Timing of renal replacement therapy in critically ill patients with acute kidney injury

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Purpose of review

Timing of renal replacement therapy in critically ill patients with acute kidney injury is highly subjective, and may influence outcome. We discuss renal and nonrenal criteria for timing considering the recent literature.

Recent findings

Two randomized and four nonrandomized controlled trials investigated the effects of timing on patient outcome. All but one randomized controlled trial indicated better outcome with early renal replacement therapy but had poor methodological quality. The heterogeneity of timing definition, study population and mode of therapy, however, hampered comparison among studies.

Summary

In the absence of large randomized controlled trials we can make no firm recommendations for timing of renal replacement therapy in acute kidney injury. Since rapid recovery of renal function is unlikely when other organ failure persists and the consequences of acute kidney injury may be more severe in critically ill patients, we suggest other organ failure is also considered. Patients with acute kidney injury, persisting shock and poorly recovering functions of other organs may benefit from early therapy. For future studies, we recommend describing renal replacement therapy timing according to the 'RIFLE' classification, as modified by the Acute Kidney Injury Network, and quantifying the severity of other organ failure. Biomarkers may refine acute kidney injury and timing definitions in the future.

Keywords

acute kidney injury, acute renal failure, biomarkers, multiple organ failure, renal replacement therapy, timing

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Abbreviations

AKI	acute kidney injury
AKIN	Acute Kidney Injury Network
ARF	acute renal failure
BUN	blood urea nitrogen
CVVH	continuous venovenous hemofiltration
CVVHDF	continuous venovenous hemodiafiltration
RCT	randomized controlled trial
RIFLE	risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease
RRT	renal replacement therapy

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Introduction

Acute kidney injury (AKI) is a common complication of critical illness and carries a high mortality, particularly if renal replacement therapy (RRT) is required [1]. A recent worldwide survey showed that 4% of patients admitted to the ICU receive RRT [1]. The incidence varies with the type of admitted patients. The observed mortality is often higher than the predicted mortality based on commonly used scores, if AKI is severe and acute renal failure (ARF) ensues [2]. It has long been postulated that patients die with ARF and not from ARF. In critically ill patients, ARF certainly is an indicator of the severity of disease. ARF rarely presents as an isolated organ dysfunction, but rather as a component of the multiple organ dysfunction syndrome, following a broad spectrum of diseases or interventions, such as severe sepsis, cardiogenic shock, major surgery or pancreatitis. Increasing evidence, however, suggests an independent effect of critical illness associated ARF on mortality [2–5]. Most likely, both the acute uremic state and the unwanted consequences of the RRT contribute to this excess mortality.

Unfortunately, there is still no consensus on the optimal management of ARF. This is even more strongly the case for the application of RRT [6•,7••]. During the last decade both mode and dosing of RRT in the critically ill patient have received increasing interest, reflected by several randomized controlled trials (RCTs) and meta-analyses [8–22]. These trials suggest that a dose of at least 35 ml/kg/h improves survival and that continuous treatments are not superior to intermittent treatments, except in patients with circulatory shock or cerebral edema. In contrast, so far only one RCT investigated whether timing of initiation of RRT ('timing') improves outcome in critically ill patients with AKI [8]. The results

were inconclusive. The aims of the present contribution are to discuss renal and nonrenal criteria for timing in critically ill patients with AKI, considering the recent literature, and to discuss the emerging need of a consensus definition of AKI.

Classical criteria for timing

Classical criteria to start RRT include oligo-anuria, metabolic complications of the uremic state, fluid overload and uremic organ injury [23]. These criteria, however, are based on the strongly held beliefs of physicians and not on evidence from RCTs. In the absence of consensus, the Acute Dialysis Quality Initiative (ADQI) could not formulate recommendations for timing beyond these classical criteria [24]. In daily clinical practice, logistical or organizational aspects of a given institution (e.g. country, type of institution, type and organization of the unit, responsible specialty and costs) additionally influence timing. Prospective, multicenter studies on the epidemiology, management, and outcome of severe ARF reported up to two-fold differences in the reported values of urea, creatinine, or urine output at the initiation of RRT [6•,25–27].

