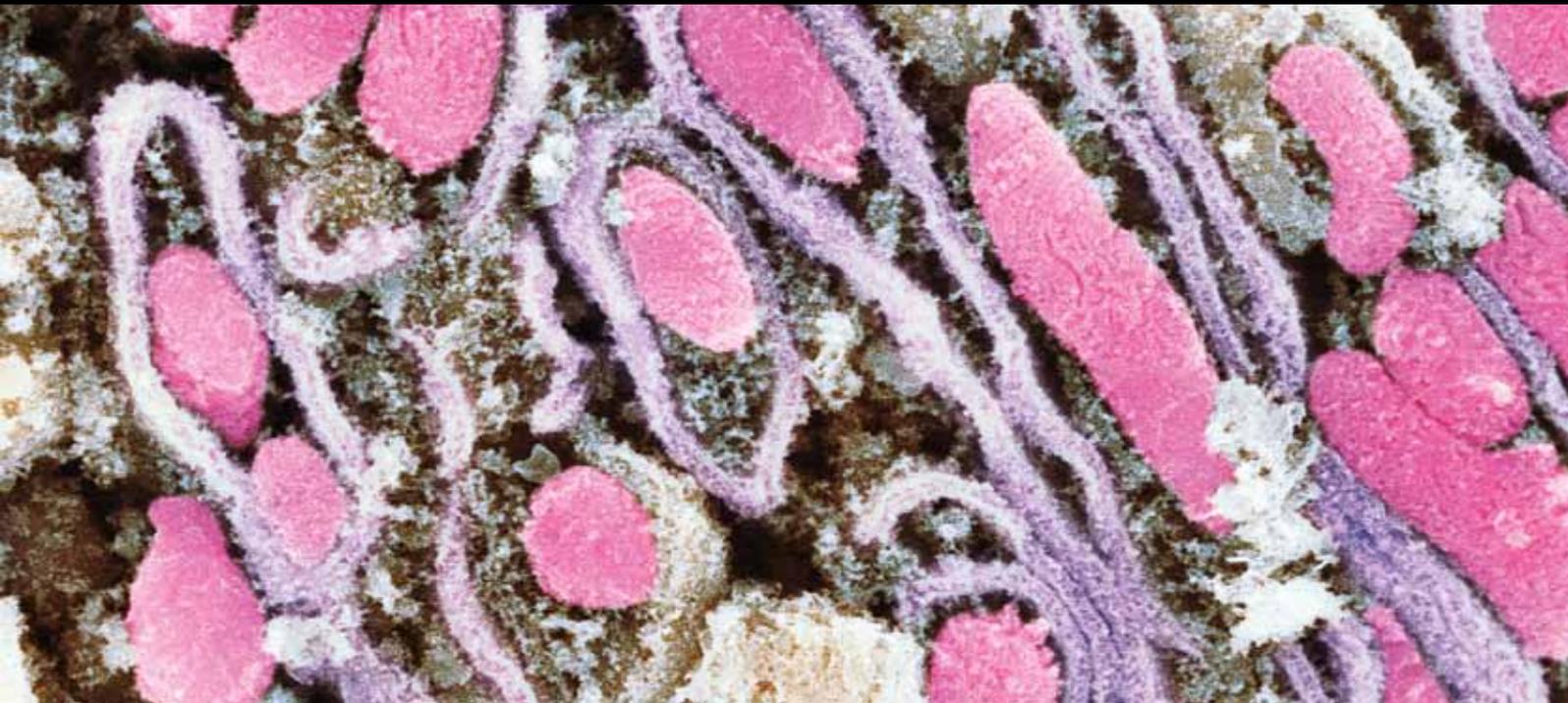


Acute Renal Replacement Therapy

Guest Editors: Achim Jörres, Wim van Biesen, Andrew Davenport,
and Michael Oppert





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International Journal of Nephrology

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Editorial

Acute Renal Replacement Therapy

Achim Jörres,¹ Wim van Biesen,² Andrew Davenport,³ and Michael Oppert¹

¹ Department of Nephrology and Medical Intensive Care, Charité University Hospital, 133 53 Berlin, Germany

² Renal Division, University Hospital Ghent, De Pintelaan 185, 9000 Ghent, Belgium

³ Centre for Nephrology, University College London Medical School, Royal Free Campus, Pond Street, London NW3 2QG, UK

Correspondence should be addressed to Achim Jörres, achim.joerres@charite.de

Received 28 April 2011; Accepted 28 April 2011

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Acute kidney injury is an important clinical condition particularly in the intensive care unit. It develops in as many as two-thirds of critically ill patients during the course of their illness and constitutes a significant independent risk factor for death. About 5% patients admitted to an ICU will eventually require renal replacement therapy. In these patients, in-hospital mortality is extremely high, exceeding 50%. The adequate delivery of acute renal replacement therapy is a key aspect in the treatment of these patients and a prerequisite for a successful outcome.

In this special issue *K. Yong* et al. first discuss recent changes in AKI classification and revisit controversies such as the timing of initiation of dialysis, the modalities of renal support, and the dialysis intensity delivered. *N. Ansari* then focuses on the use of peritoneal dialysis as a renal replacement therapy for AKI. Two further articles discuss technical aspects of extracorporeal techniques for renal replacement therapy. *F. Mariano* et al. weigh success and limits of citrate anticoagulation strategies, while *M. Abe* et al. compare sustained hemodiafiltration with acetate-free dialysate with continuous venovenous hemodiafiltration for the treatment of critically ill patients with AKI. In the last part, *C. M. Yuan* and *R. M. Perkins* provide an overview of renal replacement therapy in austere environments, that is, the provision of therapy in a setting in which resources are limited, incapacitated, or even nonexistent. Recent earthquakes and flood disasters highlight the actuality of this topic. Finally, *S. Grisaru* et al. report on their vast experience in the management of children with diarrhea-associated hemolytic uremic syndrome.

The guest editors wish to thank all authors for their valuable contributions. Without their efforts this special issue would not have been possible.

*Achim Jörres
Wim van Biesen
Andrew Davenport
Michael Oppert*

Review Article

Acute Kidney Injury: Controversies Revisited

Kenneth Yong,^{1,2} Gursharan Dogra,¹ Neil Boudville,^{1,2} Mary Pinder,³ and Wai Lim¹

¹ Department of Renal Medicine, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia

² School of Medicine and Pharmacology, University of Western Australia, Nedlands, WA 6009, Australia

³ Intensive Care Unit, Sir Charles Gairdner Hospital, Crawley, WA 6009, Australia

Correspondence should be addressed to Kenneth Yong, kenneth.yong@health.wa.gov.au

Received 1 October 2010; Accepted 7 March 2011

Academic Editor: Achim Jörres

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This paper addresses the epidemiology of AKI specifically in relation to recent changes in AKI classification and revisits the controversies regarding the timing of initiation of dialysis and the use of peritoneal dialysis as a renal replacement therapy for AKI. In summary, the new RIFLE/AKIN classifications of AKI have facilitated more uniform diagnosis of AKI and clinically significant risk stratification. Regardless, the issue of timing of dialysis initiation still remains unanswered and warrants further examination. Furthermore, peritoneal dialysis as a treatment modality for AKI remains underutilised in spite of potential beneficial effects. Future research should be directed at identifying early reliable biomarkers of AKI, which in conjunction with RIFLE/AKIN classifications of AKI could facilitate well-designed large randomised controlled trials of early versus late initiation of dialysis in AKI. In addition, further studies of peritoneal dialysis in AKI addressing dialysis dose and associated complications are required for this therapy to be accepted more widely by clinicians.

1. Introduction

In 2007, the Acute Kidney Injury Network (AKIN) replaced the term acute renal failure with acute kidney injury (AKI) in an attempt to include the entire spectrum of acute renal dysfunction [1]. AKI encompasses a complex clinical entity characterised by an abrupt decline in kidney function which clinically manifests as azotemia, rising serum creatinine, and in most cases oliguria. While recent advances in renal replacement (RRT) and critical therapies have led to improved AKI-related outcomes [2, 3], the incidence of AKI continues to rise, possibly explained by an ageing population with multiple comorbidities and an increase in sepsis-related hospitalisations [2–7]. Furthermore, AKI continues to be associated with significant mortality, hospital length of stay and economic costs, particularly in the context of critically ill patients in the intensive care setting [5, 8–12]. Even relatively modest absolute ($\geq 44 \mu\text{mol/L}$) and relative ($\geq 25\%$ from baseline) elevations in creatinine, have been shown to be associated with higher mortality in hospitalised patients [8, 11], ranging from 10% with noncritical AKI managed outside of the intensive care unit (ICU), compared with up to 80% with critical ICU AKI [13–16].

Although the incidence of AKI continues to rise, the optimum management of AKI remains uncertain with no uniform standard of care, as reflected by wide disparity in clinical practice [17–19]. While multiple studies have addressed the issue of optimal RRT modality and/or RRT dose in critical AKI, the initiation and duration of RRT in critical AKI remains unclear [20–24].

In this paper, we first aim to discuss the epidemiology and mortality outcomes of AKI across a spectrum of severity (critical versus noncritical) as defined by consensus AKI classifications [1, 25]. Secondly, we will review the current literature on dialysis therapies in AKI, more specifically the indications for and optimal timing of initiation of RRT and the role of acute peritoneal dialysis (PD). Finally, we will provide a brief overview on the current state of novel biomarkers of AKI and their potential future role in research and clinical practice.

2. Definitions of AKI: RIFLE and AKIN

Definitions for AKI vary widely between studies, ranging from absolute or relative increases in creatinine from baseline

to the requirement for RRT [1, 25, 26]. The lack of a uniform definition may explain the large differences in reported incidence and outcomes of AKI in the literature, and as a consequence in 2004, a consensus on the definition of acute renal failure known as the Risk-Injury-Failure-Loss-End stage renal disease (RIFLE) classification was reached by a group of international experts [25]. The RIFLE classification was based on two important parameters: (1) changes in serum creatinine or GFR from baseline (2) urine output at specific time points. The severity of acute renal failure was determined by the more severe of the two parameters, which were categorised into three stages. The three stages described in RIFLE include Risk, Injury and Loss, all of which have increasing prognostic significance.

However, with recent studies suggesting that even minor increments in creatinine may be associated with worse outcomes [8], the RIFLE classification was modified by the Acute Kidney Injury Network (AKIN) to include (1) re-categorisation of the original RIFLE into AKIN stage 1, 2, and 3, (2) addition of an absolute increase in creatinine $\geq 26 \mu\text{mol/L}$ (0.3 mg/dL) to stage 1 criteria, and (3) automatic classification of patients starting RRT as stage 3, regardless of creatinine or urine output [1]. Comparison of the old RIFLE and modified AKIN classification is shown in Table 1.

3. AKI Epidemiology: Critical versus Noncritical

Prior to employing the RIFLE/AKIN classifications, the reported incidence of AKI in the literature varied from 1–30%, largely due to lack of a standard definition of AKI [2, 8, 10–12, 14–16, 27–38]. The incidence of AKI varies according to the location of patients, either in the critical care or noncritical care settings. The noncritical care setting can be further subdivided into community (data from health district, Medicare or district hospital outpatient records), and hospital environments (data from tertiary hospital admissions).

