Shunt clotting	11/34 (32%)	
Infection		
Vascular access infection	2/34 (6%)	
Peritonitis		
Asymptomatic positive peritoneal cultures		19/65 (29%)

[1]Systolic blood pressure < 90 mmHg;
[2]Requiring transfusion

A paucity of data exists concerning the effect on mortality of PD versus IHD or CRRT other than PD in patients with AKI. Most studies have shown that the mortality and incidence of renal recovery with acute PD was at least comparable to IHD [27]. The major causes of death of AKI patients were different for patients treated by IHD and PD. Death from dialysis-unrelated sepsis was higher for the IHD group, while cardiac deaths were higher in the PD group due to the more frequent implementation of this therapy in patients with underlying heart disease [28].

Intermittent extracorporeal therapies

These techniques require good vascular access, special equipment and specially trained physicians and nurses to carry out the dialysis. The haemodialysis machine must meet high standards of reliability and safety with an adequate blood module, a precise dialysate-preparing module with adequate warming and de-aeration systems, and all parts must have active alarms to avoid accidents. A water treatment system including a water softener which can deionize water, a reverse osmosis module and on-line ultrafilters are needed to achieve a bacteria- and pyrogen-free dialysate [29].

Intermittent haemodialysis

Patients who are haemodynamically stable can be managed with IHD techniques, the requirements for the technical aspects of dialysis being the same as those for chronic HD. Poor haemodynamic tolerance of intermittent IHD is a common problem for patients in an ICU. This poor outcome appears to be related to the high prevalence of associated organ failures and to underlying diseases (Figure 1). In these patients, hypotensions should be avoided to prevent a reduction in tissue oxygen delivery that may lead to organ dysfunction. This is particularly important for the kidney in the case of ARI, because of the impairment of renal blood flow autoregulation. In case of acute tubular necrosis, hypotension induces new ischaemic tubular damage and further reduces the glomerular filtration rate (GFR). Therefore, RRT should be kept as safe as possible to avoid a delay in recovery of renal function and improvement of other organ failures [30]. Maintaining haemodynamic stability is probably one of the most important aspects of dialysis technique as well as one of the most difficult challenges [31]. To improve haemodynamic tolerance of IHD, specific guidelines were implemented in the practice (Table 4).

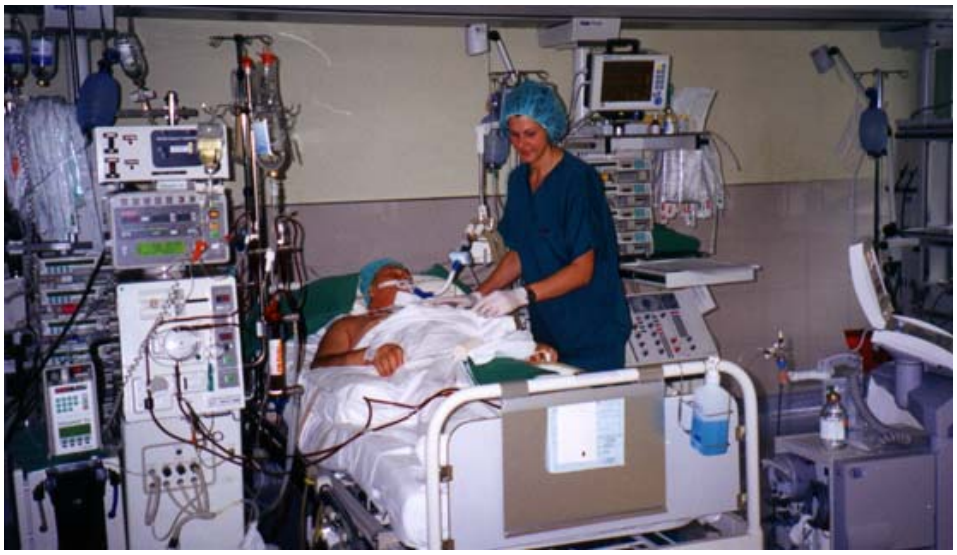

Figure 1 – Intensive care unit – Intermittent haemodialysis in acute kidney injury patient

Слика 1 – Оддел за интензивна нега – интермитентна хемодијализа на пациент со акутно бубрежно оштетување

Severe AKI in now profoundly different from the disease seen by nephrologists 25 years ago. It is seen predominantly in ICU, is usually associated with MOF, and is often accompanied by sepsis, is typically multifactorial, and has a very high mortality rate. To achieve optimal care for a complicated AKI patient, nephrologist and intensivist must work side by side. Such an approach has led to the development of an area defined as critical care nephrology.

The practice guidelines are based on dialysis strategies experienced in chronic HD patients suffering from cardiovascular insufficiency. Various procedures of adapted IHD strategy may be useful to preserve myocardial function and plasma volume during fluid removal, and to adapt vascular resistances. Using biocompatible membranes is an aspect of dialytic conditions adapted to patients with MOF, which may influence the patients' outcome. Two prospective comparative studies have suggested that in critically ill patients with ARF the mortality and delay of recovery from renal failure could be reduced by using a biocompatible synthetic membrane (polysulphone) in place of cuprophane [15, 16]. Because of their high flux, the use of synthetic membranes during IHD requires a pyrogen-free dialysate, because of the risk of backfiltration. For this reason, Kes *et al*. [32] used a modified cellulosic membrane, whose compatibility is better than cuprophane, in place of a synthetic membrane. A total of 297 AKI patients were included in the prospective, randomized study and followed until death or discharge from the hospital and off IHD. Four types of dialysis membranes were used with different characteristics of biocompatibility and per-