Clinical studies on timing and patient outcome

During the last decade, one RCT on ARF, one on acute pancreatitis [8,28] and four non-RCTs on ARF [29–32] primarily investigated the effect of timing (early versus late) of RRT on mortality and recovery of renal function in critically ill patients (Table 1) [33].

(1) In a two-center randomized controlled trial ($n = 106$) including critically ill ventilated patients with vasopressor-dependent circulation and oliguric ARF (creatinine clearance less than 20 ml/min and diuresis less than 180 ml in 6 h, despite fluid resuscitation, inotropic support and high-dose diuretics) [8], 28-day survival and recovery of renal function were not increased when continuous venovenous hemofiltration (CVVH) was started early (within 12 h after the onset of oliguria) compared with late (urea > 40 mmol/l, or severe pulmonary edema with $PO_2/FiO_2 < 150$ mmHg despite a positive end expiratory pressure of 10 cmH_2O). Of note, in this study, late was not as late as in earlier studies. For pulmonary reasons, nearly half of the patients in the late group started CVVH before serum urea reached 40 mmol/l. Median delays between the development of oliguria and the start of treatment were 42 h in the late group and 7 h in the early group. Moreover, early was not very early because measured creatinine clearance had to be below 20 ml/min before inclusion.

(2) In a small randomized controlled trial ($n = 37$) in patients with severe pancreatitis without documented ARF [28], early CVVH (within 48 h after the onset of abdominal pain) improved hemodynamics and 14-day survival compared with late CVVH (96 h after onset of abdominal pain).

(3) A single-center, retrospective, nonrandomized cohort study ($n = 100$) in trauma patients [31] used blood urea nitrogen (BUN) as a surrogate for 'timing of

Table 1 Clinical studies on timing of initiation of renal replacement therapy (RRT) in acute kidney injury (AKI) and patient outcome

	Study design	Clinical setting	Definition of timing	Confounding CRRT factors	Survival advantage early group
Bouman [8]	RCT ($n = 105$)	Oliguric ARF and MOF	Early: creatinine clearance < 20 ml/min and < 12 h after onset of oliguria (< 180 ml in 6 h) Late: urea ≥ 40 mmol/l or severe pulmonary edema[a] after onset of oliguria	No	No
Jiang [28]	RCT ($n = 37$)	Severe pancreatitis renal function is not reported	Early: < 48 h after onset of abdominal pain Late: > 96 h after onset of abdominal pain	No	Yes
Gettings [31]	Retrospective ($n = 100$)	Post trauma	Early: urea < 60 mg/dl[b] Late: urea ≥ 60 mg/dl	Various CRRT modes Dose not reported	Yes
Piccini [32]	Retrospective ($n = 80$)	Sepsis with oliguric ARF and ALI	Early: < 12 h after ICU admission Late: urea > 35 mmol/l or creatinine > 600 μmol/l	Dose early $>>$ dose late	Yes
Elahi [30]	Retrospective ($n = 64$)	Post cardiac surgery	Early: oliguria < 100 ml in 8 h Late: urea > 30 mmol/l or sCr > 250 μmol/l	Dose not reported	Yes
Demirkilic [29]	Retrospective ($n = 61$)	Post cardiac surgery	Early: oliguria < 100 ml in 8 h Late: sCr > 5 mg/dl[c]	Dose not reported	Yes

CRRT, continuous renal replacement therapy; ARF, acute renal failure; MOF, multiple orgain failure; ALI, acute lung injury; sCr, serum creatinine. Adapted with permission from Bouman and Oudemans-van Straaten [33].

[a] $pO_2/FiO_2 < 150$ mmHg and positive end expiratory pressure (PEEP) = 10 cmH_2O.

[b] 21 mmol/l.