In the critical care setting, the incidence of AKI ranges from 5–20%, typically occurring in patients with severe multiorgan failure [39]. The incidence of AKI as single-organ failure in the ICU setting is as low as 11% compared to 69% in non-ICU settings [13]. There have been two large multi-centre cohort studies examining the incidence of AKI in patients in the critical care setting. The first study was the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) which included 29,629 critically ill adult patients admitted to 54 ICUs throughout 23 countries [16]. Using a definition of AKI as oliguria (urine output $< 200 \text{ mL}/12\text{hrs}$) and/or urea $> 30 \text{ mmol/L}$ (84 mg/dL), the authors reported a 5.7% period prevalence of AKI, (ranging from 1.4%–25.9% across all study centres) usually in association with septic (47.5%) or cardiogenic (27%) shock. Approximately two-thirds of patients who developed AKI required RRT (4% of total cohort). The second study was the Program to Improve Care in Acute Renal Disease (PICARD) study. This was a 2-year prospective observational study of 618 ICU patients with AKI across 5

centers in the USA [15]. The authors defined AKI as “new-onset” by a rise in creatinine $\geq 44 \mu\text{mol/L}$ ($\geq 0.5 \text{ mg/dL}$) or “AKI on chronic kidney disease (CKD)” as an increase in creatinine $\geq 88 \mu\text{mol/L}$ ($\geq 1.0 \text{ mg/dL}$) in patients with baseline creatinine between $133 \mu\text{mol/L}$ to $433 \mu\text{mol/L}$ (1.5 mg/dL to 4.9 mg/dL). RRT was required in 64% of patients. Similar to the BEST Kidney study, AKI occurred predominantly in patients with multisystem organ failure. The BEST Kidney and PICARD studies are prime examples of the variations in reported incidence and outcomes of AKI when nonstandard definitions of AKI are applied.

With the exception of a few studies in hospitalised children and stem-cell transplant recipients [40, 41], the RIFLE/AKIN classifications are seldom applied in the non-critical care setting (i.e., hospital or community), and variable definitions of AKI continue to confound prevalence and incidence rates. The prevalence of hospital-acquired AKI is thought to be approximately 5–10 times greater than community-acquired AKI, with reported rates of AKI in 5–7% of hospitalised patients [35, 42]. In a study of 4622 patients in a tertiary hospital, Nash et al. reported that 7.2% of patients developed “renal insufficiency”, defined as a $44 \mu\text{mol/L}$ increase in creatinine in patients with baseline creatinine $\leq 168 \mu\text{mol/L}$, an $88 \mu\text{mol/L}$ increase in patients with baseline creatinine $177\text{--}433 \mu\text{mol/L}$, or a $132 \mu\text{mol/L}$ increase in patients with baseline creatinine $\geq 442 \mu\text{mol/L}$ [35]. In the Madrid Acute Renal Failure Study Group of 13 tertiary hospitals in Madrid, uNLiaño et al. reported an incidence of AKI of 209 cases per million population (pmp) as defined by a sudden increase in creatinine to level $> 177 \mu\text{mol/L}$ (2 mg/dL) in patients with normal renal function or an increase of at least 50% from baseline creatinine in patients with mild-to moderate chronic renal failure (creatinine $< 264 \mu\text{mol/L}$) [34]. Preexisting renal dysfunction was present in about 50% of patients who developed AKI. RRT was required in 36% of patients with AKI and was associated with a higher “severity index” of AKI.

Only a handful of studies have examined the incidence of AKI in community settings [43]. The occurrence of AKI in the community is an infrequent event, accounting for $< 1\%$ of hospital admissions in the USA [42, 44]. Early studies from the 1990s have reported overall annual incidence rates of reported community-acquired AKI varying from 22–620/million population, with most studies using need for RRT or cutoff creatinine ≥ 300 or $500 \mu\text{mol/L}$ to define AKI [45, 46]. Using changes in inpatient serum creatinine levels to define AKI, a more recent study by Hsu et al. suggests that the incidence of AKI in the community is increasing over time [4]. The authors reported an increasing incidence of nondialysis AKI and dialysis requiring AKI from 322.7 to 522.4 and 19.5 to 29.5 per 100,000 person years, respectively, between 1996 and 2003.

Overall observational trends in both the ICU and non-ICU settings also suggest the incidence of AKI has risen over time, likely as a reflection of ageing populations with multiple comorbidities (including chronic kidney disease), increased infection-related hospitalisation and increasing utilisation of nephrotoxic agents such as intravenous contrast, aminoglycosides, nonsteroidal anti-inflammatory

TABLE 1: RIFLE and AKIN classification [1, 25].

Category	RIFLE			AKIN	
	Creatinine/GFR	Urine output (UO)	Stage	Creatinine	Urine output (UO)
Risk	Cr increase by x1.5 times or GFR decrease by $\geq 25\%$	UO ≤ 0.5 mL/kg/hr for 6 hrs	Stage 1	Cr increase by x1.5 times or ≥ 26 $\mu\text{mol/L}$	UO ≤ 0.5 mL/kg/hr for 6 hrs
Injury	Cr increase by x2 times or GFR decrease by $\geq 50\%$	UO ≤ 0.5 mL/kg/hr for 12 hrs	Stage 2	Cr increase by x2	UO ≤ 0.5 mL/kg/hr for 12 hrs
Failure	Cr increase by x3 times or GFR decrease by $\geq 75\%$ or Cr ≥ 354 $\mu\text{mol/L}$ (with acute rise ≥ 44 $\mu\text{mol/L}$)	UO ≤ 0.3 mL/kg/hr for 24 hrs or anuria for 12hrs	Stage 3	Cr increase by x3 or Cr ≥ 354 $\mu\text{mol/L}$ (with acute rise 44 $\mu\text{mol/L}$) or RRT ¹	UO ≤ 0.3 mL/kg/hr for 24 hrs or anuria for 12 hrs
Loss (outcome)	Persistent ARF = complete loss of renal function > 4 weeks (but ≤ 3 months)	N/A	Nil		
ESRD (outcome)	Complete loss of renal function > 3 months	N/A	Nil		

RRT: renal replacement therapy.

¹Patients requiring RRT are automatically considered stage 3 AKIN regardless of stage at time of RRT initiation.

drugs (NSAIDs) and chemotherapeutic agents [15, 42, 43]. CKD and sepsis in particular appear to be major contributors to this process. Reports from a US hospital database estimate that patients with CKD stage 3 (eGFR < 60 mL/min per 1.73 m²) have a 2-fold increase in adjusted odds ratio (OR) of AKI compared to CKD stages 1 and 2 (eGFR > 60 mL/min per 1.73 m²), with risk progressively increasing with severity of baseline CKD [47]. In a study of sepsis-related admissions in US hospitals, Martin et al. noted an increase in incidence of sepsis-related hospital admissions from 1979 to 2000 which were paralleled by increase in renal failure [7]. Studies have shown that the risk of AKI increases accordingly with severity of sepsis. Schrier et al. reported rates of AKI of 19% in patients with moderate sepsis, 23% in patients with severe sepsis and 51% in patients with positive blood cultures and septic shock [48].

4. Aetiology of AKI: Critical versus Noncritical

The cause of AKI differs according to patient location. Acute tubular necrosis (ATN) due to sepsis is generally regarded as the most common cause of AKI in the critical care setting, accounting for up to 35–50% of all cases of AKI [13, 16, 39, 49–51]. In the BEST Kidney study, septic shock (47.5%) was the most common aetiology of AKI, followed by major surgery (34.3%) and cardiogenic shock (26.9%). Similarly, in the PICARD study, ischaemic ATN predominantly attributed to sepsis was listed as the most common aetiology of AKI [15]. The pathogenesis of septic AKI is traditionally thought to involve reduced renal blood flow secondary to systemic arterial vasodilatation and concomitant intrarenal vasoconstriction, resulting in renal hypoperfusion and ischaemia [52]. Interestingly, however, recent experimental animal models of septic AKI have failed to support this long-held hypothesis [53, 54]. Furthermore, in a recent systematic review of renal histopathology in human and experimental animal septic AKI [55], Langenberg et al. reported that only

22% of patients with septic AKI had features of ATN on either renal biopsy or postmortem findings, with the majority of patients having normal or only mild nonspecific histological changes at best. Despite the limitations of this review which include a very small sample size (117 patients), heterogenous definitions of AKI, use of postmortem findings versus renal biopsy, and use of relatively outdated criteria for classic ATN, these findings suggest that ATN is relatively uncommon in the setting of septic AKI. Further studies evaluating the true histopathology of septic AKI are clearly required.

ATN is also considered the most common cause of AKI in the hospital setting although the aetiology of ATN differs from that of critical care associated AKI. In the Madrid Acute Renal Failure Study, ATN was documented to be the cause of AKI in 75.9% of ICU patients compared to 37.6% in non-ICU patients (summarised in Table 2) [13]. ATN within the hospital setting is more likely to be multifactorial, with hypotension and nephrotoxins as important causes in addition to sepsis and surgery [42].

For community-acquired AKI, prerenal or acute-on-chronic renal failure are common and usually occurs as the result of dehydration or drug-related toxicities such as non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARB). Elderly and patients with multiple comorbidities such as diabetes are at particularly high risk of developing AKI [44]. In Third World or tropical countries, postinfectious glomerulonephritis, tropical and nontropical infections, snake or spider bites, chemical poisons and traditional herbal medicines are other common causes of community-acquired AKI [42].

5. RIFLE/AKIN: Classification as a Prognostic Marker in AKI

Employing the RIFLE/AKIN classifications has facilitated improved risk stratification in critical AKI. In a study of

1510 ICU patients, increasing mortality rates were reported with greater severity/stages of AKI as defined by RIFLE (mortality rates of 8.8% with Risk, 11.4% with Injury, and 26.3% with Failure) [56]. In a systematic review by Ricci et al. of 24 studies of patients with acute renal failure, application of the RIFLE classification was associated with a stepwise increase in relative risk (RR) for mortality with increasing stages of acute renal failure and across diverse patient populations. In comparison to patients without acute renal failure, the RIFLE Risk category was associated with RR 2.40 (95% CI 1.94–2.97) of mortality, while Injury and Failure were associated with RR 4.15 (95% CI 3.14–5.48) and 6.37 (95% CI 5.14–7.90) of mortality respectively [57]. Although these were retrospective studies and 12 of the 24 studies included only patients with acute renal failure/AKI in the critical care setting, the authors concluded that RIFLE was easily applicable to clinical practice and was a useful tool to help stratify mortality risk in patients with AKI. In a more recent retrospective study by Bagshaw et al. [58] of 120,123 patients from the Australia New Zealand Intensive Care Society Adult Patient Database (ANZICS APD), use of the RIFLE classification identified 36.1% of patients with AKI out of 120,123 patient admissions to the ICU. AKI was associated with a significant increase in hospital mortality compared to patients without AKI (OR 3.29; 95% CI 3.19–3.41; $P < .0001$). Similarly, each increase in the severity of RIFLE category was also associated with a correspondingly increased risk of hospital mortality.