meability: low-flux modified cellulose (LF-MC; cellulose acetate, cellulose diacetate, hemophan), high-flux modified cellulose (HF-MC; cellulose diacetate, cellulose triacetate), low-flux synthetic (LF-S; polysulfone) and high-flux synthetic (HF-S; polysulfone, polyacrylnitrile, polymethyl methacrylate). All HD treatments were performed with volumetric-control monitors that allowed precise UF. Dialysis water was obtained from reverse osmosis, and bicarbonate-based dialysate was used in all AKI patients. Dialysate flow rate was between 500 and 600 ml/min, and blood flow rate was maintained between 200 and 350 ml/min. Dialysate concentrations of sodium, potassium, calcium and glucose, UF, and anticoagulant dose were adapted at each HD session by the nephrologist according to patient needs. There was no difference between the four membrane groups in survival (LF-MC 59.3% *vs.* LF-S 61%, and HF-MC 55.6% *vs*. HF-S 53.3%) or in the recovery of renal function (LF-MC 47.8% *vs*. LF-S 48.6%, and HF-MC 90% *vs*. HF-S 100%). The main cause of death in the ARF patients treated with LF MC or S membranes was MOF, followed by sepsis. Most of the patients who developed AKI after open heart surgery and were dialysed with HF MC or S membranes died because of heart failure, and the second cause of death was MOF. There was no difference in MC and S membrane (LF or HF) treated AKI patients in number of HD sessions, duration of HD treatments, and hospitalization [32]. Several invasive haemodynamic studies in AKI patients have shown an impairment of the myocardial performance during acetate-based dialysis, and a poorer haemodynamic tolerance compared to bicarbonate bath [33]. To avoid rapid solute removal, the HD blood-flow rate must be limited and the duration of the session must be prolonged to preserve the delivered dialysis dose. High dialysate sodium concentration prevents a major reduction in plasma osmolality, promotes fluid shift from the interstitial to the intravascular compartments, and preserves plasma volume [34]. Several studies have shown that hypothermia increases peripheral vascular resistances, resulting in better preservation of arterial blood pressure during IHD without apparent deleterious effect. It is also important to avoid warming up the patient during HD, which promotes vasodilatation and hypotension [35]. Performing UF alone, without diffusive solute removal, may also contribute to improved haemodynamic tolerance to volume depletion, because of a better adaptation of total vascular resistances. In critically ill patients with AKI necessitating RRT, the haemodynamic response to IHD is strongly dependent on the strategy used. Despite the overall severity of ICU AKI patients, adaptation of the IHD technique to prevent haemodynamic impairment resulted in improved haemodynamic tolerance.

Because mortality is inversely related to dialysis adequacy in patients with ESRD on maintenance IHD, one could argue that part of the persistently high mortality in patients with dialysis requiring AKI might be related to an inadequate dose of dialysis. However, the targets for adequate solute clearance in AKI remain unknown, and the importance of removing middle and large

uraemic toxins in the setting of AKI remains to be determined. In recent years, there has been a growing effort to measure dialysis adequacy in AKI, using single-pool urea kinetic modelling. In patients with AKI, using "single-pool" urea

Table 4 – Табела 4

Intermittent hemodialysis practice quidelines
Препораки за интермитентна дијализа

Recommendations for systematic use:
– Use only modified cellulosic or synthetic membranes in place of cuprophane
– Connect simultaneously both lines of the circuit filled with 0.9% saline to the central venous catheter
– Set dialysate sodium concentration ≥ 145 mmol/l
– Limit the maximal blood flow at 150 ml/min with a minimal session duration of 4 hours
– Set dialysate temperature ≤ 37° C
Advice for the most haemodynamically unstable patients:
– Start session by dialysis and continue with UF alone
– Cool dialysate at 35° C
Additional recommendations:
– Stop vasodilator therapy
– Start session without UF, then adapt UF/h rate according to haemodynamic response

kinetic modelling, Jaber *et al*. [36] have observed Kt/V values that were 27% to 28% lower than prescribed. The difference was not attributable to early termination of dialysis, but probably relates to constrained use of anticoagulation and access recirculation, an unavoidable complication of venous catheters [37]. Paganini *et al*. [38] assessed the outcome of 842 critically ill patients with AKI who required CRRT or IHD. The authors used the Cleveland Clinic Foundation ARF acuity score, a scoring system that was developed from 23 different demographic and laboratory parameters to estimate the severity of illness. The delivered dose of dialysis (measured by blood-based and dialysate-based urea kinetics) did not appear to have any association with outcomes at the two ends of the scoring system. Indeed, patients with very low (< 4) and very high (> 15) scores had survival rates of 78% and 0%, respectively, regardless of dialysis dose. However, patients with intermediate scores seemed to be the most affected by dialysis dose delivery, with higher delivery (urea reduction ratio [URR], > 58%) associated with a significant reduction in mortality. Schiffl *et al*. [39] randomized 72 patients with AKI to either daily or alternate-day IHD. There was no difference in baseline characteristics, including age, severity of AKI, and APACHE II scores, as well as the dialysis technique, dialyzer type (high-

flux PS or AN69), and weight loss per session. Compared with the alternate-day treatment group, overall mortality was significantly lower in the daily treatment group (21% *vs*. 47%; $P < 0.025$) [39]. These preliminary analyses did not adjust for age, co-morbid conditions, and severity of illness. Although the impact of delivered IHD on survival of patients with AKI remains unclear, and until a link between urea control and clinical outcomes in AKI is established, the aforementioned data indicate suboptimal dialysis delivery, using the DOQI guidelines for patients with ESRD [40]. Consequently, physicians should consider empirical increases in dialytic time and IHD frequency and judicious use of anticoagulation to improve dialysis adequacy.

Haemofiltration

For haemofiltration (HF), treatment time is dependent on the rate of UF and the total amount of fluid to be exchanged. Blood flow is around 300 ml/min. A highly permeable membrane (e.g., polysulfone) is used and solutes are removed by convection. The ultrafiltrate is completely or partially replaced with sterile substitution fluid and solute concentrations in plasma are essentially normalized. Net fluid balance is the difference between UF and reinfusion. High permeability membranes allow different sized molecules to be removed. The standard treatment duration for a 30 L exchange HF is 3 to 4 hours.

In HF, the removal of larger uraemic toxins, interleukins, arachidonic acid metabolites and complement factors is obtained by convection and adsorption on the membrane. Many mediators of sepsis are water-soluble molecules with a molecular weight below the cut-off point high-flux membranes. The UF volume will determine the removal rate, and the characteristics of the membrane surface and the frequency of membrane exchanges influences the elimination of mediators [41].

Haemodiafiltration

Haemodiafiltration (HDF) combines HD and HF techniques. Highly permeable membranes are used allowing clearance of a wide molecular weight range of solutes. A total of 10 to 15 litres of ultrafiltrate are produced in each session and substitution fluid is reinfused according to the patient's fluid requirement.