[c] 420 μmol/l.

intervention'. Survival was 39% in the early group [RRT started at a mean BUN of 42.6 mg/dl (15 mmol/l)] compared with 20% in the late group [RRT started at a mean BUN of 94.5 mg/dl (34 mmol/l)]. This approach, however, is likely to be seriously flawed because BUN may reflect many factors other than time of initiation. Increased BUN/creatinine ratio is a marker of severity of disease. BUN may be raised in patients who have gastrointestinal hemorrhages, severe catabolism, low urine flow rate, intravascular volume depletion, and after administration of drugs, while relatively low creatinine indicates low muscle mass.

(4) In a single center retrospective study ($n = 80$) in patients with septic shock and oliguric AKI [32], the application of early CVVH improved hemodynamics, gas exchange, successful weaning, and 28-day survival compared with a historical control group receiving conventional therapy. Only 75% of the patients in the conventional group received CVVH, despite overt renal failure, and the applied CVVH dose was lower (20 ml/kg/h) than in the early treatment group (mean daily dose 30–35 ml/kg/h).

(5) In a single center retrospective cohort study in cardiac surgery patients [30], hospital mortality was higher in the late CVVH group ($n = 28$) compared with the early CVVH group ($n = 36$) (43% versus 22%, $P < 0.05$). In the late group, CVVH was started for conventional reasons: urea of at least 30 mmol/l, creatinine of at least 250 μmol/l, or potassium of at least 6 mmol/l despite glucose infusion, regardless of urine output. In the early group, CVVH was started when urine output was less than 100 ml within 8 h, despite furosemide infusion.

(6) In a single center retrospective study in patients with ARF following cardiac surgery [29] hospital mortality decreased after the introduction of early continuous venovenous hemodiafiltration (CVVHDF) compared with a historical control group (23.5% versus 55%, $P = 0.02$). In the early group ($n = 34$) CVVHDF was started for oliguria (urine output < 100 ml within 8 h), and in the late group ($n = 27$) CVVHDF was started for conventional criteria (creatinine > 444 μmol/l).

In summary, a trend toward a better outcome with earlier timing of RRT emerges from the above studies, except for one RCT on AKI. The methodological quality of the trials favoring early timing is poor, however. Comparison among studies is hampered by the application of nonuniform definitions for timing, and by the heterogeneity of the study population and mode of RRT.

Timing and definition of acute kidney injury

The absence of agreement regarding the timing of RRT is illustrated in Table 2, summarizing the criteria used in the decision to start RRT in the most recent RCTs on dose and mode of RRT. The majority of studies started RRT when the patients fulfilled criteria for ARF. No two studies, however, applied similar criteria. This highlights the difficulty in this field: nonuniform and in many cases arbitrary definitions hinder direct comparisons among studies and prohibit valid quantitative aggregation (e.g. metaanalyses) of results from different studies. In response to the need for a common definition and classification of ARF, the Acute Dialysis Quality Initiative developed a consensus definition that goes under the acronym of RIFLE (risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease) (Table 3) [34,35]. Since then, several clinical studies have shown that the

Table 2 Timing of initiation of renal replacement therapy (RRT) in randomized controlled trials evaluating dose and mode (intermittent versus continuous) of RRT in critically ill patients with acute kidney injury

