Renal replacement therapy in critically ill patients with acute kidney injury—when to start

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Abstract

Background. Despite the frequent use of renal replacement therapy (RRT) for patients with acute kidney injury (AKI) in the intensive care unit (ICU), there is no accepted consensus on the optimal indications and timing.

Methods. The aim of this paper is to identify optimal triggers for RRT in critically ill patients with AKI.

Results. We examined data from 2 randomized controlled trials, 2 prospective studies and 13 retrospective trials and found large variation in the different parameters and cutoffs for initiation of RRT. No single biochemical parameter was adequate to define the optimal indication and time to commence RRT. Degree of fluid overload, oliguria and associated non-renal organ failure appeared to be more appropriate parameters for initiation of RRT. We propose a clinical algorithm based on regular assessment of the patient’s condition and trends in these parameters. It is intended to aid the process of deciding when to start RRT in critically ill adult patients with AKI.

Conclusion. Available evidence suggests that the decision when to start RRT in critically ill patients with AKI should be based on trends in the patient’s severity of illness, presence of oliguria and fluid overload and associated non-renal organ failure rather than specific serum creatinine or urea values.

Keywords: acute kidney injury; outcome; renal replacement therapy; renal support

Introduction

Renal replacement therapy (RRT) is a key component of modern critical care. Although RRT was established >20 years ago, clinical practice is variable [1, 2]. Several fundamental clinical aspects remain uncertain, including optimal indication and timing.

In the setting of chronic kidney disease, the European Best Practice Guidelines recommend starting chronic RRT when a patient with an estimated glomerular filtration rate (GFR) of <15 mL/min/1.73m² has symptoms or signs of uraemia, fluid overload or malnutrition in spite of medical therapy or before estimated GFR has fallen to <6 mL/min/1.73m² in an asymptomatic patient [3]. The situation is very different for patients with acute kidney injury (AKI) where RRT is generally viewed as a type of organ support aimed at achieving metabolic homeostasis and preventing fluid overload and new organ failure. These benefits of RRT must be balanced by potential harm, including risks related to central venous access, infections and anticoagulation [4].

There are several absolute indications where initiation of RRT is considered life saving, i.e. severe hyperkalaemia with cardiac compromise, life-threatening metabolic acidosis or uraemic pericarditis. However, these conditions are not commonly encountered [2]. Although RRT should be started before the onset of any serious complications of uraemia, the optimal indications and triggers remain unclear. Data from the Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy study which compared 2 different doses of continuous venovenous haemofiltration (CVVH) in critically ill intensive care unit (ICU) patients with AKI showed that 60% of patients had severe oedema when RRT was started, and 40–50% of patients had either a serum creatinine >300 µmol/L (>3.4 mg/dl) or serum urea >25 mmol/L (>70 mg/dl) [5]. Eight per cent of patients were hyperkalaemic (serum K⁺ >6.5 mmol/L) at the time of RRT.

