



Miet Schetz
Lui G. Forni
Michael Joannidis

Does this patient with AKI need RRT?

Received: 13 November 2015
Accepted: 9 December 2015
Published online: 21 December 2015
© Springer-Verlag Berlin Heidelberg and ESICM 2015

M. Schetz (✉)
Clinical department and Laboratory of Intensive Care Medicine,
Division of Cellular and Molecular Medicine, KU Leuven
University, Herestraat 49, 3000 Leuven, Belgium
e-mail: marie.schetz@uzleuven.be

L. G. Forni
Department of Intensive Care Medicine, Royal Surrey County
Hospital NHS Foundation Trust, Egerton Road, Guildford, Surrey
GU2 7XX, UK

L. G. Forni
Surrey Perioperative Anaesthesia Critical Care Collaborative
Research Group (SPACeR) and Faculty of Health Care Sciences,
University of Surrey, Guildford, UK

M. Joannidis
Division of Intensive Care and Emergency Medicine, Department
of Internal Medicine, Medical University of Innsbruck,
Anichstrasse 35, 6020 Innsbruck, Austria

A 65-year-old patient is admitted to the ICU 5 days after right upper lobectomy with oliguria (urine output over the past 24 h 0.17 mL/kg/h = AKI stage 3) and relative hypotension. Serum creatinine has increased from a baseline of 1.36 mg/dL (eGFR 53) to 3.78 mg/dL (AKI stage 2). He has an ileus with vomiting. Antibiotics were commenced 24 h earlier because of rising CRP. Postoperative medications included ACE inhibition and NSAIDs. Following ICU admission further fluid resuscitation is commenced as is norepinephrine (0.15 mg/kg/min) and the antibiotic spectrum is broadened empirically as the CRP has increased further (505 mg/L). Next morning his creatinine has increased to 4.53 mg/dL (AKI

stage 3), urine output has decreased to 0.1 mL/kg/h over the past 12 h resulting in a positive fluid balance of 3300 mL. Arterial blood gas analysis reveals a pH of 7.39. PaO₂ is 87 mmHg, bicarbonate 25 meq/L, K⁺ 3.9 meq/L and urea 128 mg/dL. He is breathing spontaneously on 2L O₂ with a respiratory rate of 20 breaths/min and chest X-ray shows bilateral basal infiltrates and a limited hydropneumothorax on the lobectomy side.

Does this patient need renal replacement therapy (RRT)? Which factors may guide this decision?

1. Does this patient have an absolute indication for commencing RRT immediately? Generally accepted classical indications for urgent RRT include potentially fatal changes in fluid, electrolyte and acid–base balance and severe azotaemia with complications (uraemic encephalopathy, pericarditis etc.) [1] but agreement on the thresholds for treatment is lacking [2]. None of these indications appear to apply to our patient.
2. Should we wait until the development of classical indications or will commencing RRT earlier improve our patient outcome? Over the past 15 years three small (underpowered) randomized trials [3–5] have addressed this question. No mortality difference was observed but RRT was avoided in 17–37 % of the late starters. Moreover, in the most recent trial, protocol-driven classical indications were achieved in only one-third of the patients in the “late” group; in the other two-thirds perceived fluid overload and/or oligoanuria was the main indication for RRT [5]. Observational trials with high risk of residual confounders show conflicting results with one study demonstrating improvement only when RRT is commenced when classical indications are present [6], whereas others observe a higher mortality in patients exhibiting the classical indications on starting RRT, especially when RRT is delayed [7, 8]. Several observational studies