	Timing of initiation of renal replacement therapy
Dose studies	
Ronco [11]	ARF defined as abnormal BUN and creatinine and oliguria 200 ml/12 h, despite fluid resuscitation and furosemide
Schiffl [13]	Attending nephrologists decide when to start RRT
Saudan [12]	ARF, criteria not defined
Bouman [8]	Inclusion: creatinine clearance < 20 ml/min and oliguria < 180 ml/6 h despite fluid resuscitation, circulatory support and furosemide Early timing: <12 h of inclusion Late timing: BUN > 40 mmol/l or severe pulmonary edema
ATN study [18]	ARF defined as increase in serum creatinine of 2.0 mg/dl in men and 1.5 mg/dl in women, over no more than 4 days, or the presence of oliguria (≤20 ml/h) for more than 24 h despite fluid resuscitation
Renal study [16]	Oliguria (<100 ml/6 h) despite fluid resuscitation or potassium >6.5 mmol/l or pH <7.20 or urea >25 mmol/l or creatinine >300 μmol/l or clinically significant organ edema, in the setting of ARF
IVOIRE study [17]	RIFLE risk criteria
Mode studies	
Mehta [10]	ARF defined as a sustained rise in serum creatinine ≥ 1 mg/dl compared with baseline, or in the absence of prior values, BUN ≥ 40 mmol/l or creatinine ≥ 2 mg/dl
Gasparovic [21]	ARF defined as at least two of the following criteria: threefold increase in creatinine, $K^+ \geq 6.5$ mmol/l, BE ≥ −6
Augustine [20]	Attending nephrologists decided when to start RRT
Uehlinger [22]	ARF defined as creatinine ≥ 350 μmol/l or oliguria < 20 ml/h
Vinsonneau [15]	ARF defined as urea ≥ 36 mmol/l or creatinine ≥ 310 μmol/l or oliguria < 320 ml/16 h
Schwenger [19]	ARF, criteria not defined

ARF, acute renal failure; BUN, blood urea nitrogen; ATN, Acute Renal Failure Trial Network; RIFLE, risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease; BE, base excess.

Table 3 The RIFLE (risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease) classification of acute kidney injury

RIFLE grade	GFR	Serum creatinine	Urine output (ml/kg/h)
Risk	Decrease > 25%	Increase × 1.5	<0.5 for 6 h
Injury	Decrease > 50%	Increase × 2.0	<0.5 for 12 h
Failure	Decrease > 75%	Increase × 3.0 or sCr > 4 mg/dl[a] and acute rise > 0.5 mg/dl[b] within 48 h	<0.3 for 24 h or anuria for 12 h
Loss	Persistent loss of kidney function > 4 weeks		
ESRD	Dialysis dependent > 3 months		

RIFLE, risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease; GFR, glomerular filtration rate; ESRD, end-stage renal disease; sCr, serum creatinine. Reproduced from [34].
[a] 350 μmol/l.
[b] 44 μmol/l.

proposed RIFLE classification is suitable for definition of AKI in the ICU and correlates with hospital mortality [36–40,41•]. Notably, all studies showed that mortality increased when RIFLE class goes up. The stage of AKI is already associated with increased mortality. Given the importance of early recognition of AKI, the Acute Kidney Injury Network (AKIN) promotes the term AKI and has recently modified the RIFLE classification. AKI is classified in three stages. Stage 1 is slightly more sensitive than risk, stages 2 and 3 correspond to injury and failure (Table 4) [42••]. The AKI staging system offers a useful tool to describe the timing of initiation of RRT.

Timing and other organ failure

In addition to renal criteria, the decision of when to start RRT should consider the severity of other organ failure. Renal function is unlikely to recover soon if circulation remains vasopressor dependent and other organs fail as well. Under these circumstances clinicians are inclined to start RRT early. Animal studies support an early start in severe sepsis [43••]. Early initiation is also supported by several observational studies describing a better survival than predicted when hemo(dia)filtration is started early in patients with refractory septic shock [44–46]. The catalyzing effect of ARF on severity of disease has a physiological base. Several uremic solutes have proinflammatory effects [47]. Moreover, uremic toxins in a proinflammatory milieu may undergo oxidative modification. Oxidation modifies the properties of the solutes which may thus become proinflammatory [48]. Early initiation of RRT in the most severely ill patients may prevent further clinical deterioration. Evidence for this suggestion, however, is poor.