Studies aimed at determining the optimal time for starting RRT have evaluated various arbitrary cut-offs for serum creatinine, serum urea or urine output, fluid balance, time from ICU admission or duration of AKI and often differentiated between ‘early’ and ‘late’ RRT [6–22] (Table 1). Three meta-analyses concluded that earlier institution of RRT in critically ill patients with AKI might be associated with a survival benefit [23–25]. However, the studies were heterogenous and of variable quality with a paucity of randomized controlled trials (RCTs). Potential benefits of earlier initiation are attributable to more rapid metabolic/uraemic control and more effective prevention and management of fluid overload [26]. Some data also suggest that RRT before the onset of severe AKI may attenuate kidney-specific and non-kidney organ injury from acidaemia, uraemia, fluid overload and systemic inflammation and
### Table 1. Parameters at the time of RRT and subsequent outcome\(^a\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Time period</th>
<th>RRT mode</th>
<th>Patient population</th>
<th>Parameters at the time of RRT</th>
<th>Outcome (early RRT versus late RRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagshaw et al. [8];</td>
<td>2000–01</td>
<td>CRRT; IHD</td>
<td>1238 mixed ICU</td>
<td>Serum creatinine ≤309 mmol/L;</td>
<td>Hospital mortality, 71 versus 53.4%;</td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td></td>
<td>patients</td>
<td>serum urea ≤24.2 mmol/L; AKI</td>
<td>P &lt; 0.00001; P = 0.48;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>as per RIFLE classification;</td>
<td>Hospital mortality, 43 versus 75%;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>no AKI or RIFLE Risk</td>
<td>P = 0.002</td>
</tr>
<tr>
<td>Shiao et al. [11];</td>
<td>2002–05</td>
<td>CVVH; IHD</td>
<td>98 patients post-</td>
<td>Serum creatinine &gt;309 mmol/L;</td>
<td></td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td></td>
<td>abdominal surgery</td>
<td>serum urea &gt;24.2 mmol/L; AKI</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>as per RIFLE classification:</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>RIFLE Injury or Failure</td>
<td></td>
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<tr>
<td>Chou et al. [22];</td>
<td>2002–09</td>
<td>CVVH; SLED;</td>
<td>370 patients with</td>
<td>Serum creatinine ≤309 mmol/L;</td>
<td></td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td>IHD</td>
<td>AKI and sepsis in</td>
<td>serum pH &lt;7.2</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>surgical ICU</td>
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</tr>
<tr>
<td>Ostermann et al. [13];</td>
<td>1989–99</td>
<td>CRRT; IHD</td>
<td>1847 mixed ICU</td>
<td>Serum creatinine &gt;309 mmol/L;</td>
<td></td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td></td>
<td>patients</td>
<td>serum pH &gt;7.2</td>
<td></td>
</tr>
<tr>
<td>Wu et al. [17];</td>
<td>2002–05</td>
<td>CRRT; IHD</td>
<td>80 patients with</td>
<td>Serum urea ≤28.6 mmol/L</td>
<td></td>
</tr>
<tr>
<td>prospective study</td>
<td></td>
<td></td>
<td>AKI and acute liver failure</td>
<td>Serum urea ≤28.6 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Liu et al. [9];</td>
<td>1999–2001</td>
<td>CRRT; IHD</td>
<td>243 mixed ICU</td>
<td>Serum urea ≤27.1 mmol/L</td>
<td></td>
</tr>
<tr>
<td>prospective study</td>
<td></td>
<td></td>
<td>patients</td>
<td>Serum urea ≥27.1 mmol/L</td>
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</tr>
<tr>
<td>Gettings et al. [10];</td>
<td>1989–97</td>
<td>CRRT</td>
<td>100 trauma patients</td>
<td>Serum urea ≤21.4 mmol/L</td>
<td></td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td></td>
<td></td>
<td>Serum urea ≥21.4 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Carl et al. [20];</td>
<td>2000–04</td>
<td>CRRT</td>
<td>147 patients with AKI and sepsis</td>
<td>Serum urea ≥35.7 mmol/L</td>
<td></td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td>IHD</td>
<td></td>
<td>Serum urea ≥40 mmol/L or K⁺ &gt;6.5 mmol/L or severe pulmonary oedema</td>
<td></td>
</tr>
<tr>
<td>Elahi et al. [12];</td>
<td>2002</td>
<td>CRRT</td>
<td>64 patients post-cardiac surgery</td>
<td>Urea ≥250 mmol/L or serum creatinine ≥250 mmol/L or K⁺ &gt;6 mmol/L</td>
<td></td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td>IHD</td>
<td></td>
<td>Serum urea ≥40 mmol/L or K⁺ &gt;6.5 mmol/L or severe pulmonary oedema</td>
<td></td>
</tr>
<tr>
<td>Bouman et al. [6];</td>
<td>1998–2000</td>
<td>CRRT</td>
<td>106 patients with AKI, circulatory and respiratory failure</td>
<td>Urine output ≤30 mL/h for 6 h and creatinine clearance ≤20 mL/min</td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td></td>
<td>IHD</td>
<td></td>
<td>Serum creatinine ≥40 µmol/L or K⁺ &gt;5.5 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Demirkilic et al. [16];</td>
<td>1992–2001</td>
<td>CRRT</td>
<td>61 patients with AKI post-cardiac surgery</td>
<td>Urine output &lt;100 mL within 8 h post-surgery</td>
<td>ICU mortality, 18 versus 48%, P = 0.014; hospital mortality, 23.5 versus 56%, P = 0.016;</td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td>IHD</td>
<td></td>
<td>Serum creatinine &gt;40 µmol/L or K⁺ &gt;5.5 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Iyem et al. [19];</td>
<td>2004–07</td>
<td>CVVH</td>
<td>185 patients with AKI post-cardiac surgery</td>
<td>Urine output &lt;0.5 mL/kg/h and a 50% increase in preoperative urea and creatinine</td>
<td></td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td>IHD</td>
<td></td>
<td>48 h after urine output &lt;0.5 mL/kg/h and 50% increase in urea and creatinine</td>
<td>ICU mortality, 25 versus 87%, P = 0.00001</td>
</tr>
<tr>
<td>Manche et al. [18];</td>
<td>1995–2006</td>
<td>IHD</td>
<td>71 patients with AKI post-cardiac surgery</td>
<td>Urine output &lt;0.5 mL/kg despite fluid challenge and single dose of diuretic</td>
<td>AKI which failed to respond to all supportive medical measures</td>
</tr>
<tr>
<td>retrospective study</td>
<td></td>
<td>IHD</td>
<td></td>
<td>Urine output ≤20 mL/h for 2 h</td>
<td></td>
</tr>
<tr>
<td>Sugahara et al. [7];</td>
<td>2001–02</td>
<td>CRRT</td>
<td>28 patients post-cardiac surgery</td>
<td>Urine output ≤20 mL/h for 3 h</td>
<td>ICU mortality, 14 versus 86%, P &lt; 0.01</td>
</tr>
</tbody>
</table>
Results