High flux dialysis

High flux dialysis (HFD) requires a highly permeable membrane and precise UF control equipment. A pressure rise in the dialysate compartment

counterbalances the excessive UF provided by the high-flux biocompatible membrane and creates a typical mechanism of filtration–back-filtration in the dialyzer. As a consequence, a certain degree of convection is still maintained in conjunction with diffusion. The back-filtration in the distal part of the dialyzer ensures a correct fluid balance [42]. The use of a sterile or ultra-pure dialysate is strongly recommended.

Continuous renal replacement therapies

Haemodialysis-associated hypotension is estimated to occur in approximately 20–30% of treatments. Some of the causes are dialysis specific, such as excessive or rapid volume removal, changes in plasma osmolality, autonomic dysfunction, and anaphylactic membrane reactions. Interventions such as sodium modelling, increased dialysate calcium concentration, intermittent isolated UF, and cool dialysate are among those shown to improve haemodynamic stability during IHD [30, 32, 35, 40, 43]. In 1977, Kramer *et al*. [44] first described a continuous approach to RRT for critically ill patients haemodynamically intolerant of IHD, usually because of sepsis or severe cardiac dysfunction. Since its adoption in 1977, a myriad of different technologies, techniques, and technical advances have been introduced into CRRT (Figure 2). With CRRT, the continuous regulation of volume homeostasis could lessen the hourly rate of required UF, thereby improving haemodynamic stability compared with IHD. Control of azotaemia with modern veno-venous CRRT is at least equivalent to alternate-day IHD, and superior to daily IHD in large or hypercatabolic patients [45, 46]. Although acute therapy of severe hyperkalaemia, metabolic acidosis, or intoxications is more efficiently achieved with IHD, lesser abnormalties are corrected relatively quickly and controlled effectively with CRRT. Clinical data suggest that CRRT should be strongly considered for patients with severe hyperphosphataemia (tumour lysis syndrome, rhabdomyolysis), elevated intracranial pressure (ICP), cerebral oedema complicating acute liver failure, might be a useful component of therapy for lithium intoxication, and because of the continuous nature of the process prevents the post-dialytic "rebound" elevation of plasma concentration of uraemic toxins typically seen with IHD. In patients with cerebral oedema, IHD but not CRRTs (CAVH/CVVH, CAVHD/CVVHD or CAVHDF/CVVHDF) raised intracranial pressure and decreased cerebral perfusion pressure [23, 47, 48] (Table 5). Raised intracranial pressure in this setting is due to acute solute removal and resulting plasma hypoosmolality, causing a shift of water into the brain, with further reductions in cerebral perfusion pressure caused by dialysis-induced hypotension [31]. The clinical benefits of CRRT have also been reported for cardiac surgery patients. The possible mechanisms include decreased fluid overload, myocardial oedema, a decrease in

left ventricular end diastolic pressure, optimization of the Starling relationship, increased myocardial performance, and the removal of circulating myocardial depressant factors [49]. Sepsis and the non-infectious systemic inflammatory response syndrome (SIRS) are a major cause of AKI [31]. CRRT appears to have beneficial effects on haemodynamics in SIRS, sepsis or septic shock. Standard CRRT equipment has been modified either by using a more permeable membrane, coupling continuous plasma filtration with continuous adsorption or increasing the plasma water exchange rate. These modifications are aimed at moving CRRT from the simple treatment of AKI to the adjunctive treatment of sepsis [50], but whether they can yield clinically significant benefits remains unknown.

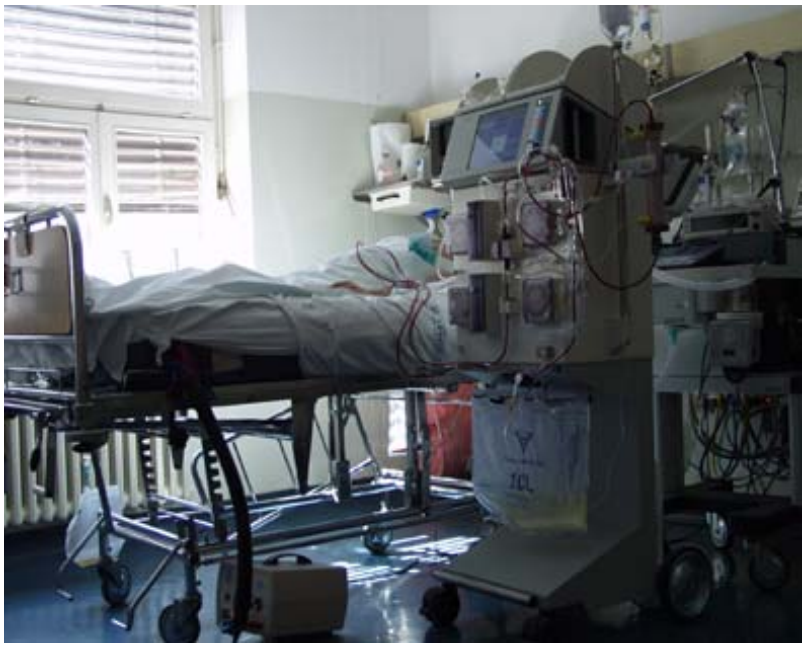

Figure 2 – Intensive care unit – Continuous renal replacement therapy in acute kidney injury patient

Слика 2 – Оддел за интензивна нега – континуирана ренална заместителна терапија на пациент со акутно бубрежно оштетување

Machine specifically designed to perform all the CRRT techniques. The system includes a high-resolution LCD colour screen, four roller pumps, four robust high precision scales, two individually bag heating systems, and heparin pump. The special construction of the scales enables the machine to hold up to 24 L of haemofiltration solution to perform high volume CVVH according to the increasing need of RRT's. The user menu clearly displays all process and parameter sequences leading the user step by step. Pre, post, and simultaneous pre–post dilution modes are available.

Table 5 – Табела 5

Indications for specific continuous renal replacement therapies
Индикации за специфична бубрежно заместителна терапија

Therapeutic goal	Haemodynamic condition	Preferred RRT
Fluid removal	Unstable	Slow continuous ultrafiltration (SCUF); PD
Urea clearance	Stable	IHD
	Unstable	CRRT: convection, CVVH; diffusion, CVVHD ; both, CVVHDF
Severe hyperkalaemia	Stable/unstable	IHD
Severe metabolic acidosis	Stable	IHD
	Unstable	CRRT
Severe hyperphosphataemia	Stable/unstable	CRRT

***Definition of abbreviations*:** CRRT = continuous renal replacement therapy; CVVH = continuous veno-venous haemofiltration; CVVHD = continuous veno-venous haemodialysis; CVVHDF = continuous veno-venous haemodiafiltration.