Table 4 Acute Kidney Injury Network classification/staging of acute kidney injury

AKI stage	Serum creatinine	Urine output (ml/kg/h)
1	Absolute increase ≥ 0.3 mg/dl[a] or increase above baseline ≥ 1.5–2×	<0.5 for 6 h
2	Increase above baseline ≥ 2–3×	<0.5 for 12 h
3	Increase above baseline ≥ 3× or sCr ≥ 4 mg/dl[b] with an acute rise of 0.5 mg/dl[c] in ≤24 h	<0.3 for 24 h or anuria for 12 h
	Patients receiving RRT	

The time constraint of the changes is 48 h or less. AKI, acute kidney injury; sCr, serum creatinine; RRT, renal replacement therapy. Reproduced from [42••].
[a] 26.4 μmol/l.
[b] 350 μmol/l.
[c] 44 μmol/l.

Timing and biomarkers

The use of renal criteria as defined in the RIFLE and AKIN classification (creatinine and diuresis) remain a poor reflection of AKI. In particular, the earlier stages do not differentiate between so-called prerenal failure, a compensatory decrease in urinary output and glomerular filtration rate, and injury to the kidney. It seems reasonable to presume that early initiation of RRT in cases of renal compensation is less indicated because renal function is likely to recover after resuscitation of the circulation. If AKI is the result of cellular injury due to ischemia, reperfusion, inflammation or oxidant stress, however, early initiation of RRT may mitigate further damage. The development and introduction of various biomarkers for AKI is an exciting new area of research. The various biomarkers for AKI in blood and urine were recently reviewed [49•,50•]. The use of biomarkers may prove to be helpful in detecting AKI at an early stage, to differentiate renal compensation from AKI, to describe the type of AKI, to evaluate preventive strategies and to decide when to start or stop RRT [37,51].

Possible drawbacks

An important drawback for the early initiation of RRT is the fear that the patient is unnecessarily submitted to an extracorporeal technique. In the RCT of Bouman *et al.* [8], patients were included when diuresis decreased to less than 180 ml within 6 h and measured creatinine clearance was less than 20 ml/min, which is comparable to the RIFLE risk to failure classification (AKI stage 2–3). In this study, four patients in the late group had spontaneous recovery of renal function without hemofiltration, and all survived. Two patients in the late group, however, died before the initiation of hemofiltration. The number of included patients is too small to firmly conclude whether early RRT is unnecessary or essential; however, it is important to realize that no deleterious effects were seen in the early groups. Biomarkers may contribute to sharpen the indications for RRT.

Conclusion

In the absence of large RCTs, we can make no firm recommendations for RRT timing in AKI. When initiation of RRT in AKI is considered, it is important

to realize that the consequences of uremic toxicity, metabolic acidosis and fluid overload are likely to be more severe in critically ill patients. Moreover, rapid recovery of renal function is unlikely when other organ failure persists. We therefore suggest considering AKI along with other organ failure when deciding to initiate RRT. An early start may be beneficial in patients with AKI, persisting shock and poorly recovering functions of other organs, although strong evidence for this clinical knowledge is still missing. For more robust recommendations, we need properly designed RCTs. For future studies, we recommend describing RRT timing according to renal and nonrenal criteria using the 'RIFLE' classification, as modified by AKIN, and quantifying the severity of other organ failure. Definitions of AKI and timing may be refined in the future by using biomarkers.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 750–751).

1 Uchino S, Kellum JA, Bellomo R, *et al.* Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294:813–818.

2 Metnitz PG, Krenn CG, Steltzer H, *et al.* Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 2002; 30:2051–2058.

3 Chertow GM, Levy EM, Hammermeister KE, *et al.* Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998; 104:343–348.

4 de Mendonca A, Vincent JL, Suter PM, *et al.* Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000; 26:915–921.

5 Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality: a cohort analysis. JAMA 1996; 275:1489–1494.

6 • Ricci Z, Ronco C, D'Amico G, *et al.* Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. Nephrol Dial Transplant 2006; 21:690–696.

Survey on the responses of 560 contributors to a questionnaire submitted during an international course on critical care nephrology concerning practice patterns in the management of ARF, including RRT.

7 •• Uchino S, Bellomo R, Morimatsu H, *et al.* Continuous renal replacement therapy: a worldwide practice survey: the Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators. Intensive Care Med 2007; 27 June [Epub ahead of print].