- used retrospective definitions of early and late (based on urea, creatinine, time in ICU, AKI stage, time since AKI stage 3 or degree of fluid overload) which do not inform as to the reason for starting RRT. Mostly a beneficial effect of early start is demonstrated [9]. However, there is a high risk of bias in these studies as none included a control group without RRT and many patients (especially those in the early group) may have received unnecessary RRT. A few recent trials did include a control group without RRT and showed that, even after propensity score matching, the use of RRT increased mortality, especially in less severe forms of AKI [10, 11]. It is evident that this study design also has a high risk of residual confounding. Vaara et al. showed lower mortality with pre-emptive RRT in propensity-matched analysis but a considerable proportion of patients could not be matched [8].
3. Is sepsis an indication to start RRT earlier? Given that RRT is theoretically capable of clearing inflammatory mediators, several authors consider the presence of sepsis as an indication for early RRT. However, this is not substantiated by clinical data. A randomized trial comparing early continuous venovenous haemofiltration (CVVH) versus standard medical treatment in severe sepsis did actually describe a worse outcome in the CVVH group with increased number and severity of organ failures [12].
 4. Does RRT help the holistic management of our patients (concept of organ support therapy)? Or does withholding RRT impede us in providing adequate therapy e.g. parenteral nutrition, drugs/antibiotics given potential problems with volume overload complicating AKI? In clinical practice diuretic-resistant oliguria with (established or presumed poorly tolerated) fluid overload and/or large obligatory fluid input is a frequent indication for RRT [2]. Whereas the association between fluid overload and outcome is undoubted, the causative link between both remains to be established. Indeed, a prospective trial on prevention or reversal of fluid overload with early RRT does not exist and it remains even doubtful whether fluid mobilization in the early phase of critical illness is at all feasible. However, in certain subgroups of patients manipulation of fluid balance to prevent fluid overload appears beneficial (stable ARDS, congestive heart failure) [13]. Besides an assessment of the reversibility of kidney dysfunction, the tolerance to fluid overload (mainly cardiac and respiratory acute illness and comorbidity) may therefore become an important factor in the decision to start RRT.
 5. It is evident that RRT should not be started if the probability of spontaneous recovery is high. Unfortunately our ability to predict need for RRT in the early stages of AKI is poor although response to loop diuretics may perform better than biomarkers [14]. In clinical practice trends in kidney function and non-renal factors such as severity and potential for short-term reversibility of the underlying disease (e.g. nephrotoxic drugs, low cardiac output due to hypovolaemia versus cardiac failure or septic shock) can be very helpful.
 6. In the absence of hard data the decision whether or not to start RRT should weigh the harm of unnecessary treatment against the harm of late treatment in the patients that will need RRT. "First do not harm". The demonstration that AKI is an independent predictor of mortality has fostered the paradigm that earlier initiation of RRT might influence outcome. AKI indeed has many systemic consequences [15]. However, our current RRT modalities can only correct some of them, i.e. electrolyte and acid base disturbance, fluid overload and uraemia. In addition, doubling the RRT dose has not been shown to improve outcome and unnecessary RRT is not without harm. RRT (especially intermittent haemodialysis) may cause hypotension that in turn may delay recovery

Table 1 Absolute and relative indications for commencing or not commencing RRT

Reasons to start	Reasons not to start
Absolute	
Severe hyperkalemia	Futile therapy
Severe acidosis	
Organ dysfunction due to diuretic-resistant fluid overload	
Uraemic complications (pericarditis, encephalopathy etc.)	
Life-threatening intoxications with substances which can be dialysed (low protein binding (<50 %), low volume of distribution and low molecular weight)	
Relative	
Diuretic-resistant fluid overload	Oliguria without clinically important fluid overload
Limited tolerance to fluid overload	Sufficient cardiocirculatory and respiratory reserve to tolerate fluid overload
Rapidly worsening kidney function	Slow deterioration in kidney function
Underlying disease not rapidly reversible	Potential for short-term reversibility of the underlying disease
Reduced risk of harm from RRT	Potential harm of RRT (may include unavailability of CRRT)
Furosemide stress test with UO 2 h < 200 mL	Furosemide stress test with UO 2 h > 200 mL

[16]. RRT can result in loss of essential substances (nutrients, drugs etc.), electrolyte imbalance with potential for arrhythmias, anticoagulation-related bleeding, disequilibrium syndrome, infectious or mechanical complications of the dialysis catheter, bio-incompatibility issues, hypothermia, errors in fluid balance and last but not least costs [17].

7. It is evident that RRT should not be started when further treatment is considered futile [1].

Premorbidly, our patient was fit and well. Thus starting RRT is appropriate especially as the surgery was potentially curative. He did not present with classical indications and, although oliguric, had normal oxygenation. He has been treated until recently with drugs that potentially impair renal function (NSAIDs, ACEI) and his AKI may be at least partially fluid-responsive (history of ileus and vomiting). RRT was not started. His creatinine further increased to 5.2 on the next day but thereafter decreased steadily.