Although much attention has been focussed on the perceived benefits of CRRT compared with IHD, comparatively less attention has been focussed on the potential for increased risks with CRRT therapy (Table 6). In AKI patients stable enough to tolerate IHD, this benefit should be balanced against aspects of CRRT that might adversely affect the outcome, such as continuous anticoagulation, prolonged membrane exposure, hypothermia, and nonselective removal of nutrients, inflammatory mediators, and drugs. Drug dosing in AKI CRRT treated patients is usually based on regimens for moderate renal insufficiency (GFR 10 to 50 ml/min) for dose adjustments during CRRT with standard 1- to 2–l/h flow rates. For narrow therapeutic index drugs, therapeutic drug monitorring is appropriate. Filter clotting is the Achille's heel of CRRT, and may cause hours of lost therapy, which is quantitatively important because these are inefficient solute removal processes, which must be as close to continuous as possible in order to achieve dose equivalence with IHD [31]. The use of low molecular

weight heparin (LMWH) or low-dose heparin infused directly into the haemofilter with minimal systemic anticoagulation achieves adequate filter longevity in many patients (at least 24h, ideally 96h or more). CRRT without anticoagulation (using intermittent saline filter flushes) may be successful in some coagulopathic patients (e.g., patients with end-stage liver disease). In septic patients with thrombocytopenia and elevated prothrombin time/partial thromboplastin time (PT/PTT) due to diffuse intravascular coagulation (DIC), increased filter clotting is the rule if no anticoagulation is used. In newly postoperative patients and others with contraindications to systemic anticoagulation, regional anticoagulation of the haemofilter alone, the use of regional heparin (prefilter heparin, postfilter protamine), or the use of regional citrate anticoagulation (infusing citrate prefilter to chelate calcium and prevent filter clotting, and administering calcium through a central vein to prevent systemic ionized hypocalcaemia) has been used. [51]. Emerging alternatives include hirudin and prostacyclin. Differences in cost between IHD and CRRT techniques vary widely between institutions and countries, because of variations in IHD frequency, supply charges, and staffing practices (ICU nurse *vs*. dialysis staff versus both). It appears that CRRT is twice as expensive as IHD in most countries.

Table 6 – Табела 6

Comparison of intermittent and continuous renal replacement therapy
Споредба помеѓу интермитентната и континуираната бубрежно заместувачка терапија

Intermittent haemodialysis

Advantages

- Short duration makes more time available for diagnostic and therapeutic procedures
- Lower risk of systemic bleeding as a result of less heparin use
- More suitable for severe hyperkalaemia
- Optional online bicarbonate dialysate production
- Less labour-intensive and therefore less expensive

Disadvantages

- Technically sophisticated requiring specific infrastructure
- Qualified dialysis staff required to supervise the procedure
- Periodic solute control with subsequent disequilibrium
- Dialysis dose and nutritional support might be inadequate at low treatment frequencies
- Frequent hypotensive episodes with aggressive UF

Continuous renal replacement therapy

Advantages

- Machines are generally easy to operate and do not require specific infrastructure
- Intensive care unit staff can operate machines and perform monitoring
- Prolonged gradual solute and volume removal achieves superior solute and fluid control
- UF over a longer period provides better haemodynamic stability
- Adequate nutritional support possible

Disadvantages

- Higher requirement for heparin and higher risk of systemic bleeding
- Impairs mobilization of patients
- Treatment frequently interrupted due to filter problems, and diagnostic and therapeutic procedures
- Expensive sterile substitution solutions substantially increase treatment costs

Despite apparent advantages over IHD in unstable patients, the superiority of CRRT with respect to mortality or recovery of renal function has not been demonstrated. Mehta *et al*. [52] compared IHD and CRRT in 166 critically ill patients with severe AKI, with the finding of a significantly higher ICU mortality rate in patients who were randomly assigned to CRRT (60% *vs.* 42%; $P = 0.02$). However, despite randomization, patients who were assigned to CRRT were found subsequently to be more likely to have had a higher overall severity of illness, as determined by Acute Physiology, Age, Chronic Health Evaluation III (APACHE III) score. After adjustment for these factors, the increased risk that was attributed to CRRT was no longer statistically significant. However, within each tertile of severity of illness, randomization to CRRT was associated with a trend towards higher rather than lower risk [52]. In a recently reported randomized trial, 125 AKI patients were randomly assigned to CRRT (CVVHD) or IHD from a single-centre hospital ICU. In hospital, mortality rates did not differ by treatment assignment (47% *vs* 51%, CVVHD *vs.* IDH; $P = 0.72$) [53]. More recently, Vinsonneau *et al*. [54] reported the results of the largest, best powered, prospective, randomized, multi-centre study reported to date comparing the results of IHD with CRRT. A total of 360 critically ill patients were randomly assigned. In an intention-to-treat analysis, there was no difference in the primary end point of 60-day survival (32% in the IHD group *vs.* 33% in the CRRT group). The authors also noted that there was an unexpected progressive and significant increase in survival rates in the IHD group over time (relative risk 0.67/year; $P < 0.001$) [54]. This suggests that there may have been a lear-

ning curve for optimizing IHD therapy in this study environment. Therefore, published data from randomized trials do not support the contention that CRRT is a superior therapy. Most physicians would agree that CRRT is preferred to provide RRT for a significant proportion of haemodynamically unstable ICU AKI patients. In patients stable enough to tolerate IHD, this benefit should be balanced against aspects of CRRT that might adversely affect the outcome.

IHD and CRRT should be regarded as complementary techniques, which should both be available in institutions that care for critically ill patients, allowing RRT to be individualized to the needs of the complex patients who develop AKI in the ICU. AKI in ICU patients is increasingly a component of SIRS, sepsis or septic shock, and the development of rational strategies for initiation, dosing, and effective delivery of RRT in this setting is among the greatest challenges facing nephrologists and intensivists today. It is hoped that a multidisciplinary approach and new technology will yield progress in this complex and challenging field. There is increasing evidence that a beneficial effect obtained by CRRT in patients with SIRS or septic shock seems to lie in the capacity of these therapies to remove chemical mediators from the patients' circulation. This hypothesis has spurred new interest in the application of therapies with an increased amount of convection, or with membranes characterized by increasing sieving coefficients [50].