The largest prospective multicenter study on continuous RRT practice patterns in 23 countries.

8 Bouman CS, Oudemans-van Straaten HM, Tijssen JG, *et al.* 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 2002; 30:2205–2211.

9 Kellum JA, Angus DC, Johnson JP, *et al.* Continuous versus intermittent renal replacement therapy: a meta-analysis. Intensive Care Med 2002; 28:29–37.

10 Mehta RL, McDonald B, Gabbai FB, *et al.* A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int 2001; 60:1154–1163.

11 Ronco C, Bellomo R, Homel P, *et al.* Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000; 356:26–30.

12 Saudan P, Niederberger M, De Seigneux S, *et al.* Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006; 70:1312–1317.

13 Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 2002; 346:305–310.

14 Tonelli M, Manns B, Feller-Kopman D. Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. Am J Kidney Dis 2002; 40:875–885.

15 Vinsonneau C, Camus C, Combes A, *et al.* Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet 2006; 368:379–385.

16 Bellomo R. Augmented versus normal renal replacement therapy in severe acute renal failure. http://www.clinicaltrials.gov/ct/show/NCT00221013?order=3. [Accessed June 2007]

17 Joannes-Boyau O. The IVOIRE study. http://www.clinicaltrials.gov/ct/show/NCT00241228?order=1. [Accessed June 2007]

18 Palevsky PM, O'Connor T, Zhang JH, *et al.* Design of the VA/NIH Acute Renal Failure Trial Network (ATN) Study: intensive versus conventional renal support in acute renal failure. Clin Trials 2005; 2:423–435.

19 Schwenger V. Comparison of dialysis strategies in critically ill patients with acute renal failure. http://www.clinicaltrials.gov/ct/show/NCT00322530?order=1. [Accessed June 2007]

20 Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis 2004; 44:1000–1007.

21 Gasparovic V, Filipovic-Grcic I, Merkler M, Pisl Z. Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD): what is the procedure of choice in critically ill patients? Ren Fail 2003; 25:855–862.

22 Uehlinger DE, Jakob SM, Ferrari P, *et al.* Comparison of continuous and intermittent renal replacement therapy for acute renal failure. Nephrol Dial Transplant 2005; 20:1630–1637.

23 Bellomo R, Ronco C. Indications and criteria for initiating renal replacement therapy in the intensive care unit. Kidney Int Suppl 1998; 66:S106–S109.

24 Kellum JA, Mehta RL, Angus DC, *et al.* The first international consensus conference on continuous renal replacement therapy. Kidney Int 2002; 62:1855–1863.

25 Brivet FG, Kleinknecht DJ, Loirat P, Landais PJ. Acute renal failure in intensive care units: causes, outcome, and prognostic factors of hospital mortality; a prospective, multicenter study. French Study Group on Acute Renal Failure. Crit Care Med 1996; 24:192–198.

26 Cole L, Bellomo R, Silvester W, Reeves JH. A prospective, multicenter study of the epidemiology, management, and outcome of severe acute renal failure in a 'closed' ICU system. Am J Respir Crit Care Med 2000; 162:191–196.

27 Himmelfarb J, Tolkoff RN, Chandran P, *et al.* A multicenter comparison of dialysis membranes in the treatment of acute renal failure requiring dialysis. J Am Soc Nephrol 1998; 9:257–266.

28 Jiang HL, Xue WJ, Li DQ, *et al.* Influence of continuous veno-venous hemofiltration on the course of acute pancreatitis. World J Gastroenterol 2005; 11:4815–4821.

29 Demirkilic U, Kuralay E, Yenicesu M, *et al.* Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg 2004; 19:17–20.

30 Elahi MM, Lim MY, Joseph RN, *et al.* Early hemofiltration improves survival in postcardiotomy patients with acute renal failure. Eur J Cardiothorac Surg 2004; 26:1027–1031.

31 Gettings LG, Reynolds HN, Scalea T. Outcome in posttraumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. Intensive Care Med 1999; 25:805–813.