Studies utilising the AKIN classification in diverse patient populations have also demonstrated comparable findings to studies utilising the RIFLE classification [59–63]. In a large retrospective study of 325,395 critically ill patients from the Veterans Administration ICU system, the development of AKI was associated with mortality risk (OR 2.2, 6.1, and 8.6 for AKIN stage I, II, and III, resp.) [60].

At least, six studies have directly compared the utility of both the RIFLE and AKIN classifications in the prediction of mortality in critical patients with AKI and five of these studies concluded that RIFLE and AKIN were similar in terms of diagnosing AKI and assessing mortality risk [40, 62, 64–68]. In the analysis of the ANZICS APD, Bagshaw et al. found a less than one percent difference in the identification of patients with AKI using either RIFLE/AKIN classifications within the first 24 hours of admission to the ICU [62]. Use of the AKIN classification slightly increased numbers of patients with stage 1 injury (equivalent to “Risk”) from 16.2% to 18.1%, but it decreased the numbers of patients with stage 2 injury (equivalent to RIFLE “Injury”) from 13.6% to 10.1%. The area under ROC for hospital mortality was similar for RIFLE (0.66) and AKIN (0.67) and the authors concluded the AKIN classification did not further improve the sensitivity, robustness or predictive ability of RIFLE in the first 24hrs of ICU admission.

6. Mortality in AKI

AKI is associated with extremely high mortality rates ranging from 30–80% in the critical care setting [12, 14–16, 27, 30,

TABLE 2: Demographics and AKI outcomes in ICU compared to non-ICU (Madrid Acute Renal Failure Study Group) [13].

	ICU	Non-ICU
Demographics and RRT		
Age (mean \pm SD) ^a	56.4 \pm 16.4 yrs	62.6 \pm 18.8 yrs
Males ^b	72.7%	61.4%
Severity index (mean \pm SD) ^a	0.65 \pm 0.22	0.32 \pm 0.17
Single-organ failure AKI ^a	11%	69%
RRT ^a	70.8%	18.4%
Cause of AKI		
ATN ^a	75.9%	37.6%
Prerenal ^b	17.8%	28.1%
Acute-on-chronic ^c	7.9%	15.2%
Mortality		
Unadjusted mortality ^a	71.5%	31.5%
Corrected mortality	56%	15%
Mortality of single-organ failure AKI ^a	30%	23%

^a $P < .001$.

^b $P < .002$.

^c $P < .005$.

37]. In the BEST Kidney and PICARD studies, the overall reported mortality rates were 60% and 37%, respectively [15, 16].

Studies have consistently observed that patients who develop AKI have a worse mortality than patients without AKI. Bagshaw et al. reported crude hospital mortality rates of 42.7% and 13.4% in patients with and without AKI, respectively ($P < .0001$) [2]. Mortality of patients with AKI is substantially increased even further in the setting of concurrent multiorgan failures, sepsis and requirement for RRT. Metnitz et al. demonstrated that patients with AKI requiring RRT had significantly higher in-hospital mortality rates (62.8%) compared with patients with AKI not requiring RRT (15.6%) [12]. Similarly, Bagshaw et al. observed that the presence of sepsis in patients with AKI (compared with nonsepsis related AKI) was associated with greater hospital mortality (70.2% versus 51.8%; $P < .001$), severity of illness, higher rates of multiorgan failures, a greater requirement for ionotropic and ventilatory support, and a longer duration of hospitalisation [69].

Although it is clear that the presence of AKI in the critical care setting is associated with higher mortality and poor prognosis, uncertainty remains as to whether AKI is directly causal or simply a marker for greater severity of illness and poor patient outcomes.

Evidence for the role of AKI as a “bystander” comes from an observational cohort study of 1396 patients admitted to the ICU showing that patients with AKI had a higher mortality (23%) than patients with end-stage renal disease (ESRD) (11%) and patients without AKI (5%) [70].

In contrast, other studies suggest that AKI is directly responsible for the high mortality in this group, perhaps through a sustained inflammatory response associated with uraemia. The systemic inflammatory response syndrome

(SIRS) has been described as a nonspecific generalised inflammatory response to critical illness, initially characterised by systemic release of proinflammatory cytokines followed by a counter anti-inflammatory response syndrome (CARS) aimed at controlling and limiting this inflammatory process. Disruption of these natural responses to inflammation by clinical states such as uraemia, in which proinflammatory and anti-inflammatory cytokines are released simultaneously as opposed to sequentially, has been implicated as a key mechanism in the pathogenesis of multiorgan failure, septic shock, and death [71, 72]. Supporting this hypothesis has been a study demonstrating that patients with critical AKI have simultaneously elevated pro- and anti-inflammatory cytokines, which are independent predictors of mortality [73]. Anti-inflammatory cytokines have been shown to induce monocyte hyporesponsiveness to endotoxin and other noxious stimuli, which may in part explain their association with a greater severity of septic shock and possibly poorer patient outcomes [74–76].

As with critical AKI, the presence of AKI in hospitalised non-ICU patients remains an important predictor of mortality [8–11], even after allowing for confounding variations in definitions of AKI. In the study by Nash et al. of AKI in hospitalised patients, mortality associated with renal failure was 19.4% [35]. Levy et al. reported higher mortality in patients with AKI postradiocontrast procedure (34%) compared with age- and baseline creatinine matched controls undergoing similar procedures (7%) [11]. The presence of renal failure defined as an increase in serum creatinine $\geq 25\%$ from baseline to at least $177 \mu\text{mol/L}$ (2 mg/dL) was associated with an adjusted mortality odds ratio (OR) of 5.50 (95% CI 2.91–13.19; $P < .001$) but the results were confounded by the fact that no distinction was made between AKI secondary to contrast injury or atheroembolism, which is a common complication of invasive angiography and associated with high mortality.

Finally, in a study of 42,773 patients undergoing cardiac surgery, Chertow et al. reported an overall mortality of 63.7% in patients who developed AKI (defined crudely as requiring RRT within 30 days of surgery) compared to 4.3% in patients with no AKI (adjusted OR for death 26; 95% CI 22–34) [10]. In another report of 9210 patients, Chertow et al. demonstrated that a minor change in serum creatinine ($\geq 44 \mu\text{mol/L}$ or 0.5 mg/dL) from baseline was associated with a 6.5-fold increased risk of death (95% CI 5.0–8.5) [8].

7. Mortality Comparisons between Critical AKI and Noncritical AKI

While it is widely accepted that mortality associated with critical AKI is higher than noncritical AKI, this may be related to associated multiorgan failure seen in the critical care setting. In a followup study from the Madrid Acute Renal Failure Study Group, Liano et al. prospectively assessed the outcomes of 748 individual AKI episodes comprising of 253 ICU cases and 495 non-ICU patients (results summarised in Table 2) [13]. The authors reported a significantly higher crude mortality in ICU-associated AKI (71.5%)

compared with non-ICU AKI (31.5%) over a 9 month period ($P < .001$). However, AKI in the absence of multiorgan failure (i.e., isolated AKI) was rare in the critical care setting compared with the noncritical care setting (11% ICU versus 69% non-ICU; $P < .001$) but mortality in patients with isolated AKI was comparable between those treated in the critical and noncritical settings (30% ICU versus 23% non-ICU; $P = \text{NS}$). Furthermore, analysis of patients with AKI in the presence of multiorgan failure demonstrated a significant linear increase in mortality with increasing number of organ failures, regardless of the location of the patients. The use of RRT was associated with significantly higher mortality in both critical care (79.3% versus 53%; $P < .001$) and noncritical care settings (40% versus 30%; $P < .001$). It remains debatable as to whether use of RRT was directly responsible for the increased mortality, possibly by enhancing the patient's inflammatory responses.

In a separate retrospective study of 114 patients with dialysis-requiring AKI, Routh et al. reported that there was no association between critical AKI and mortality [77]. Although overall patient survival was significantly lower in critical care compared with noncritical care patients (36% versus 63%; $P < .01$), the authors suggested the discrepancy in survival between patient groups was related to the severity of the precipitating illness and concluded that aggressive supportive care was sufficient to eliminate the “morbidity and mortality due to ARF *per se*”. However, a significant limitation of this study was that AKI was defined as having at least one dialysis session in addition to “standard clinical and biochemical criteria” which were not specified. In addition to this, patients in this study were younger compared to patients in more recently published literature, preexisting comorbidities were not recorded and dialysis technologies were significantly different during the study period (1969–1978) compared to the present day. Furthermore, the applicability of this data to current clinical practice is not clear given the trends towards increasingly complex patient disease states and changes in treatment technologies over the last 40 years.

Thus, while mortality is greater in patients with critical AKI compared with noncritical AKI, this may reflect the severity of the underlying illness. Patients with isolated single-organ AKI appear to have a better prognosis compared to patients with AKI in the presence of multiorgan failure and regardless of location, patients with AKI requiring RRT have significantly higher mortality than do patients with AKI that do not require RRT.

8. Acute Kidney Injury: Current Controversies

AKI is highly prevalent and is associated with considerable morbidity and mortality, particularly in critically ill patients. Despite this, the optimal use of RRT for AKI remains unclear and has been plagued by controversies which include the optimal timing for initiation of RRT, modality (intermittent haemodialysis (HD) versus continuous renal replacement therapy (CRRT)) and dosing [78].

The issue of optimal RRT dose has only recently been better defined by two large multicentre prospective randomised controlled trials; the VA/NIH Acute Renal Failure Trial Network (ATN) study in the USA and the Randomised Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL) study in Australia and New Zealand [23, 79]. These landmark trials were designed to compare “less intensive” to “intensive” RRT and both failed to demonstrate a survival benefit with higher CRRT doses beyond the current conventional dose of 25 mL/kg/hr in critically ill patients with AKI. Furthermore, with CRRT doses <20 mL/kg/hr, a dose-response relationship towards worse patient outcomes is likely to exist [78, 80]. This last finding has important implications, given that 46.4% and 18% of patients from international surveys such as the BEST Kidney and Do-Re-Mi studies reportedly received a CRRT dose of <20 mL/kg/hr [19, 81]. Given that there are often discrepancies between prescribed and delivered CRRT doses as highlighted by the RENAL and ATN trials (delivered dose 10–15% lower than prescribed), it is advisable that clinicians adjust RRT prescription accordingly [78, 80].

The lack of survival benefit with increased RRT dosing places even more importance upon other aspects of RRT, such as the optimal timing for initiation of RRT, as we continue to seek improvements in current AKI outcomes and is discussed below.

9. Factors Affecting RRT Initiation

For patients with AKI, the timing and rationale for initiation of RRT varies between critical care and noncritical care settings. In the noncritical care patient with AKI, RRT is regarded as a supportive therapy to be used for prevention of acute uraemic complications. Traditional indications for RRT have been based on criteria used for ESRD patients, such as refractory fluid overload or hyperkalaemia, severe metabolic acidosis, overt uraemia (pericarditis/encephalopathy/neuropathy) or symptomatic progressive azotaemia [24, 95].

However, this approach may not be appropriate in assessing the requirement for RRT in patients with critical AKI, particularly in the setting of multiorgan failure [82]. Thus, in contrast, the rationale for initiation of RRT in patients with critical AKI includes factors outside the traditional paradigm described above. Table 3 summarises the relative and absolute recommendations for dialysis [82, 96].