In the ICU. Studies that had only been published in abstract format were contained data on timing of RRT in critically ill adult patients with AKI cohort studies between 1985 and early 2011. We included papers that defined timing of RRT but the exact cut-offs were variable between studies.

The only two RCTs were performed by Bouman et al. and Sugahara et al. [6, 7]. Bouman et al. [6] randomized 106 predominantly cardiac surgical patients who were oliguric despite fluid resuscitation, inotropic support and high-dose diuretic therapy to three groups: early high-volume CVVH (n = 35), early low-volume CVVH (n = 35) and late low-volume CVVH (n = 36). The differentiation between early and late RRT was based on urine output, serum urea, creatinine clearance, hyperkalaemia and presence of pulmonary oedema. There were no significant differences in 28-day mortality or duration of AKI between the groups. At the time of hospital discharge, all hospital survivors had recovered renal function except for one patient in the early low-volume CVVH group. Interestingly, in the late CVVH arm, four patients recovered renal function spontaneously and two patients died before the criteria for CVVH were met. The authors concluded that there was no significant benefit with either early CVVH or high filtration rates for patients with oliguric AKI.

The only other RCT was performed by Sugahara et al. [7] who evaluated the role of early RRT in 28 patients with AKI post-cardiac surgery. Fourteen patients were started on continuous haemodialysis when their urine volume decreased to <30 mL/h for 3 h. In patients in the ‘late’ arm (n = 14), RRT was delayed until urine output had fallen to <20 mL/h for 2 h. Survival was significantly better in the group of patients who started RRT earlier. There were no differences between the two groups with respect to age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II score and serum creatinine level at the time of initiation of RRT. The authors concluded that RRT for patients with AKI post-cardiac surgery should be triggered by a falling urine output instead of the actual serum creatinine results.

