

# A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: part 2: renal replacement therapy

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## ABSTRACT

This paper provides an endorsement of the KDIGO guideline on acute kidney injury; more specifically, on the part that concerns renal replacement therapy. New evidence that has emerged since the publication of the KDIGO guideline was taken into account, and the guideline is commented on from a European perspective. Advice is given on when to start and stop renal replacement therapy in acute kidney injury; which modalities should be preferentially be applied, and in which conditions; how to gain access to circulation; how to measure adequacy; and which dose can be recommended.

## INTRODUCTION

The broad clinical syndrome of acute kidney injury (AKI) encompasses various aetiologies and is a serious condition that affects kidney structure and function acutely as well as in the

long term [1–3]. The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI [4] were designed to systematically compile information on this topic by experts in the field. These guidelines are based on systematic review of relevant trials published before February 2011. Nevertheless, for many sections of the guidelines, appropriate supporting evidence is lacking in the literature. As a consequence, variations in practice will inevitably occur when clinicians take into account the needs of individual patients, available resources and limitations unique to a region, an institution or type of practice. Therefore, in line with its philosophy [5], European Renal Best Practice (ERBP) wanted to issue a position statement on these KDIGO for AKI guidelines.

A working group was established to produce guidance from the European nephrology perspective, based on the compiled evidence as presented, with an update of the literature up to March 2012, following the methodology as explained in the ERBP instructions to authors [6]. The present document will deal with aspects related to renal replacement therapy (RRT) in patients with AKI, whereas the diagnosis and prevention of AKI,

and contrast-induced nephropathy (sections 1, 2, 3 and 4 of the KDIGO document), and the specific condition of crush-related AKI, were discussed in a separate position statement [7, 8].

As a general rule, we will only mention those guideline statements of the KDIGO document that we have amended, even when the change is small, e.g. a change in grading. If a KDIGO recommendation is not repeated, it can be considered as endorsed by ERBP as is.

## TIMING OF RENAL REPLACEMENT THERAPY IN AKI

- (i) Initiate RRT when life-threatening changes in fluid, electrolyte and acid–base balance exist that cannot be managed by conservative treatment. (not graded)
- (ii) Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single blood urea nitrogen (BUN) and creatinine thresholds alone—when making the decision to start RRT. (not graded)

‘Life-threatening’ changes in fluid, electrolyte and acid–base balance that cannot be managed by conservative interventions are considered ‘classic’ indications for RRT. Besides these hard indications, the optimal time for starting RRT remains unclear while the definition of an ‘early’ and ‘late’ start is variable and there is a wide range of clinical practice [9]. A variety of arbitrary cut-off variables like serum creatinine, serum urea, urine output, fluid balance, time from intensive care unit (ICU)-admission or duration of AKI have been studied in order to distinguish ‘early’ from ‘late’ start of RRT [10]. Most of the data come from observational studies focusing on blood urea or BUN as a biomarker, resulting in the situation that patients who do receive ‘early’ dialysis probably did not need dialysis as they had less severe disease, and thus a better prognosis independent of whether they received RRT. A recent systematic review and meta-analysis [11] identified 15 eligible studies (2 randomized, 4 prospective cohort, 9 retrospective cohort), and concluded that ‘earlier’ institution of RRT in critically ill patients may have a beneficial impact on survival. However, this conclusion is based on heterogeneous studies with variable quality, and, as explained, with incorrect premises and comparing non-logical patient groups. The only well performed larger randomized controlled trial (RCT) in 106 critically ill patients did not find differences in hospital or ICU mortality or in renal recovery between ‘early’ (12 h of oliguria or CrCl <20 mL/min) versus ‘late’ (classic indications) initiation of RRT [12]. Use of the Risk, Injury, Failure, Loss, End-stage kidney disease-classification as a marker poorly predicted the benefits of early or late RRT in patients with septic AKI [13]. A very recent systematic review of the literature described a large variation in the different parameters and cut-offs for initiation of RRT [14]. No single biochemical parameter was adequate to define the optimal indication and timing of RRT. The severity of illness and the degree and trend of fluid overload, oliguria and associated non-renal organ failure appeared to be more appropriate clinical parameters. The underlying disease and therefore the likelihood of recovery of kidney function are also important.