Cruz et al. suggest that the presence of specific “critical” conditions should be considered prior to determining whether to initiate RRT in patients with critical AKI. Examples given by the authors include clinical syndromes associated with high catabolic states such as septic shock, burns, or trauma or in other high “metabolic” scenarios such as gastrointestinal bleeding or rhabdomyolysis which often place a greater demand upon renal reserve [97]. Furthermore, based on studies demonstrating an association between positive fluid balance and worse outcomes in critically ill patients with AKI, sepsis, acute lung injury (ALI) and postsurgery, fluid balance management has been

identified as another important consideration in the management of patients in the critical care setting [98–104]. It has been hypothesised that fluid overload results in accumulation of fluid in the extracellular compartment due to leaky capillaries. This then leads to visceral oedema, which in turn promotes intra-abdominal hypertension and renal interstitial oedema, both of which may perpetuate AKI [105]. Finally, there is growing data suggesting an important role of the kidneys in the clearance of inflammatory molecules, which may be critical in the pathogenesis of ALI and acute respiratory distress syndrome (ARDS) as well as precipitating and/or exacerbating AKI [106]. While the “criteria” for initiation of RRT based on hypercatabolic states, specific clinical states, fluid status and a pro-inflammatory state remain unclear, these data may be seen to favour earlier initiation of RRT compared with traditional indicators for RRT.

10. Timing of Initiation of RRT—Haemodialysis

At present, there is no consensus regarding when to initiate RRT, resulting in a wide variation in clinical practice [17, 18].

A major barrier towards determining the optimal timing for RRT initiation has been the lack of agreement over the absolute indications for RRT. A review by Palevsky in 2008 highlighted a few common scenarios of AKI in a critical care setting, whereby the decision for RRT is debatable [24]. It remains unclear whether there is survival benefit in early consideration of RRT in the management of asymptomatic oliguric patients with progressive azotemia or in those with diuretic-resistant renal failure. Furthermore, there are no definitive criteria regarding what levels of hyperkalaemia, acidosis, oliguria or urea/creatinine are acceptable before RRT is initiated for survival benefit. As many of these “criteria” for RRT are based upon physician belief or practice and are derived from studies in ESRD patients, one could question their applicability to AKI patients. Thus, the recommendations published by the Acute Dialysis Quality Initiative (ADQI) for RRT initiation in AKI should be regarded as guidelines only [107]. Moreover, decisions on initiating dialysis in patients with AKI may also be influenced by nonmodifiable or external factors, including age, presence of comorbidities, resource availability, cost and physician preference [24]. A summary of the studies comparing timing of RRT is presented in Table 4 and discussed below.

Despite the presence of several studies attempting to address the optimal timing of RRT in patients with AKI [84–94, 108, 109], their interpretation should take into account the large heterogeneous populations in these studies. Most of the studies are retrospective observational data in which causality between timing of RRT in AKI and outcome cannot be established, and many of the prospective studies have methodological flaws, insufficient sample size and are therefore, underpowered to detect a difference between groups. The lack of a clear-cut definition for AKI, including what constitutes “early” and “late” initiation of RRT further compounds the difficulties in interpreting the data. Finally, an inherent methodological flaw in the literature is that

TABLE 3: Recommended relative and absolute indications for RRT in critically ill patients with AKI [82].

Dialysis indication	Criteria	Absolute/relative
Metabolic	Urea > 27 mmol/L	Relative
	Urea > 35.7 mmol/L	Absolute
	Hyperkalaemia > 6 mmol/L	Relative
	Hyperkalaemia > 6 mmol/L plus ECG changes	Absolute
	Dysnatraemia	Relative
	Hypermagnesaemia > 4 mmol/L	Relative
Acidosis	Hypermagnesaemia > 4 mmol/L plus anuria or areflexia	Absolute
	pH > 7.15	Relative
Anuria/oliguria	pH < 7.15	Absolute
	Risk (RIFLE class)	Relative
	Injury (RIFLE class)	Relative
	Failure (RIFLE class)	Relative
Uraemic complication	UO < 200 mL for 12 hrs or anuria	Absolute
	Encephalopathy	Absolute
	Pericarditis	Absolute
	Myopathy	Absolute
	Neuropathy	Absolute
	Bleeding	Absolute
Fluid overload	Diuretic responsive	Relative
	Diuretic resistant (with pulmonary oedema)	Absolute

studies have been limited to patients receiving RRT, thus excluding the patient group with AKI who die or recover without RRT. Therefore, any observed benefit of early RRT may be subject to bias by indication, as this may be due to inclusion or exclusion of patients with less severe illness and better prognosis regardless of treatment received.

Earlier studies using various cutoff values of serum urea and creatinine or urine output as criteria for initiation of dialysis regarded commencement of RRT at urea levels >75 mmol/L as late initiation of RRT, a level considered unacceptably high by current standards [83, 84]. In contrast, more recent studies define late initiation as a predialysis urea >25–28 mmol/L at time of RRT commencement [89, 94].

However, the reliance on urea, creatinine and fluid status/urine output as indicators for initiation of RRT in patients with AKI is controversial. In particular, serum urea, and creatinine are not true markers of kidney injury, require time to accumulate before detection at abnormal levels (48–72 hrs), and are often influenced by nonrenal factors such as muscle mass, rhabdomyolysis, gastrointestinal haemorrhage and drugs such as corticosteroids [110].

The timing of RRT in patients with AKI was first assessed by Teschan et al. in 1960, who evaluated the effects of “prophylactic” haemodialysis in patients with oliguric AKI [109]. In this case series, the mortality rate of patients with AKI in whom RRT was initiated prior to the urea reaching a level of 71.4 mmol/L was 33%. This compared favourably with a reported mortality rate of 25–40% in historical controls. Subsequent reports were based on retrospective case series comparing the effects of early to late RRT initiation over

a diverse range of urea cutoff levels (35–75 mmol/L), all of which suggested improved survival with early RRT [83–85].

Retrospective studies comparing early to late initiation of RRT have generally favoured early RRT. In a retrospective single-center study of 100 trauma patients, patients who developed AKI and received early initiation of RRT (urea < 22.5 mmol/L, mean urea at RRT initiation of 15 mmol/L) had improved survival (39% versus 20%; $P = .041$) compared with patients receiving late initiation of RRT (urea \geq 22.5 mmol/L, mean urea at RRT initiation of 34 mmol/L; $P < .0001$) [88]. A greater proportion of patients in the late initiation group had multiorgan failure and sepsis, but there were more oliguric patients in the early group (56%) than the late group (39%; $P < .01$). Furthermore, the rationale for starting RRT in the early or late ungroups was unclear. Two retrospective single-centre studies have compared initiation of RRT early (urine output < 100 mL for 8 hrs) or late (based on conventional biochemistry parameters) in postcardiac surgery patients with AKI. Both Elahi et al. (22% versus 43%; $P < .05$) and Demirkiliç et al. (23.5% versus 55.5%; $P = .016$) reported that early initiation of RRT was associated with lower mortality. The mean time to initiation of RRT was significantly different between early and late groups for both studies [90, 91].

Timing of RRT has also been assessed in ICU patients with septic shock and oliguric AKI. In a retrospective single-centre study, Piccinni et al. compared early initiation of RRT within 12 hrs of ICU admission ($n = 40$) to late initiation of RRT for conventional indications in historical controls ($n = 40$) [92]. Early initiation was associated with

TABLE 4: Summary of studies of timing of initiating of RRT [24].

Study	Size	Design	RRT criteria		Survival (%)		P value
			Early	Late	Early	Late	
Parsons et al. 1961 [83]	33	Retrospective	Urea 45-56	Urea > 75	75	12	N/A
Fischer et al. 1966 [84]	162	Retrospective	Urea ~ 56	Urea > 75	43	26	N/A
Kleinknecht et al. 1972 [85]	500	Retrospective	Urea < 35	Urea > 61	73	58	<.05
Conger et al. 1975 [86]	18	RCT	Urea < 26 or Cr < 442	Urea ~ 56 or Cr ~ 884	64	20	NS
Gillum et al. 1986* [87]	34	RCT	Urea < 22.5 and Cr ~ 442	“clinically” indicated Urea ~ 37.5 and Cr ~ 795	41	53	NS
Gettings et al. 1989 [88]	100	Retrospective	Urea < 22.5	Urea > 22.5 Urea > 42	39	20	N/A
Bouman** et al. 2002 [89]	106	RCT	<12 hrs after AKI diagnosis	K > 6.5 or pulmonary oedema	69 (LV) 74 (HV)	75 (LV)	see Table 5
Demirkilic et al. 2004 [90]	61	Retrospective	Urine output < 100 mL/8hr	Cr > 442 or K > 5.5 Urea ≥ 30	77	45	0.016
Elahi et al. 2004 [91]	64	Retrospective	Urine output < 100 mL/8 hr	Cr ≥ 250 Or K > 6 “conventional” indications	78	57	<.05
Piccinni et al. 2006 [92]	80	Retrospective	<12 hrs post-ICU admission	Urea > 28.5 Urea ≥ 24.5	55	28	<.05
Liu et al. 2006 [93]	243	Prospective	Urea ≤ 28.5 Urea ≤ 24.5	Or Cr ≥ 309 Or >5 days from ICU admission	65	59	.09
Bagshaw*** et al. 2009 [94]	1238	Prospective	Cr ≤ 309 Or <2 days from ICU admission	Or Cr ≥ 309 Or >5 days from ICU admission	63.4 (urea) 53.4 (Cr) 59 (time)	61.4 (urea) 71.4 (Cr) 72.8 (time)	<.001 (stratified by days since ICU admission)

SI units for urea (mmol/L) and Cr (μ mol/L) and K(mmol/L).

* Patients randomly assigned when serum Cr reached 707 μ mol/L to maintain predialysis urea/Cr to early and late criteria as listed.

** Patients assigned to 3 treatment groups: early high volume (HV) CVVHDF; early low volume (LV) CVVHDF; and late low volume (LV) CVVHDF.

*** Early and late RRT assessed separately by urea, Cr and time in ICU criteria.

TABLE 5: Time to RRT initiation, predialysis urea and patient cohort survival from Bouman et al. [89].

	Early high volume Group (<i>n</i> = 35)	Early low volume Group (<i>n</i> = 35)	Late low volume Group (<i>n</i> = 30)
Time between inclusion and first RRT (hrs)	6.0 (3.0–9.7)	7.0 (5.0–10.0)	41.8 (21.4–72.0) ^a
Predialysis urea before first RRT (mmol/L)	16.3 (13.7–20.6)	17.1 (14.4–23.5)	37.4 (22.0–41.4) ^a
Survival (%) ^b	74.3	68.8	75.0

Data presented as median and interquartile ranges.

^a*P* < .001 between late low volume group and early groups.

^b*P* = .8 between groups.

improved 28-day survival (55% versus 27.5%; *P* < .05), gas exchange, haemodynamics and ventilatory wean. However, information on the time between onset of AKI and initiation of RRT was not provided and patients in the late RRT group received a lower dialysis dose.