Serum creatinine

Five studies contained data on the role of serum creatinine as a trigger for RRT [8, 11, 13, 16, 21] (Table 1). The results are conflicting. Shiao et al. [11] retrospectively analysed the data of 98 patients with AKI post-abdominal surgery and showed that patients who were started on CVVH at RIFLE stage Risk (i.e. after rise in serum creatinine by 150–200%) had a significantly lower hospital...
mortality than patients who started RRT with either RIFLE Injury or RIFLE Failure (i.e. after serum creatinine rise by >200%). In contrast, Chou et al. [21] showed no difference in hospital mortality in 370 AKI patients between the group who started RRT with RIFLE—Risk or even before they fulfilled the RIFLE criteria and patients in whom AKI had progressed to RIFLE—Injury or RIFLE—Failure when RRT was started. Two larger retrospective analyses concluded that mortality was significantly higher in patients who had a serum creatinine <310 μmol/L when RRT was started compared to those with higher creatinine values [8, 13]. Finally, as mentioned earlier, Sugahara et al. [7] showed that a low urine output was a better parameter than the actual serum creatinine levels.

Serum urea

Different levels of serum urea were used as triggers for RRT in eight studies [6, 8–10, 12, 13, 17, 20]. Liu et al. [9] reported a significantly lower mortality in 122 patients who had a serum urea ≤27 mmol/L (<76 mg/dL) at the time of initiation of RRT compared to patients with a higher value. When adjusted for age, hepatic failure, sepsis, thrombocytopenia and serum creatinine, the relative risk of death with a higher urea level at the time of RRT was 1.85 [95% confidence interval (CI) 1.16–2.96]. Improved mortality was also reported in retrospective studies when RRT was instituted at a serum urea <21 mmol/L [10], <29 mmol/L [17] or <35.7 mmol/L [20], suggesting that RRT at lower serum urea levels is better than late RRT. In contrast, two larger studies did not find a correlation between serum urea at the time of RRT and outcome [8, 13].

Urine output

Data on the role of specific urine volumes as triggers for RRT were included in eight studies [6, 7, 12, 13, 16, 18, 19, 22] often combined with serum urea or creatinine criteria. The majority of studies showed better outcomes when oliguria was used as the trigger for RRT instead of serum creatinine or urea values [12, 16, 18, 19, 22]. However, the definitions for oliguria varied from urine output <100 mL/h in 8 h [12, 16] to <400 mL/24 h [13] and <30 mL/h for 6 h [6]. It can therefore be concluded that RRT for AKI should be considered when urine output declines to <500–600 mL/24 h.

Fluid accumulation

There is increasing evidence that fluid overload in patients with AKI is associated with poor outcome [14, 30]. Bouchard et al. [30] showed that ICU mortality was significantly higher in patients whose body weight on the first day of RRT was 1–20% above that on ICU admission compared to patients without weight gain during this period. There was a direct correlation between the degree of fluid gain and ICU mortality. Similar results were reported by Payen et al. [14] who performed a subgroup analysis of the multicentre ‘Sepsis Occurrence in Acutely Ill Patients (SOAP) study’. Two hundred and thirteen patients were treated with RRT within 2 days of ICU admission compared to 65 patients who had RRT after 2 days in ICU. Although patients in the early RRT group had higher severity of illness scores, their ICU and 60-day mortality was lower. A potential explanation for this difference was the higher cumulative fluid balance and greater need for mechanical ventilation in the late RRT group. Consequently, it may be appropriate to consider starting RRT in patients with AKI prior to fluid accumulation of ≥10% of body weight [31].

Non-renal factors

A large retrospective analysis of 1847 ICU patients treated with RRT for AKI highlighted that the most important independent risk factors for ICU mortality were need for mechanical ventilation, associated organ failure, pre-existing chronic health problems, acidosis, oliguria and age [13]. Patients who were oliguric (urine output <400 mL/24 h) and acidic with serum pH <7.2 at the time of RRT had an ICU mortality of 79.1%. Serum urea and creatinine were not found to be independently associated with outcome. The results of this study suggest that the decision to start RRT should depend less on specific serum creatinine or urea values but more on degree of acidosis, urine output and associated organ failure.

Whether the presence of pre-existing chronic medical problems should be incorporated into the decision-making process is not clear. To date, no study has evaluated clearly whether there is any benefit in starting RRT earlier in patients with AKI and limited physiological reserve, i.e. patients with chronic heart or respiratory failure who may not tolerate fluid overload well.