Benefits of RRT, like the control of metabolic and volume homeostasis, must be weighed on an individual basis versus the ‘traumatizing’ negative effects, like catheter-related complications, haemorrhage from anticoagulation and other RRT-related problems such as too pronounced removal of drugs hampering the adequacy of pharmaceutical treatment. The workgroup encourages development and testing of clinical algorithms based on regular assessment of different clinical and laboratory parameters is recommended in order to improve clinical decision-making when to start with RRT in the ICU-setting.

## VASCULAR ACCESS FOR RENAL REPLACEMENT THERAPY IN AKI

- (i) We suggest initiating RRT in patients with AKI via an uncuffed non-tunnelled dialysis catheter, rather than a tunnelled catheter. (2D)
- (ii) We suggest to use (in a descending order of preference) the right jugular vein, the femoral vein, the left jugular vein or the subclavian vein for insertion of a dialysis catheter in patients with AKI. (not graded)
- (iii) We suggest using ultrasound guidance for dialysis catheter insertion. (2A)
- (iv) We recommend obtaining a chest radiograph promptly after placement and before first use of an internal jugular or subclavian dialysis catheter. (ungraded statement)
- (v) We suggest not using topical antibiotics over the skin insertion site of a non-tunnelled dialysis catheter in ICU patients with AKI requiring RRT. (2C)
- (vi) We suggest not using antibiotic locks for prevention of catheter-related infections of non-tunnelled dialysis catheters in AKI requiring RRT. (2C)

While functional vascular access is a prerequisite for RRT, there is only limited data available regarding the optimal type, route of insertion and maintenance in acute patients. The corresponding guidelines are therefore mainly based on evidence derived from studies of dialysis catheters in chronic patients, or on studies evaluating non-dialysis central lines in acute patients.

The suggestion to initiate RRT in patients with AKI via a non-cuffed non-tunnelled dialysis catheter rather than a tunnelled catheter reflects current clinical practice in most ICUs, where a non-cuffed dialysis catheter is typically inserted by the intensivist, immediately before use. In contrast, the insertion of tunnelled catheters is often performed by surgeons or radiologists and usually requires considerably more time and effort. In keeping with the ERBP position for vascular access in chronic dialysis [15], a tunnelled catheter is preferable for patients in whom a prolonged (>1–3 weeks) use is anticipated. However, in a substantial number of patients with AKI this will not be the case.

It has to be kept in mind that the infection rate of central venous lines sharply increases after >1 week of use; while a programmed exchange of a central line after that time does not reduce catheter-related sepsis rates [16], intensivists will usually consider changing all central lines when new signs of

infection occur that are otherwise unexplained; this procedure is facilitated if non-cuffed non-tunnelled catheters are used.

The suggested preferences for the initial choice of the insertion site are potentially helpful to reduce complications such as infections, thrombosis/stenosis and malfunction. While the USA Center for Disease Control guidelines generally recommend avoiding a femoral access if possible [17], a large prospective study in 750 patients with AKI requiring RRT (the Cathedia Study) [18] found no difference between jugular and femoral dialysis catheter infection rates, except in patients with BMI >28.4. More recently, these findings were supported by a cross-over study in 134 patients from the Cathedia study who required a second catheterization [19]. However, the ERBP group advocates that the situation of each individual patient needs to be taken into consideration before a femoral access is chosen. Importantly, a patient who is anticipated to be mobilized, e.g. in order to facilitate weaning from mechanical ventilation, should preferably receive cervical vein catheterization.

It should also be taken into account that subclavian dialysis catheters are prone to generate central vein stenosis and may jeopardize quality and function of arterio-venous fistulae in patients who might later on become chronic dialysis patients.

Ultrasound guidance for dialysis catheter insertion and obtaining a chest radiograph promptly after placement and before first use of an internal jugular or subclavian dialysis catheter is in line with standard ICU practice and helps to reduce complications. However, the ERBP group wants to point out that the major factor to avoid complications is experience of the operator. As such, we accept that routine placement of uncomplicated cases by skilled and experienced operators without use of ultrasound guidance is not contraindicated.

The ERBP group supports the suggestion not to use topical antibiotics over the skin insertion site of a non-tunnelled dialysis catheter and antibiotic locks for prevention as these procedures have the potential to promote fungal infections and to cause resistance to antibiotics.