High volume haemodiafiltration

The metabolic control of AKI generally requires at least 30 L of urea clearance per day. The combination of diffusion and convection has shown that satisfactory clearances of small and medium large molecules can generally be achieved. In the case of sepsis, patients may present increased concentration of substances in the middle molecular weight range (500–5000 Da) such as proinflammatory mediators of the humoral response to endotoxin. In this case, the treatment should control not only waste products, but also the circulating levels of these proinflammatory substances. To achieve such a complex task, high convective rates may be required and can be obtained in CVVHF, CVVHDF, or in continuous high flux HD with continuous dialysate volume control. If the therapy is performed for 24h, clearances in the range of 80 L/day may be obtained. In HFD, substitution fluid is not required and the balance is obtained by a mechanism of internal back-filtration. If performed continuously, the treatments can provide weekly Kt/V in the range of 7–10 [48, 50]. These therapies have been shown to produce a beneficial effect on patients' haemodynamics, with a significant reduction of vasopressor drug requirement.

Continuous plasmapheresis-plasma exchange

Plasma filters differ from high flux membranes in that they have larger pores and sieving coefficients and can remove molecules with higher molecular weights including proteins and inflammatory mediators. They may be used in combination with CRRT technique performed with lower flow rates and for an extended period of time. The patient's plasma is filtered across highly porous membranes and large quantities of plasma substitutes such as fresh-frozen plasma are required for this procedure [55]. There appear to be some advantages in clinical trials; however, it is too early to predict its benefits as further large-scale trials are needed to confirm this. At this time, both the high costs of excessive plasma substitution fluids and unregulated losses of beneficial plasma constituents may limit this modality of treatment.

Cntinuous plasma filtration-adsorption

Coupled plasma filtration adsorption (CPFA) is a technique of blood purification in which plasma is separated from the whole blood and circulated in a sorbent cartridge. The plasma is then returned to the blood circuit which then undergoes standard HD or filtration through a cartridge containing a mixture of hydrophobic resin and uncoated charcoal. Because the patient's own plasma is used for reinfusion, there is no need for substitution fluids and unwanted protein losses are avoided. This modality has been shown to remove cytokines with high efficiency and most impressively has the ability to restore leucocyte responsiveness to endotoxin in *ex vivo* testing, suggesting an added immunomodulatory effect [56]. The potential for CPFA in the treatment of SIRS seems exciting but its role in the management of AKI has not been established and further clinical testing to appreciate its value is awaited.

Continuous haemoperfusion-haemodialysis

HP or HD alone do not provide sufficient purification for the treatment of AKI but in combination with CVVH or CVVHDF are able to provide a broader purification removing molecules that are not removed by CVVH or HD alone. The technique is based on the placement of a sorbent cartridge in series with the dialyzer in the attempt to remove those toxins that are not removed by classic blood purification techniques [57]. The critical factor to make this therapy effective is early application when a high concentration of circulating endotoxin can be detected in plasma, but systemic effects have not yet occurred.

'Hybrid' renal replacement therapies

This technique utilizes equipment originally developed for treatment of patients with chronic renal failure and does not require industrially produced substitution fluid. The term "sustained low-efficiency dialysis" (SLED) is the most widely used, but alternatives used in the literature include "extended daily dialysis" (EDD) and "slow continuous dialysis" (SCD). This means of RRT combines several advantages of both IHD and CRRT, most notably excellent detoxification and cardiovascular tolerability akin to that associated with CVVH.

Hybrid therapies using a variety of machines are safe and convenient, providing excellent control of electrolytes and fluid balance. Urea kinetics follows single compartment models and the delivered dose of dialysis is high. Larger solute clearance is enhanced by concurrent use of high flux membranes and on-line diafiltration. Machines for hybrid therapy should ideally have the characteristics of flexible options for dialysate flow (QD) (allowing for low flows should the clinical situation mandate low solute clearance and UFR), flexible options for hybrid treatment duration (allowing prolonged or even continuous treatments), clear interface with the nurse managing the treatment preferably via a dedicated hybrid therapy screen, and standard procedures for changing between IHD and hybrid therapy (allowing either modality to be conveniently chosen at treatment commencement without any resultant delay) [58]. Current machines include the Fresenius 4008S and Genius (both have a built-in option for hybrid therapy and may be selected from the startup screen without any delay or further adjustment), and the Gambro 200S Ultra (the lower limit of QD on this machine is 300 ml/min). The Genius system consists of a single-pass batch dialysis machine that provides up to 75 L of an ultrapure germ- and endotoxin-free pure bicarbonate dialysate per dialysis session and a station for automated production of dialysate and filling of the machine. The technically simple machine has one roller pump into which both blood and dialysate tubing are inserted and that pumps blood and dialysate countercurrently with a ratio fixed at 1 : 1 or 2 : 1, depending on the diameter of the blood and dialysis tubing used. Thus, the blood-flow determines the duration of treatment, i.e., the time in which the 75L dialysate tank is used up. Treatment time can be varied simply by changing the speed of the blood pump from 4 hours (conventional IHD with a 1: 1 system and blood flow of 300 mL/min) to as much as 24 hours (extended dialysis with a 2 : 1 system and blood flow of 100 mL/min) [58] (Figure 3). The blood flow and treatment time can be modified within the treatment session.