In a cohort of 98 patients with AKI after major abdominal surgery from the National Taiwan University Surgical ICU Associated Renal Failure (NSARF) Study Group database, Shiao et al. retrospectively applied a simplified RIFLE classification (use of GFR criteria only) to stratify patients receiving early (RIFLE-0/Risk) and late (Injury/Failure) RRT [108]. During the study period, indications for RRT were azotemia with uraemic symptoms (urea > 28 mmol/L and creatinine > 177 μmol/L), oligoanuria (urine output < 200 mL/8 hrs), refractory fluid overload, hyperkalaemia (*K* > 5.5 mmol/L) and metabolic acidosis (pH < 7.20). About 80% of patients commenced RRT for azotaemia or oligoanuria and 52% were classified into the early RRT group. Early initiation of RRT was associated with lower in-hospital mortality (43.1% versus 74.5%; *P* = .002) and predictors of mortality included late RRT (hazard ratio (HR) 1.846; *P* = .027), old age, cardiac failure and pre-RRT Sequential Organ Failure Assessment (SOFA) score. A major limitation of this study was that the RIFLE classification used and criteria for initiation of RRT were discrete and separate scoring systems. Therefore the validity of applying RIFLE to stratify into early or late RRT is questionable, especially given that urine output criteria were used in one and not the other.

Initial prospective trials purporting to compare early versus late dialysis can be criticised for having only achieved a comparison between intensive and non-intensive dialysis dose. In a small cohort of 18 patients with post-traumatic AKI during the Vietnam War [86], patients were matched on the basis of similarity of injuries and assigned sequentially and alternately to “intensive” dialysis to maintain a predialysis urea < 26 mmol/L and creatinine < 442 μmol/L, or to “non-intensive” dialysis in which RRT was initiated only when clinically indicated or if the urea and creatinine levels reached 56 mmol/L or 884 μmol/L, respectively. This latter group was assumed to have delayed initiation of dialysis, although details regarding time to initiation of dialysis were not provided. There was a trend toward improved survival in the intensive dialysis compared to non-intensive groups (64% versus 20%; *P* > .05) in this small study. However, these differences are more attributable to dose of dialysis rather than timing of initiation. Similarly, in a larger prospective controlled trial involving 34 patients with

critical AKI, Gillum et al. randomised patients with AKI to intensive haemodialysis targeting a maximum predialysis urea 22.5 mmol/L and creatinine 442 μmol/L, respectively, compared with non-intensive haemodialysis targeting a maximum predialysis urea and creatinine of <37.5 mmol/L and 795 μmol/L, respectively, [87]. While the mortality rates between intensive and non-intensive groups were similar (58.8% versus 47.1%; *P* < .05), the average time from onset of AKI until initiation of dialysis was similar between the intensive and non-intensive groups (5 ± 2 days versus 7 ± 3 days; *P* value not provided), and thus, the study failed to examine the effect of timing of initiation of dialysis. The authors concluded that there was no advantage of intensive dialysis in this cohort of patients. As the blood urea and creatinine prior to initiation of dialysis were similar in both groups, no comment can be made regarding the effect of timing of initiation of dialysis.

Bouman et al. randomised 106 critically ill patients requiring ventilator and inotropic support with AKI into 3 groups: (1) early high-volume CVVHDF (*n* = 35), (2) early low-volume CVVHDF (*n* = 35), and (3) late low-volume CVVHDF (*n* = 30) [89]. AKI was defined as creatinine clearance < 20 mL/min and urine output < 180 mL over 6hrs despite volume resuscitation. In the early group RRT was commenced within 12 hrs of diagnosis of AKI. In the late group, RRT was initiated when urea > 40 mmol/L or severe pulmonary oedema occurred. The median times and predialysis urea before first RRT sessions are summarised in Table 5. There were no significant differences in 28-day survival across the 3 groups (74.3% versus 68.8% versus 75%; *P* = .80) and renal function recovered in all survivors at hospital discharge except one patient in the early low-volume group. While this study achieved significant separation in timing of initiation of early versus late dialysis and suggests that timing of initiation and dose of dialysis had no effect on outcome, there were significant limitations to this study. Late RRT was not as late in comparison to other studies. Fifteen patients in the late group (50%) commenced RRT with urea < 40 mmol/L due to severe pulmonary oedema and the early group did not receive RRT as early as originally planned due to the requirement for measured creatinine clearance < 20 mL/min before inclusion. Furthermore, the overall mortality rate of 27% was unexpectedly low, reflecting possibly a lower disease burden within the patient cohort.

Data from prospective observational studies on timing of RRT is also conflicting. In a multicentre study based on PICARD, Liu et al. assessed the effects of timing of initiation

of dialysis in 243 patients with severe AKI and no pre-existing CKD [93]. Patients were stratified into early (urea ≤ 28.5 mmol/L; $n = 122$) or late RRT (urea > 28.5 mmol/L; $n = 121$) groups based on urea at initiation of RRT. Late initiation of RRT was associated with an increased relative risk death (RR 1.85; 95% CI 1.16–2.96) in comparison to the early group, despite a lesser burden of organ failures.

In a large prospective observational multicentre study from the BEST Kidney cohort, Bagshaw et al. compared early versus late initiation of RRT according to urea (24.2 mmol/L), creatinine (309 μ mol/L) and time after ICU admission (early < 2 days, delayed 2–5 days, late > 5 days) in 1238 patients with AKI requiring RRT [94]. Stratification of RRT timing by urea level showed similar mortality for early and late initiation (63.4% versus 61.4%; OR 0.92; 95% CI 0.73–1.15; $P = .48$), but when stratified by creatinine, late initiation of RRT was associated with lower mortality (71.4% versus 53.4%; OR 0.46; 95% CI 0.36–0.58; $P < .001$). When assessed for timing relative to ICU admission, late RRT was associated with higher mortality than delayed or early RRT, respectively, (72.8% versus 62.3% versus 59%; $P < .001$), as well as longer duration of RRT, hospital stay, and greater rates of dialysis dependence. The authors argued the unreliability of AKI biomarkers such as urea and creatinine which vary with clinical states such as fluid overload, GI haemorrhage and muscle mass. They felt that this study supported early initiation of dialysis therapy as defined as time from ICU admission for AKI until such time as more reliable biomarkers of renal injury are available to facilitate early and accurate diagnosis of AKI.

Although not designed to assess the effects of timing of RRT, data from the RENAL and ATN studies have also suggested similar findings with regards to late dialysis as defined by days from time of ICU admission [78]. RRT was commenced much earlier in the RENAL study than the ATN study (median time from ICU admission to first RRT 2.1 days vs 6.7 days). However, just over 60% of patients in the ATN study had received some form of RRT prerandomisation (0% in RENAL) and predialysis urea levels before RRT initiation were similar (24.2 mmol/L versus 23.8 mmol/L) in the RENAL and ATN studies respectively. Mortality in the RENAL study was lower (45% mortality at 90 days) than that of the ATN study (53% mortality at 60 days) and the rate of renal recovery or RRT independence in survivors at 28 days was far superior in the RENAL study (87% versus 55%). Similar differences in favour of the RENAL study are noted when comparisons of renal outcomes at day 60 and 90 between the two studies are made. However, other factors such as differences in patient populations or treatment-related factors between the two trials could account for these findings. For example, 100% of patients received CRRT in the RENAL trial, while 30% of patients in the ATN trial were treated with intermittent HD as the first RRT of choice. Therefore, no firm conclusions can be drawn at present.

Finally, a recent meta-analysis of the timing of RRT in patients with AKI has reviewed 23 studies, (5 randomised or quasirandomised trials and 1 prospective and 16 retrospective cohort studies) but did not include the more recent large

prospective trial by Seabra et al. [111]. When analysis was confined to randomised trials, early RRT was associated with a 36% reduction in mortality, but this did not reach statistical significance. In cohort studies, with larger sample size, early RRT was associated with a significant 27% reduction in mortality risk which did reach statistical significance. Due to the significant heterogeneity between studies (including use of multiple definitions of RRT) and possible publication bias, the authors concluded that while early initiation of RRT in AKI might be associated with better patient survival, the results were inconclusive and larger adequately powered studies were required.

Therefore, the literature on timing of initiation of dialysis has significant limitations and although recent studies suggest that early RRT may be associated with better outcomes, no definitive conclusions can be made. Currently, the decisions on initiation of RRT must be made within the context of each patient, taking into account age, comorbidities, severity of illness and overall clinical state.

11. Peritoneal Dialysis (PD) and AKI: Current Status

Compared with HD/CRRT, PD is often overlooked as a form of RRT for AKI in developed countries. In the BEST Kidney study, PD was utilised in only 3.2% of patients requiring RRT, compared to 80.2% and 16.9% for CRRT and intermittent HD, respectively, [16]. However, driven by resource availability, PD is often the only option available for treatment of AKI in developing countries, with potential benefits that include ease of administration, technical simplicity, low bleeding risk, cardiovascular stability, and the absence of an extracorporeal circuit. Furthermore, PD has proven to be a vital resource in situations of natural disaster and massive crush injury whereby basic infrastructure requirements such as adequate power, water supply and manpower are often unavailable [112]. Finally, the use of PD in AKI may be associated with more rapid renal recovery, as suggested by a randomised controlled trial reporting that high volume PD (HVPD) was associated with a significantly shorter time to recovery of renal function (7.2 ± 2.6 days) compared with daily HD (10.6 ± 4.7 days; $P = .04$) [113]. The potential for more rapid recovery of renal function is an attractive but relatively unstudied benefit of PD which warrants future investigation. Although only observational data on this aspect of PD and AKI exist, there is biological plausibility given that PD is associated with superior preservation of residual renal function in ESRD patients [53, 114], and is considered a less inflammatory, more physiological form of RRT characterised by greater cardiovascular stability and absence of negative phenomena such as myocardial stunning [78, 79, 115, 116].

The declining use of acute PD in developed countries is predominantly the result of a widely held perception that PD fails to achieve adequate solute clearance, particularly in hypercatabolic patients [117, 118]. Consequently, the lack of exposure to acute PD has further compounded the situation, resulting in a growing loss of physician familiarity with PD

prescription for AKI, techniques, complications and access issues. Other perceived shortcomings of acute PD include the technical expertise required for PD catheter insertion, prerequisite requirement for an intact peritoneal membrane which precludes patients with major abdominal surgery or trauma, risk of peritonitis, protein loss, hyperglycaemia potential for diaphragmatic splinting and inferior fluid balance control [119]. However, limited studies of PD and AKI in selected patients have not reported significant problems with ultrafiltration, hyperglycaemia, or protein loss, and report peritonitis rates that are comparable to catheter infection rates in patients receiving daily HD [113, 120].