In conclusion, hard evidence to guide the optimal timing to start RRT in patients with AKI is lacking, resulting in a wide variation in clinical practice. The decision to start RRT should be individualized, taking into account not only the severity of AKI and the trend in kidney function but also the severity and reversibility of the underlying disease, the risk/tolerance of fluid overload and, importantly, the potential harm associated with unnecessary RRT (Table 1). We can only hope that the two ongoing RCTs (NCT01682590, NCT01932190), with results expected in 2016, will provide more answers to this clinical dilemma.

Compliance with ethical standards

Conflicts of interest Dr. Forni has received honorarium/travel expenses from Fresenius, Astute Medical, Ortho Clinical Diagnostics and Baxter/Gambro/Renal. Dr. Joannidis has received honoraria from Baxter/Renal. There are no other conflicts of interest to report.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury (2012) *Kidney Intern* 2:1–138
2. Joannidis M, Forni LG (2011) Clinical review: timing of renal replacement therapy. *Crit Care* 15:223
3. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J (2002) Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med* 30:2205–2211
4. Jamale TE, Hase NK, Kulkarni M, Pradeep KJ, Keskar V, Jawale S, Mahajan D (2013) Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. *Am J Kidney Dis* 62:1116–1121
5. Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A, Thorpe K, McIntyre L, Lamontagne F, Soth M, Herridge M, Lapinsky S, Clark E, Garg AX, Hiremath S, Klein D, Mazer CD, Richardson RM, Wilcox ME, Friedrich JO, Burns KE, Bagshaw SM (2015) Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int* 88(4):897–904. doi: [10.1038/ki.2015.184](https://doi.org/10.1038/ki.2015.184)
6. Libório AB, Leite TT, Neves FM, Teles F, Bezerra CT (2015) AKI complications in critically ill patients: association with mortality rates and RRT. *Clin J Am Soc Nephrol* 10:21–28
7. Lim CC, Tan CS, Kaushik M, Tan HK (2015) Initiating acute dialysis at earlier Acute Kidney Injury Network stage in critically ill patients without traditional indications does not improve outcome: a prospective cohort study. *Nephrology (Carlton)* 20:148–154
8. Vaara ST, Reinikainen M, Wald R, Bagshaw SM, Pettilä V, FINNAKI Study Group (2014) Timing of RRT based on the presence of conventional indications. *Clin J Am Soc Nephrol* 9:1577–1585
9. Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, Bagshaw SM (2011) A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit Care* 15:R72
10. Wilson FP, Yang W, Machado CA, Mariani LH, Borovskiy Y, Berns JS, Feldman HI (2014) Dialysis versus non-dialysis in patients with AKI: a propensity-matched cohort study. *Clin J Am Soc Nephrol* 9:673–681
11. Clec'h C, Darmon M, Lautrette A, Chemouni F, Azoulay E, Schwebel C, Dumenil AS, Garrouste-Orgeas M, Goldgran-Toledano D, Cohen Y, Timsit JF (2012) Efficacy of renal replacement therapy in critically ill patients: a propensity analysis. *Crit Care* 16:R236
12. Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C, Vicaut E, Hemofiltration and Sepsis Group of the Collège National de Réanimation et de Médecine d'Urgence des Hôpitaux extra-Universitaires (2009) Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. *Crit Care Med* 37:803–810
13. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network1, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL (2006) Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 354:2564–2575
14. Koyner JL, Davison DL, Brasha-Mitchell E, Chalikhonda DM, Arthur JM, Shaw AD, Tumlin JA, Trevino SA, Bennett MR, Kimmel PL, Seneff MG, Chawla LS (2015) Furosemide stress test and biomarkers for the prediction of AKI severity. *J Am Soc Nephrol* 26:2023–2031

15. Druml W (2014) Systemic consequences of acute kidney injury. *Curr Opin Crit Care* 20:613–619
16. Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, Cass A, Gallagher M (2013) Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med* 39:987–997
17. Clark EG, Bagshaw SM (2015) Unnecessary renal replacement therapy for acute kidney injury is harmful for renal recovery. *Semin Dial* 28:6–11