Different combinations of dry and liquid *concentrates* can be mixed to theoretically generate up to 240 dialysate compositions, allowing treatments to be tailored to the needs of individual patients. The most common dialysate solution contains potassium at 4.0 mmol/L, bicarbonate from 30 to 35 mmol/L, and calcium from 1.5 to 2.5 mmol/L The extremely flexible, yet highly effici-

ent, SLED treatment modality fulfils all ICU requirements: it offers immediate, highly effective dialysis therapy for acute hyperkalaemia, whereas for less urgent indications, treatment durations can be extended up to 18h. *Dialysate flow rate* is varied according to clinical need and dialysis machine specifications. The main factor governing QD is tolerance to ultrafiltration. If the targeted UFR is tolerated, treatment duration can be shorter (e.g. 6 to 10 hours), and QD should be higher in this setting (e.g. 300 mL/min). If tolerance is low,

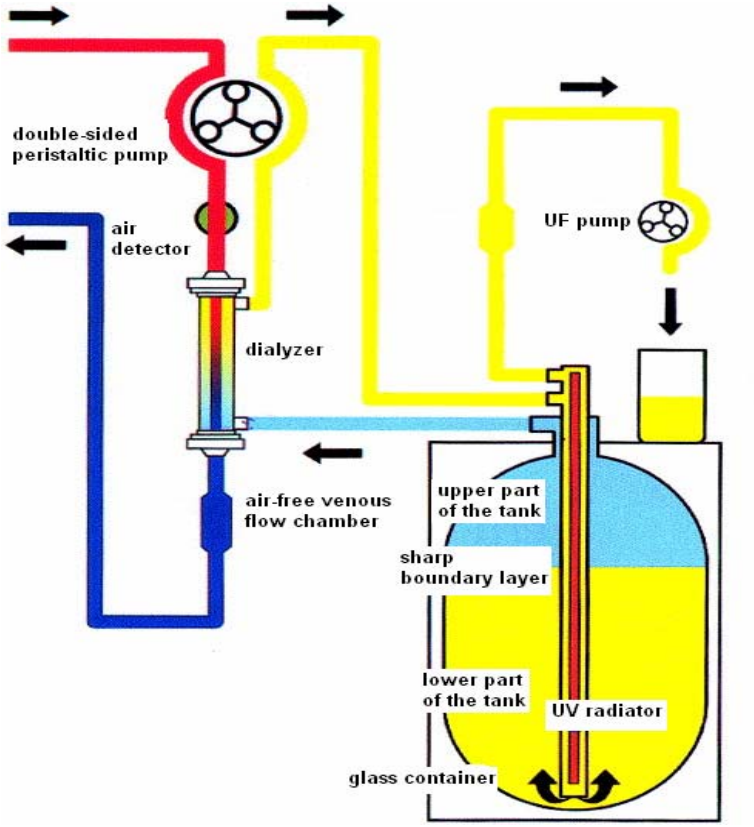

Figure 3 – *The Genius single-pass dialysis machine*

Слика 3 – *Машината Genius за single-pass дијализа*

The Fresenius Genius machine utilizes a 75 L or 90 L insulated but not heated glass container, in which all the dialysate destined for one treatment is stored. This dialysate is mixed from pre-packed salts and ultra pure water prior to treatment. Fresh dialysate is pumped from the top of the tank around the extracorporeal circuit and then into the bottom of the tank, where temperature and density differential keeps this spent dialysate from mixing with the fresh dialysate on the top. Constant UV light maintains tank sterility. One 75L tank will last about 18 hours ata flow of 70 ml/min, and a 90L tank about 8 to 12 hours at 150–200 ml/min.

duration will be correspondingly longer (eg, 10 to 18 hours, even continuous), and QD correspondingly lower (e.g. 100 to 200 mL/min). *Ultrafiltration* goals are determined by clinical need, and the main factor governing UFR is cardiovascular stability. If a prescribed ultrafiltration goal can be achieved over a shorter period, higher UFR is prescribed as tolerated, but if not, UFR will be lower, and treatment duration correspondingly longer. Standard *extracorporeal circuit tubing* and *haemodialyzers* are used. Unfractionated heparin is the most commonly utilized *anticoagulant*. Heparin regimens typically consist of a 1,000 to 2,000 IU bolus, followed by an infusion of 500 to 1,000 IU/h to keep the activated partial thromboplastin time 10 to 20 seconds above or 1.5 times control. Mean heparin requirements are reported to be between 4,000 and 10,000 IU per treatment-day, between 50% and 75% less than for CRRT [59, 60]. Regional citrate anticoagulation has been used for both batch and single pass machines to successfully maintain extracorporeal circuit patency during hybrid treatments. *Drug clearance* can be considerable with hybrid therapy and intermediate between that IHD and CRRT. Dosing decisions need to be made on an individual basis.

Sustained low-efficiency dialysis offers several advantages over CRRT, including less cumbersome technique, patient mobility, and decreased requirements for anticoagulation, while providing similar haemodynamic stability and volume control. A randomized, prospective trial comparing the two treatment modalities in a large cohort of patients is necessary to determine the relative impact of SLED on mortality. More definitive information will become available from impending multicentre prospective randomized trials (The Acute Renal Failure Network Trial; and CRRT vs SLED – Substudy of the Stuivenberg Hospital Acute Renal Failure Trial). In the mean time several controlled studies [58, 59, 61, 62] have been published by groups that use SLED to treat ICU patients with renal failure. Kielstein *et al.* [62] randomly treated 39 ventilated critically ill patients with oliguric acute renal failure with either continuous venovenous haemofiltration (CVVH; n = 19; age, 50.1 ± 3.2 years; Acute Physiology and Chronic Health Assessment II [APACHE II] score, 32.3 ± 1.2; 79% sepsis) and a substitution fluid rate of at least 30 mL/kg/h for 24 hours or with SLED for 12 hours (n = 20; age, 50.8 ± 3.6 years; APACHE II score, 33.6 ± 1.0; 85% sepsis). The latter was performed using an easy-to-handle, single-pass, batch dialysis system. Average mean arterial blood pressure, heart rate, cardiac output, systemic vascular resistance, and catecholamine dose were not significantly different in the two therapies. Urea reduction rate was similar with SLED compared with CVVH therapy (53% ± 2% vs 52% ± 3%) despite an average rate of substitution fluid with the latter of 3.2 ± 0.1 L/h. This was corroborated by the finding of similar amounts of urea eliminated in the collected spent total haemofiltration and dialysis fluid. Correction of acidosis was accomplished faster with SLED than CVVH, and the amount of heparin used was significantly lower with SLED ($P < 0.01$). The authors concluded that SLED combines