12. Peritoneal Dialysis and AKI—Dose and Small Solute Clearance and Techniques

Inadequate clearance and RRT dose in critically ill patients with AKI is associated with worse outcomes [121–123]. Unfortunately, the issue of RRT dosing and clearance in acute PD is fraught with controversy. Firstly, there is no consensus on target RRT dose in AKI. Secondly, no studies have examined the effects of different doses of acute PD on outcomes in AKI. Target doses have instead been inferred from studies based on HD/CRRT. Thirdly, whilst RRT dose in AKI is traditionally measured as small-solute (i.e., urea) clearance, the validity of urea kinetic modelling and the derived Kt/V_{urea} formula is questionable given that it was originally designed for use in ESRD patients. Specific criticisms of the application of Kt/V_{urea} to unstable patients with AKI include the inherent unreliability of urea in hypercatabolic states, difficulties in accurately determining volume of urea distribution (often underestimated), and the requirement for a steady state (usually 6 weeks after starting dialysis in ESRD) [124, 125]. However, despite the limitations outlined above, standardised Kt/V_{urea} remains the most commonly used measure of dose for all dialysis modalities in AKI due to lack of better alternatives.

Based on a prospective study from the Cleveland Clinic Foundation (CCF), the accepted minimum RRT dose for AKI is a single pool Kt/V_{urea} of 1.0 per session, which is equivalent to a standardised Kt/V_{urea} of 2.10 per week (assuming 3–4 sessions of intermittent HD per week) [121]. In this nonrandomised cohort of 844 ICU patients with AKI and requiring first time RRT (intermittent HD), improved survival was observed in patients receiving $Kt/V_{\text{urea}} > 1.0$ per HD session. Despite conflicting results from subsequent trials by Schiffel et al. [123] and Palevsky et al. [23], a standardised Kt/V_{urea} of 2.10 is now also regarded as an acceptable minimum target dose of PD for AKI [119]. However, it must be remembered that this is a general recommendation only and not a fixed target for all patients, as ultimately the optimal RRT dose for AKI remains unclear.

Selection of an appropriate PD technique is vital for achieving adequate solute clearance and various techniques from chronic PD have been adapted and applied to AKI [126]. Use of flexible PD catheters and techniques such as continuous PD (CPD), tidal PD (TPD) and HVPD

have demonstrated the ability to achieve adequate solute clearances.

CPD is similar to continuous ambulatory PD (CAPD) in ESRD patients, in that it involves long 2–6 hr dwells of up to 2 L dialysate (roughly 4 exchanges/day) [127]. TPD consists of an initial infusion of dialysate (usually 2 L volume) into the peritoneal cavity. This is followed by partial drainage (50%) of the dialysate (tidal drain volume) which is then replaced by fresh dialysate (tidal fill volume). Thus a reserve volume of dialysate perpetually remains in the peritoneal cavity for the duration of the tidal cycle. TPD is aimed at improving dialysis efficacy by minimising time lost during dialysate outflow, increasing dialysate flow rate, and facilitating greater middle molecule clearance by allowing a longer duration of dialysate contact with the peritoneum [128]. In a randomised cross-over study, Chitalia et al. reported a standardised Kt/V_{urea} of 1.80 ± 0.32 and 2.43 ± 0.87 for CPD and TPD, respectively [118].

HVPD is a form of continuous PD therapy designed to achieve high small solute clearance through frequent 2 L exchanges (18–48 exchanges/day) via a flexible Tenckhoff catheter and automated cyler (total dialysate volume 36–70 L/day) [129]. In a prospective study of 30 patients with AKI, Gabriel et al. reported a delivered standardised Kt/V_{urea} of 3.85 ± 0.62 , using about 36–44 L dialysate/day. Ultrafiltration volume was also adequate at 2.1 ± 0.62 L/day, and serum albumin levels remained stable [129].

13. Peritoneal Dialysis and AKI—Middle Molecule Clearance

With recent shifts in philosophy towards middle molecule clearance (500–2000 Da) in AKI [130], PD may be potentially advantageous over HD, as it is generally assumed that middle clearance is superior with PD [131]. However, this may no longer be true with modern-day use of high flux synthetic dialysis membranes [132], and there are no studies available on middle molecule clearance in acute PD. Peritoneal clearance of middle molecules is dependent on both convection and diffusion and is largely determined by the dialysate dwell time [133]. Therefore, increased frequency of exchanges to improve small molecule clearance may impact negatively upon middle molecule clearance in acute PD. Furthermore, the peritoneum is a complex biological entity which actively metabolises and secretes proteins, and this may result in clearance of very different types of middle molecules in comparison to dialysis membranes and filters. Currently, dialysis dose remains determined largely by small solute clearance with no recommendations for middle molecule clearance, and it is suggested that continuous forms of PD therapy which avoid “dry” dwell times such as HVPD be employed for treatment of AKI [119].

14. Peritoneal Dialysis and AKI—Comparison to HD/CRRT

There are very few head-to-head comparison of PD and HD in AKI, and the results suggest that with use of correct

technique, PD is comparable to HD except in one study. Phu et al. randomised patients with AKI requiring dialysis secondary to sepsis/malaria to haemofiltration ($n = 34$) or PD ($n = 36$) [134]. PD was administered via a rigid catheter with use of 2 L exchanges and 30 minute dwell times (total approximately 70 L/day) and an average dialysis session length of 26 hrs. Dialysis dose and solute clearances were not reported. Compared to haemofiltration, PD was associated with increased mortality (47% versus 15%; $P = .005$), risk of death (OR 5.1; 95% CI 1.6–16), and increased risk of requiring future dialysis (OR 4.70 95% CI 1.3–17). The authors concluded that haemofiltration was superior to PD for treatment of infection-associated AKI. However, this study had significant limitations including the use of a rigid catheter, PD exchanges being performed manually with short dwell times, the use of PD solutions which were prepared by the hospital pharmacy and no comparison of dialysis dose or clearance across the different modalities.

Gabriel et al. compared both CPD ($n = 60$) and HVPD ($n = 60$) to daily HD ($n = 60$) in two separate randomised trials [113, 135]. In the first study comparing CPD and daily HD, standardised Kt/V_{urea} was significantly lower with CPD compared to HD (3.59 ± 0.61 versus 4.76 ± 0.65 ; $P < .01$). There were no differences in metabolic control, survival (58% versus 52%; $P = .48$) or dialysis dependence at 30 days (17% versus 21%; $P = .45$) between CPD and HD groups, respectively. However, patients in the CPD group had a shorter duration of therapy (5.5 days versus 7.5 days; $P = .02$) [135]. Similarly in the second study comparing HVPD and daily HD, standardised Kt/V_{urea} was lower with HVPD in comparison to HD (3.6 ± 0.6 versus 4.7 ± 0.6 ; $P < .01$). Metabolic control, mortality (58% versus 53%; $P = .71$) and recovery of renal function at 30 days (83% versus 77%; $P = .45$) were similar between the HVPD and daily HD groups. Once again, HVPD was associated with a significantly shorter time to recovery of renal function (7.2 ± 2.6 days versus 10.6 ± 4.7 days; $P = .04$) [113].

15. Future Directions: Novel AKI Biomarkers

Biomarkers were initially discovered with use of screening cDNA microarray technology, which identified several gene subsets undergoing rapid upregulation within hours of initial renal injury [136, 137]. Our current understanding of biomarkers is that two groups exist: (1) proteins/enzymes which are normal constituents of renal tubular epithelial cells and are released into the urine as a result of cellular injury (e.g., cystatin C), and (2) inducible proteins which are upregulated in response to cellular injury and are otherwise not normally present (e.g., neutrophil gelatinase-associated lipocalin).

A recent 2008 systematic review has identified several serum and urinary biomarkers including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CysC), interleukin-18, kidney injury molecule-1 (KIM-1) and N-acetyl- β -D-glucosaminidase (NAG), with promising utility for early diagnosis of AKI, diagnosis of established AKI and prediction of outcomes from AKI (requirement for RRT

and mortality). However, several issues remain and these biomarkers require further validation in large studies of heterogeneous populations, particularly with regards to the applicability of biomarkers to different types of AKI and their additional prognostic value over and above currently used clinical parameters [138]. In addition to this, recent evidence suggests that the predictive ability of biomarkers for AKI is reduced in patients with CKD (baseline eGFR < 60 mL/min per 1.73 m^2) [139].

As an example, NGAL is highly sensitive for the early diagnosis of AKI in children undergoing cardiac surgery and patients undergoing renal transplantation [140, 141]. Plasma NGAL is also predictive of the requirement for RRT in critically ill adult patients with AKI in the ICU [142]. However, when applied to more heterogeneous populations such as the emergency department [143], adults undergoing cardiac surgery [144], and both adults or children in the ICU [142, 145, 146], the ability of NGAL to detect AKI early is reduced. Furthermore, there is evidence suggesting that NGAL is elevated in the presence of sepsis, multiple pre-existing comorbidities and according to the severity of illness, thus confounding its association with AKI [142, 145, 146].

Therefore, further research is required to validate these biomarkers, and ultimately, it would seem that a biomarker panel for AKI which utilises the strengths of each biomarker is required to accurately identify patients with AKI in a timely fashion to allow risk stratification and predict outcomes and the need for RRT. In the research setting and in conjunction with the RIFLE/AKIN classification, biomarkers of AKI may assist in identifying patients at risk of AKI at an earlier stage and may allow clearer delineation of early versus delayed time points for initiation of RRT which can then be applied in a prospective randomised controlled trial.

16. Summary

Standardised definitions for AKI, namely, the RIFLE/AKIN classifications, are an essential tool for understanding the epidemiology, aetiology, appropriate management, and prognosis of AKI. Critical and noncritical AKI is highly prevalent with a rising incidence and is associated with high mortality, particularly in the ICU setting. The RIFLE/AKIN classifications have been shown to be good prognostic tools for morbidity and mortality associated with AKI.

The key management controversy in relation to AKI lies around the timing of initiation of RRT. Based on current evidence, the optimal timing for initiation of RRT for patients with AKI remains uncertain and no recommendations can be made beyond the traditional indications currently employed in clinical practice. Well-designed randomised controlled trials of early versus late RRT initiation can be achieved by using the RIFLE consensus definition of AKI to ensure that the early and late treatment arms are uniformly matched with regards to severity of AKI and the use of validated biomarkers of AKI which allows for early identification and randomisation of suitable patients with AKI. Furthermore, treatment decisions should be made upon predetermined criteria (biochemical or others). Finally, in order to reduce

allocation bias, patients who avoid RRT or die with AKI having not received AKI should be included and analysed on an intention-to-treat basis.

Regarding RRT options for AKI, in patients with an intact peritoneal membrane and AKI, PD seems an acceptable treatment choice with potential benefits. A major barrier towards more widespread use of PD is the lack of consensus on optimal dose of PD and controversial application of data inferred from studies in HD. Further studies of PD in AKI addressing dose, importance of middle molecule clearance and potential PD-related complications such as peritonitis-risk, fluid balance and increased protein loss are required for this therapy to be accepted more widely by clinicians.

Finally, research around emerging AKI biomarkers is promising in identifying markers of early renal injury, which when combined with RIFLE/AKIN classifications may allow timely recognition of AKI to facilitate the much needed trials of early versus late initiation of RRT.