## DIALYZER MEMBRANES FOR RENAL REPLACEMENT THERAPY IN AKI

- (i) We recommend to use dialysers with a bio-compatible membrane for intermittent hemodialysis (IHD) and CRRT in patients with AKI. (1C)

Blood-membrane contact during extracorporeal dialysis leads to various biological responses such as complement activation, cytokine release and oxidative stress that may have clinical correlates in hypotension, vasodilatation, leucopenia, hypoxia and fever [20]. Despite a plethora of studies reporting on laboratory abnormalities following dialysis with 'bio-incompatible' membranes, clinical studies in patients with AKI comparing bio-compatible versus bio-incompatible membranes have so far failed to produce conclusive results [21]. In most parts of the world, and especially in Europe, membranes manufactured from unsubstituted cellulose are meanwhile being very

rarely used, or have even disappeared from the market. As a consequence, the 'original' bio-compatibility discussion has lost most of its clinical relevance in large parts of the world. Nevertheless, if for economic or other reasons, only unsubstituted cellulose membranes are available or preferable, it is better to dialyse patients with AKI, rather than not dialyse them because bio-compatible membranes cannot be obtained.

More current discussions relate to the question of preferring high-flux over low-flux membranes or of using specific membranes with larger pores for removal of middle-molecular-weight compounds such as cytokines or other mediators. However, given the lack of prospective clinical outcome studies in this area, it is at present not possible to make a well-founded recommendation or suggestion.

Importantly, as is pointed out in the KDIGO AKI guideline, clinicians must be aware that even with modern 'bio-compatible' dialysis membranes the potential for adverse reactions as a consequence of blood-membrane interaction remains present.

## MODALITY OF RENAL REPLACEMENT THERAPY FOR PATIENTS WITH AKI

- (i) We recommend to use continuous and intermittent RRT as complementary therapies in AKI patients. (1A). We suggest to use the RRT modality which is most advantageous for each individual patient in each specific clinical situation. (ungraded statement)
- (ii) We suggest using CRRT or extended low-efficient dialysis rather than high-efficient standard intermittent RRT, for haemodynamically unstable patients. (ungraded statement)
- (iii) In this patient group, we recommend to pay special attention to the connection procedure, to start with low blood and dialysate flows, and to consider using cooler dialysate temperatures. (ungraded statement)
- (iv) We suggest using CRRT, extended low-efficient dialysis or peritoneal dialysis, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain oedema. (2D)

Several studies have attempted to address the question as to whether the choice of RRT modality affects patient outcome. However, prospective studies comparing IHD with CRRT could not demonstrate an impact of RRT modality on all-cause mortality or recovery of renal function [22–24]. Also meta-analyses of these studies [25–27] found no overall difference between IHD and CRRT in hospital and ICU mortality, length of hospitalization and renal recovery in survivors. Given this, IHD and CRRT can be regarded as complementary therapies [28]. However, there might be advantages and disadvantages for either therapy. Continuous and/or more extended therapies are claimed to provide better haemodynamic stability, although there is little or no evidence to underpin this. The ERBP workgroup feels that haemodynamic stability can also be preserved in IHD, when correct attention is given to the connection procedure, using limited blood and dialysate flow rates, lowering dialysate temperature and prolonging the procedure. CRRT is also considered the therapy of choice in

patients with, or with risk for, brain oedema, although this is based on a limited number of poor quality studies. Major advantages of IHD are the very fast removal of small solutes and toxins and the restricted treatment period, allowing less anticoagulation and more down-time for diagnostic and therapeutic interventions. Therefore, the different modalities may not be completely interchangeable in individual patients and individual clinical situations across a heterogeneous ICU population. Treatment with RRT requires balancing the pros and cons of different RRT options and modalities depending on the specific clinical situation, and in fact, all ICUs performing RRT for AKI should have all modalities available. Newer hybrid therapies such as extended duration dialysis, sustained low-efficiency dialysis or the Genius® system, which are used increasingly in Europe, allow this type of flexibility and can be used in a wide range of settings from near continuous very low efficient to intermittent high efficient, and may therefore combine some of the advantages of IHD and CCRT while avoiding their disadvantages [29].

## DOSE OF RENAL REPLACEMENT THERAPY IN AKI

- (i) We do not recommend using Kt/V as a measure of dose of dialysis in AKI when using intermittent or extended RRT in AKI. (1A)
- (ii) The dose of CRRT to be delivered should be prescribed before starting each session of CRRT as mL/kg/h filtration rate, dialysis volume or a combination thereof. (not graded) We suggest regular assessment of the actually delivered dose. (1B)
- (iii) We recommend delivering an effluent volume of 20–25 mL/kg/h for post-dilution CRRT in AKI. (1A) This dose should be increased when pre-dilution is applied.
- (iv) We recommend to adapt the administration of medication in terms of dosing and timing, to the intensity of dialysis, taking into account pharmacokinetics and dialytic clearance of the drug.