Role of new biomarkers

The recent discovery and development of new biomarkers for AKI have raised hope that they may serve as triggers for RRT. A meta-analysis including 1948 patients from nine studies confirmed that urinary or plasma neutrophil gelatinase-associated lipocalin (NGAL) indeed predicted need for RRT [32]. The pooled analysis yielded an area under the receiver operator characteristic curve (AUC) of 0.782 (95% CI 0.648–0.971). Despite this positive result, the role of NGAL as a trigger for RRT has not been formally evaluated. Serum cystatin C, a 13-kDa non-glycosylated cysteine protease inhibitor produced by all nucleated cells, is another biomarker which has been shown to predict AKI. However, its superiority over serum creatinine has not been a universal finding [33]. In a study in 442 adult ICU patients, plasma cystatin C results on admission to ICU were moderately predictive of mortality or RRT with an AUC 0.61 and performed similarly as serum creatinine [34]. In a different study in 200 patients with AKI, serum cystatin C was inferior to a basic prediction model using APACHE II score, liver disease, sepsis and mechanical ventilation in predicting the need for RRT [35]. Currently available data are not sufficient to conclude that NGAL, serum cystatin C or any other new AKI biomarkers should be used routinely for deciding when to initiate RRT [33].

Algorithm for initiation of RRT

Based on the results in the literature, we propose a clinical algorithm to aid in the decision when to consider initiation
of RRT in critically ill patients with AKI. It emphasizes the importance of regular assessments of the patient’s condition and general trends instead of absolute serum biochemical values or stages of AKI, including RIFLE or AKIN categories (Figure 1). The main message is that the criteria for RRT should be individualized based on the existing dynamic conditions rather than absolute values. The aim should be to utilize RRT to support organ function and prevent complications. It is also important to acknowledge that there may be patients with a futile prognosis in whom RRT would not be appropriate and where withholding RRT constitutes good end-of-life care [37]. This algorithm does not address aspects of management of RRT, including modality and dose, and also does not refer to non-renal indications, including extracorporeal blood purification to facilitate drug or toxin removal.

**Discussion**

AKI in critically ill patients manifests itself with varying degrees of uraemia, fluid accumulation, acid–base disturbance, physiologic derangement and non-renal dysfunction and often has as variable course. The question when to start RRT remains difficult to answer and practice is variable [2]. At present, there is little data to accurately distinguish in advance between the injured kidney that will need extracorporeal support and one that retains capacity for spontaneous recovery. Studies in the literature confirm that serum creatinine, serum urea and urine output were the most commonly used parameters to trigger RRT with varying cut-off values. However, their value is limited due to the fact that they are not renal specific. Serum creatinine levels depend on renal function but also on non-renal factors like age, muscle bulk and volume of distribution [38]. In the early phase of AKI, significant decreases in GFR can occur without any major changes in serum creatinine [39]. Furthermore, serum creatinine values may also be affected by the laboratory technologies used for measurement [40].

Urea is formed by the hepatic metabolism of amino acids and excreted primarily by glomerular filtration. Serum concentrations may vary as a result of changes in urea production and tubular urea reabsorption without changes in GFR. Both increased amino acid metabolism (i.e. in the context of a gastrointestinal bleed, enhanced tissue breakdown or high-protein diet) and increased tubular reabsorption during hypovolaemic states can lead to increased serum urea levels without changes in renal function.

The described literature shows that individual stages of AKI are not adequate in identifying the optimal time for RRT either. The RIFLE and AKIN classifications are scoring systems which were developed to grade prognosis of AKI [36, 41]. Although they correlate with mortality at the cohort level, they were never intended to predict the need for RRT. Furthermore, the same RIFLE stage encompasses a 2- to 3-fold creatinine change from baseline and potentially classifies patients with substantially different renal functions in the same stage. In a prospective observational study including data of 234 patients from six ICUs in Canada, Bagshaw et al. [2] showed no difference in mortality when timing of RRT was stratified by RIFLE class at the time of initiation of RRT. Hospital mortality of patients who started RRT at RIFLE—Risk, Injury and Failure was 83, 52.1 and 50.8%, respectively, \( P = 0.31 \).