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Review Article

Peritoneal Dialysis in Renal Replacement Therapy for Patients with Acute Kidney Injury

Naheed Ansari

Division of Nephrology, Department of Medicine, Jacobi Medical Center, 1400 Pelham Parkway, South Bronx, NY 10461, USA

Correspondence should be addressed to Naheed Ansari, naheed.ansari@nbhn.net

Received 16 August 2010; Revised 8 February 2011; Accepted 21 March 2011

Academic Editor: Achim Jörres

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Peritoneal dialysis (PD) was the first modality used for renal replacement therapy (RRT) of patients with acute kidney injury (AKI) because of its inherent advantages as compared to Hemodialysis. It provides the nephrologist with nonvascular alternative for renal replacement therapy. It is an inexpensive modality in developing countries and does not require highly trained staff or a complex apparatus. Systemic anticoagulation is not needed, and it can be easily initiated. It can be used as continuous or intermittent procedure and, due to slow fluid and solute removal, helps maintain hemodynamic stability especially in patients admitted to the intensive care unit. PD has been successfully used in AKI involving patients with hemodynamic instability, those at risk of bleeding, and infants and children with AKI or circulatory failure. Newer continuous renal replacement therapies (CRRTs) are being increasingly used in renal replacement therapy of AKI with less use of PD. Results of studies comparing newer modalities of CRRT versus acute peritoneal dialysis have been conflicting. PD is the modality of choice in renal replacement therapy in pediatric patients and in patients with AKI in developing countries.

1. Introduction

Acute kidney injury occurs in hospitals and is seen in up to 5% of hospitalized patients. 0.5% of the patients with AKI require dialysis [1]. Acute kidney injury occurs more frequently in intensive care unit (ICU) as part of the multiorgan failure and is usually associated with higher mortality rate and increased dialysis requirement in ICU setting.

There are two major types of dialysis available these days: Peritoneal dialysis (PD) and Hemodialysis (HD). PD was the modality first used for treatment of AKI [2]. Intermittent PD was widely used in the 1970s due to its various advantages. Later, continuous PD therapies became available through automated cycling machines (cyclers).

In western countries, peritoneal dialysis is not commonly used in dialytic management of acute kidney injury due to the availability of newer HD techniques and development of continuous renal replacement therapies (CRRTs). The new technological advances in the extracorporeal circuit of HD successfully compete with traditional advantages of PD. The limiting factors are the slow efficiency of the procedure, limited value in patients with recent intra-abdominal surgery

or intra-abdominal pathology, and rise in intra-abdominal pressure which may compromise pulmonary function. The rise in intra-abdominal pressure may have deleterious effects in patients with acute lung injury or the acute respiratory distress syndrome (ARDS). High glucose content of the PD solution can evoke hyperglycemia and other metabolic derangements. Increased carbon dioxide production is associated with an increase in respiratory quotient to >1.0 which may exacerbate respiratory failure in patients with compromised lung function.

This paper covers the use of peritoneal dialysis in the setting of AKI especially regarding indications, various techniques, prescription of acute PD, and various complications encountered during the procedure.

2. Indications of Acute PD

The indications for acute PD can be divided into two groups: renal and nonrenal.

2.1. Renal Indications. Peritoneal dialysis is an advantageous modality for RRT in AKI (Table 1). It is indicated in both

TABLE 1: Renal indications of peritoneal dialysis in AKI.

-
- (1) RRT in the treatment of AKI in children
 - (2) Hemodynamically unstable patients
 - (3) The presence of bleeding diathesis or hemorrhagic conditions contraindicating placement of vascular access for hemodialysis or anticoagulation
 - (4) Patients with difficult vascular access placement
 - (5) Removal of high molecular weight toxins (10 kD)
-

TABLE 2: Nonrenal indications.

-
- (1) Acute pancreatitis
 - (2) Clinically significant hypothermia or hyperthermia
 - (3) Refractory heart failure
 - (4) Liver failure
 - (5) Infusion of drugs and nutrients as a supportive therapy in critically ill patients
-

renal and nonrenal-related conditions where it is indicated due to advantages of the PD modality. PD can easily meet treatment goals for AKI patients, maintaining adequate fluid, electrolyte, and acid base balances. It also allows the use of other supportive measures like use of intravenous infusion of sedatives, vasopressors in hemodynamically unstable patients, and total parenteral nutrition to continue without limitation until the recovery of renal function. However, as compared to HD, PD is less effective in severe acute illnesses like pulmonary edema, poisoning, or drug overdose, and hypercatabolic states.

Usually small molecular clearance is lower with PD than that achieved with conventional HD. This is because small molecule concentration in peritoneal dialysate is approximately 30%–50% of the equivalent serum values after 1 hour of PD and 50%–80% after a 4-hour dwell [3]. On the other hand, the clearance of higher molecular weight solutes is higher with continuous PD than with HD [4].

The ultrafiltration rate is maximal at the beginning of a PD exchange when glucose concentration is at its maximum. As the glucose is absorbed and its concentration further drops due to movement of ultrafiltrate into the peritoneal cavity, there is further fall in the ultrafiltration rate. As a result of which the intraperitoneal volume peaks at about 120–180 minutes of dwell.

Acute PD is the preferred mode of RRT in children [5]. In patients with hemodynamic instability due to various reasons, PD is preferable to conventional HD [6]. PD can meet treatment targets for AKI and can maintain adequate fluid, electrolyte, solute clearances, and acid base balance in patients with AKI.

Earlier studies have shown that patients treated with PD had lower mortality rates and a higher incidence of renal recovery than did similar patients treated with HD [7, 8].

2.2. Nonrenal Indications for Acute PD. PD can be used in various extra renal conditions (Table 2). In acute hemorrhagic pancreatitis, PD helps in the removal of bioactive

TABLE 3: Peritoneal dialysis is contraindicated in the following clinical Situations.

-
- (1) Recent abdominal surgery
 - (2) Pleuroperitoneal communication
 - (3) Diaphragmatic severe respiratory failure
 - (4) Life-threatening hyperkalemia not responding to medical therapy
 - (5) Extremely hypercatabolic state
 - (6) Severe volume overload in a patient not on a ventilator
 - (7) Severe gastroesophageal reflux disease
 - (8) Low peritoneal clearance
 - (9) Fecal or fungal peritonitis
 - (10) Abdominal wall cellulitis
 - (11) AKI in pregnancy
-

substances presumed to be responsible for systemic inflammation associated with acute pancreatitis [9–11]. However, a multicenter prospective study found no difference in the mortality or complication rate for patients who received standard supportive therapy with or without hourly 2-L peritoneal dialysis exchanges for 3 days [12].

Clinically significant hypothermia or hyperthermia can be managed with PD where heated or cold peritoneal solutions can be used to maintain core temperature. This is usually done in patients with either hypothermia or hyperthermia who do not respond to conventional therapy [13–15].

Congestive Heart Failure (CHF) refractory to medical therapy can be treated with peritoneal dialysis when there is inadequate response to diuretics in severely volume overloaded state [16–19].

In patients with fulminant liver failure, PD has been used because it avoids need for anticoagulation. It corrects fluid and electrolyte disorder and may reduce the risk of hypoglycemia and hypothermia as compared to charcoal hemoperfusion [9]. PD may help in the removal of toxins like ammonia, bilirubin, and free fatty acids.

PD may be used as route for delivery of nutrients like glucose and amino acids and certain drugs in severely ill patients admitted to intensive care unit. This route alone may not be enough in severely malnourished individuals [20–22].

3. Contraindications to Acute PD

There are several relative contraindications to acute PD (Table 3), such as recent abdominal surgery, peritonitis (fecal or fungal), and known pleuroperitoneal fistula. Presence of abdominal drain increases the risk of local infection. The presence of abdominal hernia or intra-abdominal adhesions makes PD difficult.

The use of PD is relatively contraindicated in the presence of the abdominal wall cellulitis which may progress to peritonitis. It is also contraindicated in severe gastroesophageal reflux disease, and in adynamic ileus which may decrease efficiency of peritoneal dialysis. In patients with relative respiratory insufficiency, the use of intraperitoneal fluid may

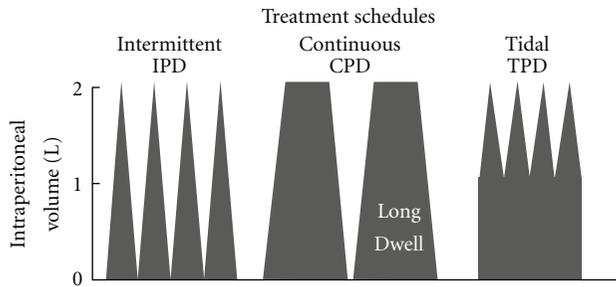


FIGURE 1: Basic mechanisms operating in various peritoneal dialysis regimens.

increase intra-abdominal pressure and hence compromise lung function and respiratory gas exchange. Acute PD is ineffective in treatment of life threatening hyperkalemia [23]. Use of PD in life threatening Hyperkalemia should be reserved in situations when HD is not available. It is not the best modality of RRT in hypercatabolic patients with a high load of azotemia [24].

4. Regimens of Acute PD

PD can be performed intermittently or continuously and either manually or via an automated device [25]. Performance of acute PD requires only an intact peritoneal cavity [25]. Various regimens of acute PD are shown in Figure 1.

4.1. IPD (Classical Intermittent Peritoneal Dialysis). IPD is the most commonly used regimen of PD. The usual exchange time is 1 hour. It can be done either manually or by using a cycling device programmed to deliver a predetermined volume of peritoneal dialysis fluid and to drain the peritoneal cavity at fixed intervals. Short exchanges of 1-2 L performed in sessions of 16–24 hours twice or three times weekly can deliver doses of about 40–60 L per session (80–180 L/week). This type of PD has been extensively used in ARF [24, 26].

4.2. CPD (Continuous Peritoneal Dialysis). It is a modified form of CAPD in which manual exchange is done every 3–6 hours depending upon patient clearance and fluid removal requirements. It provides PD in an inpatient setting [27]. It is a simple procedure, has low cost, and is less labor intensive. It differs from IPD because it uses relatively long dwell times and uses multiple daily exchanges, in which peritoneal dialysis fluid is instilled and drained continuously every 3–6 hours. These exchanges can be performed manually or by a cycler. It maintains a low flow continuous system, which itself maintains stable blood levels of nitrogenous products. It is commonly done in developing countries because of the low cost and is less labor intensive. The disadvantage is that clearances may not be adequate especially in hypercatabolic patients because of a lower dialysate flow rate.

4.3. TPD (Tidal Peritoneal Dialysis). With this technique, after an initial exchange of the peritoneal cavity with peritoneal dialysis fluid, only a portion of dialysate is drained.

The drained volume is replaced by fresh dialysate with each cycle leaving a variable amount of dialysate in constant contact with the peritoneal membrane until the end of dialysis session when the fluid is drained as completely as possible. Tidal PD was originally designed to optimize solute clearances [28] by leaving constant tidal volume of dialysate in the peritoneal cavity throughout the dialysis session. Clinical studies have not confirmed increased solute clearance with use of TPD [29–31]. The tidal volume is usually one half of initial filling by the cyclor of a large (2-L) volume of solution during a dialysis session that lasts for 8–10 hours.

5. Peritoneal Access

Access is one of the important determinants of successful peritoneal dialysis. A peritoneal catheter is inserted in the peritoneal cavity to gain access to the peritoneal space for initiation of dialysis.

There are two different types of peritoneal catheters.