To evaluate RRT efficiency, quantification of urea removal is used as a surrogate marker for other low-molecular-weight uraemic toxins in most studies. For intermittent therapies, KDIGO recommends that Kt/V urea be used. However, Kt/V urea is not a very reliable parameter, especially not in AKI patients, where neither urea generation rate nor 'V' can be defined. In AKI patients, there will be large variation in urea generation rates, due to patient-specific factors (age, sex and race), disease-specific factors (total body water, catabolic rate, muscle injury, sepsis and liver failure) and medical therapy (nutritional support and steroid treatment). Urea clearance is a marker for small solute clearance but not for larger 'middle' molecule and protein bound solute clearance which may also be an important aspect of RRT-dose in critically ill patients. Moreover, it is unclear in how far obtaining a certain value of Kt/V by changing 'K' versus the same value obtained after

changing 't' leads to comparable outcomes [30]. In addition, the recommended value is based on formulae only validated in patients with chronic renal failure, whose needs of renal replacement may be different from those in patients with acute illness and/or multiple organ failure. Next to solute clearance, there are many other important aspects of RRT prescription like electrolyte and acid-base homeostasis, possibility to provide nutritional support and, perhaps most important of all, fluid balance of the patient. The dose that meets the patient's needs will also depend on the severity of illness and the time course in the disease. Therefore, assessment of RRT efficiency solely on the basis of urea kinetics provides an incomplete assessment of the delivered therapy. Based on all these arguments, the ERBP workgroup does not recommend using Kt/V urea as a marker of adequacy in patients with AKI treated with IHD.

The ERBP group suggests to adapt the duration of IHD to allow maintenance of metabolic and volume status. For intermittent therapies, guidance can be drawn from the ATN study [23]. In this study, intermittent treatments of ~4 h with a blood flow of  $350 \pm 60$  mL/min and a dialysate flow of  $730 \pm 130$  mL/min were prescribed either on alternating days (less-intensive arm) or 6 days/week (more-intensive arm). Neither difference in mortality nor in recovery of renal function was observed.

For CRRT, usually the filtration rate (CVVH), dialysate volume (CVVD) or a combination thereof (CVVHD) (all in mL/kg/h) is used as a surrogate of urea clearance. RRT dose may be a determinant of outcome in critically ill patients with AKI. However, only two [31–34] out of seven [12, 23, 29, 35, 36] RCTs examining dose of RRT in ICU patients have shown an improved outcome with increased intensity of small solute clearance, whereas the five others did not. The two largest of these RCTs [23, 35], both showing no benefit for the highest intensity, can now provide guidance on the optimal dose of CRRT. Since no survival benefit could be demonstrated for effluent doses >25 mL/kg/h, an RRT dose of 20–25 mL/kg/h can be recommended. When pre-dilutional CVVH is used, the recommended dose should be increased. Several clinical investigations have shown that the actual delivered dose of RRT in AKI patients is frequently smaller than the prescribed dose [37] because of interruptions of RRT, use of pre-dilution in CRRT or reductions in membrane permeability during the treatment.

In view of the lack of proof of benefit, it should be avoided to aim for higher doses than 20–25 mL/min/kg, as increasing the dose of RRT will also increase losses of potentially important molecules from the circulation of the patient. For example, severe losses of phosphate with high-dose RRT have been described in the ATN [23] and RENAL [35] study as well as in another recent trial [38]. Finally, increasing the dose of RRT will have major and often inadvertent consequences on clearance rates of drugs [39, 40]. Many antimicrobial agents are cleared significantly by RRT, and subtherapeutic antimicrobial levels may adversely affect outcomes in critically ill patients, especially in those with septic AKI. In summary, increasing the dose of RRT has the potential to also increase the 'trauma' of RRT.

Thus, depending on the clinical situation of each patient, the assessment and prescription of the 'adequate' RRT dose



will need to be undertaken daily for CRRT and for each session in intermittent therapies, by weighing the benefits and risks of the actual delivered dose. In addition, more extended studies on drug dose adaptations with the more intensive dialysis regimens are encouraged. Now guidance, if available, is usually only provided for standard dialysis.

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## CONFLICT OF INTEREST STATEMENT

The declaration of interest for W.V.B., R.V. and J.T. can be found online at [www.european-renal-best-practice.org](http://www.european-renal-best-practice.org). A.J. received speaker fees from Fresenius Medical Care

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