excellent detoxification with cardiovascular tolerability, even in severely ill patients in the ICU [62]. Kumar *et al*. [58] compared SLED with standard CVVH in a prospective study. They used the 2008H (Fresenius Medical Care, Germany) machine to treat 25 critically ill patients with SLED (367 total treatment days). An additional 17 patients were treated with CVVH for a total of 113 days. Median daily treatment time was 7.5h for SLED and 19.5h for CVVH. No differences in mean arterial blood pressure or use of catecholamines were observed between the treatment groups, despite similar median net daily UFR (3,000 ml/day vs. 3,028 ml/day). By contrast, requirement for anticoagulation was significantly less in patients treated with SLED (median heparin dose 4,000 U/day vs. 21,100 U/day with CVVH) [58]. The authors found that SLED was well tolerated by the majority of patients, offered many of the same benefits provided by CVVH, and was technically easier to perform [58]. Kumar *et al*. [63] have also published an account of their 2-year experience with SLED. They concluded that this technique is well tolerated and offers many of the benefits of continuous techniques, but is technically much simpler to perform and therefore well accepted by the ICU team [63]. Marshall *et al*. [64] used a standard IHD machine (2008H, Fresenius Medical Care, Germany) at a reduced dialysate flow rate of 100 ml/min. They have used this approach to treat critically ill patients in whom IHD had repeatedly failed because of intradialytic hypotension, patients in whom haemodynamic intolerance was likely to occur, and patients in whom the prescribed solute control goals were not achieved despite daily IHD. In these settings, the authors achieved ultrafiltration goals and adequate solute removal in most of their 37 patients with 145 SLED procedures. Dialysis quantification in nine oliguric patients revealed a mean delivered double-pool Kt/V of 1.36 ± 0.38 per treatment. Hospital mortality was 62% (not significantly different from expected mortality determined from the [APACHE II] illness severity score) [64]. All of the reported experiences with hybrid therapy suggest patients' outcomes are no different from that predicted by their illness severity scores.

Substantial cost reduction can be achieved if the equipment used for SLED is also employed for chronic RRT in the same hospital. All centres offering SLED use various standard IHD machines, such as the 2008H or the Genius single-pass dialysis system, without adding or altering software or hardware. In some hospitals, flexible treatment modalities allow the same machine to be used for two IHD sessions and one overnight SLED treatment during a 24-hour period. Newer machines, like the Fresenius 4008 series, have a built-in option for SLED, which is selected from the startup screen without any delay or requirement for further adjustment. Several economic evaluations have shown SLED to be less expensive than CRRT within a widely applicable nationalized healthcare system [65]. The main sources of cost savings are reduced staff load and reduced need for industrially produced sterile substitution fluid.

The impact of modality of dialysis on mortality and recovery of renal function

Marshall *et al*. [58] presented a single-centre experience accumulated over 18 months with a SLED technique, in which standard IHD equipment was used with reduced dialysate and blood flow rates. Twelve-hour treatments were performed nocturnally, allowing unrestricted access to the patient for daytime procedures and tests. One hundred and forty-five SLED treatments were performed in 37 critically ill patients in whom IHD had failed or been withheld. The overall mean SLED treatment duration was 10.4 hours because 51 SLED treatments were prematurely discontinued. Of these discontinuations, 11 were for intractable hypotension, and the majority of the remainder were for extracorporeal blood circuit clotting. Haemodynamic stability was maintained during most SLED treatments, allowing the achievement of prescribed UF goals in most cases with an overall mean shortfall of only 240 mL per treatment. Direct dialysis quantification in 9 patients showed a mean delivered double-pool Kt/V of 1.36 per treatment. Observed hospital mortality was 62.2%, which was not significantly different from the expected mortality as determined from the APACHE II illness severity scoring system. The authors concluded that SLED is a viable alternative to traditional CRRTs for critically ill patients in whom IHD has failed or been withheld [58].

Berbece and Richardson [66] compared SLED (23 patients, 165 treatments) with CRRT (11 patients, 209 days), focussing on cost, anticoagulation, and small solute removal. SLED consisted of 8 h of HD 6 days a week, with QB of 200 ml/min, QD of 350 ml/min, and haemofiltration with 1 L of saline/h. CRRT patients were anticoagulated with either heparin or citrate, and SLED patients with either heparin or saline flushes. The weekly costs to the hospital were $1,431 for SLED, $2,607 for CRRT with heparin, and $3,089 for CRRT with citrate. Sixty-five percent of SLED treatments were heparin-free; filter clotting occurred in 18% of heparin treatments and 29% of heparin-free treatments. Weekly Kt/V was significantly higher for SLED (8.4 ± 1.8) and time-averaged SCr was lower; equivalent renal clearance was 29 ± 6 ml/min for SLED, similar to that for CRRT. The authors concluded that SLED may be routinely performed without anticoagulation, and that it provides solute removal equivalent to CRRT at significantly lower cost [65].

Kellum *et al*. [67] performed a meta-analysis of all prior randomized and observational studies that compared CRRT with IHD. Studies were assessed for baseline characteristics, intervention, outcome and overall quality through blinded review. The primary end-point was hospital mortality, assessed by cumulative relative risk (RR). The authors identified 13 studies (n = 1,400), only 3 of which were randomized. Overall there was no difference in mortality (RR 0.93 (0.79–1.09), p = 0.29). However, study quality was poor and only 6 studies compared

groups of equal severity of illness at baseline (time of enrolment). Adjusting for study quality and severity of illness, mortality was lower in patients treated with CRRT (RR 0.72; $P < 0.01$). In the 6 studies with similar baseline severity, unadjusted mortality was also lower with CRRT (RR 0.48; $P < 0.0005$). Kellum *et al*. [67] concluded that current evidence is insufficient to draw strong conclusions regarding the mode of RRT for AKI in the critically ill.

Currently, no difference has been found in mortality or renal recovery between hybrid RRT, CRRT or IHD for critically ill patients with AKI. However, future investigations should collect detailed information on long-term costs and the relative likelihood of renal recovery associated with dialysis modality. New trials aimed at showing a mortality benefit in unselected patients should be undertaken with caution because recent data suggest that the required number of patients for such a study would be very high. Nonetheless, multicentre investigations of this issue could be performed successfully, as with other common interventions in critical illness, even those laden with perceived ethical issues, such as blood transfusions. The design of new studies evaluating the impact of dialysis modality in AKI would need to account for contamination (caused by treatment crossover), illness severity (by stratification), and variations in dialysis technique, dialysis membrane, and dose. Lessons learned from the conduct of previous trials could be used to develop inclusion criteria that would minimize ethical concerns and produce a suitably homogeneous patient population. Because the mortality rate of critically ill individuals remains elevated long after leaving the ICU, outcomes should be assessed at hospital discharge, or even later.