The usefulness of urine criteria for the definition of AKI has been debated widely [42–45]. Proponents argue that urine output often portends renal dysfunction in critical care patients before changes in serum creatinine. In contrast, critics argue that urine output is affected by volume status, intrinsic levels of anti-diuretic hormone, presence of obstruction and use of diuretics. Also, urine output criteria can only be accurately assessed in patients with a urinary catheter. Despite this, there is increasing evidence that a urine output of <500 to 600 mL/24 h should be viewed as an ominous sign and trigger an evaluation of the indications for RRT. Furthermore, oliguria is closely correlated with fluid accumulation. Recent data suggest that fluid overload of >10% of body weight is an independent risk factor for mortality in AKI [30]. Consequently, it may be appropriate to consider starting RRT prior to fluid accumulation reaching a threshold of 10% of body weight.

Based on data in the literature, the decision to start RRT should be based on the general severity of illness, presence of oliguria and fluid overload, the number and types of failed non-renal organs, the risk of further organ failure and whether the patient is recovering or deteriorating [46] (http://www.renal.org/clinical/GuidelinesSection/Acute-KidneyInjury.aspx). Patients with AKI vary widely in their clinical course even if the underlying severity of the renal injury may be the same. In patients with AKI and severe multi-organ dysfunction, RRT may be of benefit when started early to maintain metabolic and volume homeostasis and to prevent further deterioration. Similarly, patients with severe fluid overload and inadequate.

**Fig. 1.** Algorithm to guide decision when to start RRT. MAP, mean arterial blood pressure. *Diagnosis of AKI based on the AKIN classification [36].
response to diuretics may benefit from early RRT and fluid removal independent of serum creatinine results. In contrast, in patients with a raised serum creatinine but no sign of fluid overload or any significant non-renal organ dysfunction, RRT may be delayed without any risk of harm.

Whatever criteria are used to define ‘early’ versus ‘late’ RRT, it is apparent that what may be ‘early’ for one patient could be ‘late’ for another patient depending on the patient’s comorbidity and clinical course [31]. Since the course of patients with AKI can be very variable with periods of improvement and setbacks, it is essential for patients to be assessed on a regular basis to ensure that RRT is started at the ‘right’ time, i.e. before the onset of uremic and metabolic complications but probably not when there are signs of general improvement and spontaneous renal recovery. We suggest that it is not necessary to formally classify the patient’s stage of AKI as per RIFLE or AKIN criteria.

New biomarkers for AKI have been shown to correlate with severity of AKI and need for RRT [32–35]. Despite the hope that they may be used in the decision-making process when to start RRT, the necessary intervention studies have not been performed. Currently available data are insufficient to conclude that timing of RRT should be based on these new biomarkers but results of future clinical trials are awaited.

Our conclusions and algorithm are based on existing data from the literature. Although we acknowledge that the algorithm is open to interpretation, we would like to emphasize the importance of frequent evaluation of the dynamic situation. Negative trends in haemodynamic status, respiratory condition, acid–base parameters and overall clinical condition in patients with AKI should trigger an evaluation whether RRT is indicated, independent of the exact creatinine or urea values. Although the algorithm is supported by data in the literature, the majority of studies on timing and indications for RRT are retrospective analyses and therefore open to the criticism that improved outcomes with RRT at an earlier or later stage may simply reflect differences in overall management. Secondly, it is also important to acknowledge that our review and the existing studies in the literature have focussed on mortality as an outcome. Clearly, there are other relevant outcomes like complications of therapy, quality of life and return of daily activities, all of which are not included in the studies covered in our review. Thirdly, the interpretation of non-randomized studies is always limited by the exclusion of patients with AKI who met criteria for early initiation of RRT but did not receive it. Finally, the results of some studies are confounded by differences in patient populations and modality and dose of RRT.

Conflict of interest statement. None declared.

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