32 Piccinni P, Dan M, Barbacini S, *et al.* Early isovolaemic haemofiltration in oliguric patients with septic shock. Intensive Care Med 2006; 32:80–86.

33 Bouman CSC, Oudemans-van Straaten HM. Guidelines for timing, dose and mode of continuous renal replacement therapy for acute renal failure in the critically ill. Neth J Crit Care 2006; 10:561–568.

34 Bellomo R, Ronco C, Kellum JA, *et al.* Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8:R204–R212.

35 Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. Curr Opin Crit Care 2002; 8:509–514.

36 Bell M, Liljestam E, Granath F, *et al.* Optimal follow-up time after continuous renal replacement therapy in actual renal failure patients stratified with the RIFLE criteria. Nephrol Dial Transplant 2005; 20:354–360.

37 Hoste EA, Kellum JA. Acute kidney injury: epidemiology and diagnostic criteria. Curr Opin Crit Care 2006; 12:531–537.

38 Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettila V. Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. Ann Thorac Surg 2006; 81:542–546.

39 Lopes JA, Jorge S, Silva S, *et al.* An assessment of the RIFLE criteria for acute renal failure following myeloablative autologous and allogeneic haematopoietic cell transplantation. Bone Marrow Transplant 2006; 38:395.

40 O'Riordan A, Wong V, McQuillan R, *et al.* Acute renal disease, as defined by the RIFLE criteria, postliver transplantation. Am J Transplant 2007; 7:168–176.

41 Uchino S, Bellomo R, Goldsmith D, *et al.* An assessment of the RIFLE criteria • for acute renal failure in hospitalized patients. Crit Care Med 2006; 34:1913–1917.

Large retrospective single center study assessing the RIFLE criteria and showing that 20% of the hospitalized patients had some degree of acute impairment in renal function and that the RIFLE criteria were useful in predicting hospital mortality.

42 Mehta RL, Kellum JA, Shah SV, *et al.* Acute Kidney Injury Network: report of •• an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11:R31.

The first paper introducing the slightly modified RIFLE criteria for staging of AKI.

43 Bouman CS, Oudemans-van Straaten HM, Schultz MJ, Vroom MB. Hemofiltration •• in sepsis and systemic inflammatory response syndrome: the role of dosing and timing. J Crit Care 2007; 22:1–12.

Descriptive analysis of animal and human studies determining the role of ultrafiltration dose and timing on the physiological and clinical effects of hemofiltration in sepsis and systemic inflammatory response syndrome.

44 Cornejo R, Downey P, Castro R, *et al.* High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. Intensive Care Med 2006; 32:713–722.

45 Honore PM, Jamez J, Wauthier M, *et al.* Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 2000; 28:3581–3587.

46 Page B, Vieillard-Baron A, Chergui K, *et al.* Early veno-venous haemodiafiltration for sepsis-related multiple organ failure. Crit Care 2005; 9:R755–R763.

47 Vanholder R, Schepers E, Meert N, Lameire N. What is uremia? Retention versus oxidation. Blood Purif 2006; 24:33–38.

48 Himmelfarb J, McMonagle E, Freedman S, *et al.* Oxidative stress is increased in critically ill patients with acute renal failure. J Am Soc Nephrol 2004; 15:2449–2456.

49 Trof RJ, Di Maggio F, Leemreis J, Groeneveld AB. Biomarkers of acute renal • injury and renal failure. Shock 2006; 26:245–253.

Review of human and animal studies on the various biomarkers for AKI.

50 Bagshaw SM, Langenberg C, Haase M, *et al.* Urinary biomarkers in septic • acute kidney injury. Intensive Care Med 2007; 33:1285–1296.

Appraisal of the literature on the value of urinary biomarkers in septic AKI.

51 Herget-Rosenthal S, Marggraf G, Husing J, *et al.* Early detection of acute renal failure by serum cystatin C. Kidney Int 2004; 66:1115–1122.