Two large multicentre randomized controlled studies aimed at resolving uncertainty about the impact of more intensive RRT on mortality are now under way: the Veterans Administration/National Institutes of Health Acute Renal Failure Trial Network (ATN) study and the Australian and New Zealand Intensive Care Society/George Institute for International Health/Australian National Health and Medical Research Council Randomised Evaluation of Normal versus Augmented Level of RRT (RENAL) study. The ATN study is a multicentre, prospective, randomized, parallel-group trial of two strategies for the management of RRT in AKI in critically ill patients. It is conducted within a network of approximately 30 tertiary-care Veterans Administration and university hospitals in the United States. Patients with suspected ATN will be randomized to either an 'intensive' or a 'conventional' management strategy. Within each group, depending on haemodynamic status, as assessed by the sequential organ failure assessment score, patients will receive either IHD, or CRRT or SLED. In patients randomized to the intensive-strategy arm, the dose of treatment will be greater (for CRRT, this will mean a dose increase from 20 to 35 ml/kg/h of estimated urea clearance). The primary end point for the ATN study is 60-day all-cause mortality. The investigators have estimated that 1164 subjects need to be

randomized to show a 10% absolute reduction in mortality from 55% to 45% with a power of 90% at a two-sided significance level of 0.05, allowing for a dropout rate of 10% [68]. The RENAL study is a multicentre, open-label, parallel-group, randomized, controlled trial of an 'augmented' CRRT regimen to deliver a dose of 40 ml/kg/h of estimated urea clearance, compared with 'normal' CRRT at a dose of 25 ml/kg/h in critically ill patients with severe AKI. The dose of 25 ml/kg/h represents current average practice in Australia and New Zealand. The primary aim of the study is to compare the effects of these two CRRT doses on all-cause mortality. The RENAL study will randomize 1,500 patients. This study will have a 90% power to detect an 8.5% absolute reduction in 90-day mortality at an end cut of 0.05, assuming a 90-day mortality of 60% in controls [68]. The ATN and RENAL study is now under way and is scheduled to finish by the end of 2007 or by early 2008 and the results should be available in 2008. Both studies will provide valuable data on many aspects of RRT (secondary outcomes, technique, timing of start of RRT, anticoagulation, risk of bleeding, complications, and filter life). The prudent clinician would do well to wait until the release of the results of these two trials before deciding what is the 'best technique' and the 'best dose' of RRT in severe AKI. Until information from such trials is available, a systematic review such as this may constitute the best possible evidence.

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Резиме

НОВИ ИСКУСТВА ВО ТЕРАПИЈАТА НА АКУТНОТО БУБРЕЖНО ОШТЕТУВАЊЕ

Кес П., Башиќ Јукиќ Н.

Клиника за дијализа, Загреб
Универзитетски болнички центар, Загреб, Хрватска

Акутното бубрежно оштетување (АБО) се среќава кај различни групи на пациенти (хоспитализирани или амбулантски пациенти, пациенти на интензивна нега, хоспитализирани деца, возрасни и стари), со различни клинички манифестации кои варираат од минималната елевација на серумската вредност на креатининот (сКр) до анурија со/или без мултиорганско откажување (МОФ), со широки варијации во зависност од причините, факторите на ризик и коморбидитетите. Не постои јасно правило кога треба да се започне лекувањето на АБО со бубрежната заместителна терапија (БЗТ), но не треба да се чека да се појават уремиските компликации. Актуелна практика е да се започне со БЗТ порано, на пример кога сКр ќе достигне вредност од 500 до 700 микромол/л, освен ако постои јасен показател дека настапува оздравување на бубрежната функција. Изборот на третманот ќе зависи од клиничката практика, техничките можности и едуцираноста на медицинскиот персонал. Идеалната БЗТ треба да ги замени функциите и физиолошките механизми на нативниот орган, да биде без компликации, со добра клиничка толеранција, да ја одржува хомеостазата, со цел да дојде до закрепнување на афектираниот орган. БЗТ е претставена со перитонеална дијализа (ПД), интермитентна хемодијализа (ИХД), континуирана бубрежна заместителна терапија (КБЗТ) и хибридни терапии. Сите наведени терапии се разликуваат според методите на изведување, во ефикасноста и клиничката толеранција.

АБО без МОФ е помалку сложена клиничка состојба и може да се лекува надвор од единиците за интензивна нега, со истите техники на БЗТ кои се користат за лекување на терминална бубрежна слабост. АБО со МОФ е сложена клиничка состојба, која се одликува со потребата од флексибилна БЗТ. Акутната ПД претставува опција за лекување на селектирани пациенти со АБО, како, на пример, деца, хемодинамиски нестабилни пациенти, пациенти со нарушена хемостаза, со потешкотии при обезбедувањето на васкуларен пристап, со потреба за елиминирање на токсини со голема молекуларна маса (> 10 КД) и клинички сигнификантна хипо или хипертермија. Пациентите кои се хемодинамиски стабилни може да бидат лекувани со ИХД. Одржувањето на хемодинамиската стабилност е еден од најважните аспекти при изведувањето на дијализните техники. Со КБЗТ е овозможена континуирана регулација на хомеостазата, односно одржувањето на хемоди-

намиската стабилност. Клиничките податоци сугерираат дека КБЗТ треба да биде строго спроведена кај пациенти со тешка хиперфосфатемија, зголемен интракранијален притисок, церебрален едем, акутна црнодробна слабост, сепса или септичен шок, литиумска интоксикација... Со КБЗТ се превенира постдијализниот скок на серумската концентрација на уремичните токсини, карактеристично за ИХД. Хибридните терапевтски техники овозможуваат одлична контрола на водено-електролитниот баланс и се одликуваат со одредени предности во споредба со КБЗТ, како мобилност на пациентот и намалената потреба за антикоагулантна терапија. При споредбата на хибридната БЗТ, КБЗТ и ИХД не е утврдена разлика во стапката на морталитетот или бубрежното оздравување кај пациентите со АБО. Идните истражувања треба да обезбедат детални информации за високите трошоци и за бубрежното оздравување асоцирано со дијализниот модалитет.

Клучни зборови: акутно бубрежно оштетување, бубрежна заместителна терапија, перитонеална дијализа, интермитентна хемодијализа, континуирана бубрежна заместителна терапија.

Corresponding Author:

Kes Petar
Department of Dialysis,
Zagreb University Hospital Centre
Zagreb, Croatia

E-mail: kespetar@net.hr