(1) *Semirigid Acute Catheter.* This can be inserted at bedside by a nephrologist and does not need surgical help [32]. It is usually inserted under local anesthesia and hence avoids complications of general anesthesia. The major disadvantages are high risk of infection, discomfort in an awake patient, and risk of bowel perforation. This type of catheter cannot be left in place for more than 72 hours due to high risk of peritonitis [32, 33].

(2) *Cuffed Permanent Catheter.* This is usually a Tenckhoff catheter. It has a much lower risk of infection, can be used immediately after insertion, has a lower risk of bowel perforation, and avoids the need for repeated punctures in intra-abdominal cavity as with semirigid catheters. This catheter is preferred in patients with acute PD on a cycler because this catheter does not trigger alarms on CCPD as sometimes experienced with use of semirigid catheters.

This type of catheter is placed under local anesthesia and requires surgical expertise for insertion. The hemodynamic status of the patient may limit the feasibility of this catheter especially in sick ICU patients.

6. Acute Peritoneal Dialysis Prescription

After the insertion of an acute or chronic peritoneal catheter preferably chronic if possible, PD orders need to be individualized depending upon hemodynamic status of the patient, laboratory work, and volume status. A standardized form with complete and clear specifications for procedure should be used if available (Table 7). PD orders must be reviewed and written daily as patients with AKI can fluctuate their acid base and electrolyte milieu. The components of PD orders are multiple and involve the following (Table 4).

A usual dialysis session lasts for 48–72 hours and each exchange is done over one hour. A typical session of acute peritoneal dialysis has 48–72 exchanges. However, the length of a PD session can vary depending on the cause and

TABLE 4: Components of acute PD prescription.

(1) Length of the dialysis session
(2) Dialysate composition
(3) Exchange volume
(4) Inflow and outflow periods
(5) Dwell time
(6) Number of exchanges
(7) Additives
(8) Monitoring of fluid balance

TABLE 5: Composition of peritoneal dialysis fluid.

(1) Sodium 132–134 (mmol/L)
(2) Potassium 0–2 (mmol/L)
(3) Calcium 1.25–1.75 (mmol/L)
(4) Magnesium 0.25–0.75 (mmol/L)
(5) Chloride 95–106 (mmol/L)
(6) Lactate 35–40 (mmol/L) or HCO ₃ (34 mmol/L)
(7) Glucose 1.5–4.25 (g/dL)
(8) pH (Neutral and physiological in newer peritoneal dialysis fluid preparations)

duration of AKI, need for water and solute removal, and the risk of infection.

PD fluid (PDF) is available in standard monohydrate glucose concentrations of 1.5, 2.5, and 4.25 g/dL and various electrolyte concentrations (Table 5). PD fluid should be warmed to body temperature prior to infusion to avoid discomfort and enhance solute transport.

To obtain better ultrafiltration, it is reasonable to initiate acute PD in most patients with the 2.5 g/dL PD fluid. An initial glucose concentration of 1.5 g/dL may be more appropriate in patients with only moderate amounts of fluid overload and in those who are hemodynamically unstable.

PD fluid with a higher glucose concentration can be substituted based on the amount of fluid removed and the patient's hemodynamic parameters. With a standard regimen, such as a two-liter exchange volume and one-hour dwell time, the following average amounts of fluid can be removed over a 24-hour period:

- (i) 2.5 liters with 1.5 g/dL glucose,
- (ii) 4.5 liters with 2.5 g/dL glucose,
- (iii) 8.5 liters with 4.25 g/dL glucose.

Various types of glucose concentration are available to use in acute PD prescription (Table 6).

- (i) 1.5 g/dL PD fluid contains 27.2 grams of glucose in 2 liter bag. It usually gives ultrafiltration of 50–150 mL per hour when using a 2-L exchange volume over 60-minute exchange time. It is the most commonly used fluid in acute PD.
- (ii) 2.5 g/dL PD fluid can give UF of 100–300 cc per exchange volume of 2 L and exchange time of one

hour. 2 L bag of 2.5 g/dL of PDF contains 45.4 grams of glucose.

- (iii) 4.25 g/dL PD fluid contains 77.2 grams of glucose in 2 liter bag and can give rise to UF of 300–400 cc/exchange. This hypertonic fluid is usually used in patients with volume overload like CHF. Continued use of the 4.25 g/dL fluid could result in removal of 7.2–9.6 L per day which can be very dangerous since it can induce hemodynamic instability due to massive ultrafiltration, and high glucose content of hypertonic PDF is deleterious to the peritoneal membrane. This degree of UF is not required usually and one can use combination of glucose concentrations to attain level of UF desired.

The most practical way to achieve fluid removal is by mixing and matching low and high glucose concentration adequate fluid. Once the patient is euvoletic, the dialysis fluid should be switched to a glucose concentration of 1.5 g/dL and the rate of exchange should be slowed.

Exchange volume is the amount of PD fluid instilled into the peritoneal cavity during an exchange. The volume instilled depends on the intraperitoneal pressure (IPP), the presence of pulmonary disease or mechanical ventilation, and the presence of abdominal hernia. An average sized adult can tolerate 2-L exchanges but in smaller patients, those with pulmonary disease or those with abdominal or inguinal hernias, the exchange volume should be reduced. In pediatric patients with AKI requiring dialysis, exchange volume is based on body weight. Usually volume of 30 mL/Kg body weight is used for PD.

The intraperitoneal pressure rises linearly with higher volume of intraperitoneal fluid used. Intraperitoneal pressure is higher in patients with higher body mass index. Age, gender, weight, height, body surface area (BSA), and Diabetes Mellitus, do not correlate with IPP [34]. The peritoneal dialysis fluid volume should be reduced in patients with a pulmonary disease (like pneumonia or COPD) or respiratory failure. The rise in intra-abdominal pressure due to PD fluid may hamper diaphragmatic excursions needed for respirations. Similarly, patients with abdominal wall or inguinal hernia may require less volume to prevent a rise in intra-abdominal pressure. Low PDF volume is used after the PD catheter placement to avoid leakage. The volume is gradually increased over the next three or four days as tolerated by the patient.

Inflow time is the time required to instill the PD fluid into the peritoneal cavity under the effect of gravity. The time is usually 10–15 minutes [25]. It depends on amount of fluid to be infused, height of the bag from patient's abdomen, and resistance to flow due to the kinking of the catheter or reduced bowel motility. The inflow time should be kept to minimal to maximize efficiency of peritoneal dialysis.

Dwell time is the time period for which the exchange volume stays in the intraperitoneal cavity for diffusion and ultrafiltration which is usually 30 minutes in single acute peritoneal dialysis exchange. A dwell time of less than 30 minutes is usually not adequate [35]. The dwell time for patients on acute CPD is about 3–6 hours which can be

TABLE 6: Dialysis fluid glucose concentration.

Glucose (monohydrate) g/dL	Fluid osmolarity mOsm/L	Ultrafiltrate volume mL per exchange over one hour
1.5 g/dL	346	50–150
2.5 g/dL	396	100–300
4.25 g/dL	485	300–400

shortened to increase the total number of exchanges to improve solute clearance.

Outflow time is the time required to drain effluent dialysate after dwell which takes place under effect of gravity. It is usually takes 20–30 minutes to complete [25]. Outflow is affected by volume of the effluent to be drained, outflow resistance to drainage, and height difference between patient and drainage bag. One should ensure complete drainage as incomplete drainage can cause a rise in intra-abdominal pressure causing respiratory embarrassment or abdominal discomfort.

The number of exchanges depends on the amount of fluid and solute removal required for a particular patient. The usual number of exchanges is about 24 per day with standard acute PD and approximately 4–6 per day with CPD.

Some drugs can be added to the PD fluid to treat certain specific conditions. Some of these drugs are the following.

Heparin. Heparin is used to prevent clot formation. Usually a dose of 500 units/liter is used [36]. Usually, heparin is also used when plugs or strands of fibrin are visible on the drained fluid. Heparin is more beneficial when added prophylactically. No systemic anticoagulation risk exists when heparin is used through a PD catheter as there is no systemic absorption of heparin through peritoneum.

Insulin. Usually insulin is used in diabetic patients on PD for glycemic control. The glucose content of the PD fluid can worsen hyperglycemia especially with hypertonic fluid, which can result in very high blood glucose levels. Intraperitoneal insulin is usually added to the PD fluid, and the dose is adjusted based on frequent blood glucose monitoring. Insulin should not be added in last 2-3 exchanges to prevent postdialysis hypoglycemia.

A usual regimen comprises of an increasing insulin dose in the dialysis bag with increasing glucose concentration as follow:

- 4-5 units/L for 1.5 g/dL PD fluid,
- 5-7 units/L for 2.5 g/dL PD fluid,
- 7-10 units/L for 4.25 g/dL PD fluid.

Potassium. Normally, there is no Potassium in the dialysis fluid but potassium can be added to the PD fluid in hypokalemic patients. Usually 3-4 meq/L is added to maintain normokalemia [36].

Antibiotics. Intraperitoneal administration of antibiotics is efficient and provides an alternative route for patients with poor vascular access and for those with peritonitis. A variety

of antibiotics can be administered through PD intraperitoneally. It is very important to maintain accurate flow sheets, maintain intake/output charts, and document net ultrafiltration in patients on acute PD. Intraperitoneal route is preferred to intravenous dosing for treating peritonitis. Both intermittent and dosing of antibiotics are equally efficacious. Empiric treatment of peritonitis should start immediately and should have both gram-positive and gram-negative coverage. In case of intermittent therapy, these antibiotics should be given intraperitoneally and allowed to dwell for 6 hours. First generation cephalosporin or Vancomycin can be used for gram-positive coverage and either third generation cephalosporin or aminoglycoside should be used to cover gram-negative organisms. Results of culture and sensitivity should be followed and antibiotics should be changed based on sensitivity of the organism. Most patients show considerable clinical improvement within 48 hours of initiation of antibiotic treatment. Total duration of antibiotic therapy for peritonitis depends upon the organism isolated and ongoing results of peritoneal fluid cell count and repeat culture. The reader should refer to International Society of Peritoneal Dialysis guidelines regarding doses of various antibiotics used intraperitoneally in PD for treatment of peritonitis [37].

7. Complications of PD

Acute PD may be associated with infectious, mechanical, or medical complications of varying severity [38, 39]. A brief overview of the complications is discussed in this section.

7.1. Infectious Complications. Peritonitis occurs in up to 12% of cases frequently developing within first 48 hours of therapy [40]. It usually occurs with an open drainage system and is due to contamination of the connection or disconnection of each new exchange. It can be caused by both gram-positive and gram-negative bacteria. Peritonitis is usually suspected when the effluent is cloudy. The diagnosis is confirmed by PDF analysis for cell count, gram staining, and culture and sensitivity. Antibiotic therapy should be initiated as soon as possible empirically to avoid serious consequences of peritonitis like sepsis, catheter removal, and so forth. One can narrow down the antibiotic administration based on results of culture and sensitivity of PDF.

7.2. Mechanical Complications

Pain. Pain is usually experienced at the incision site or may be associated with manipulation of the catheter during the

TABLE 7: Acute peritoneal dialysis orders.

Nephrologist should make sure that PD catheter is adequately inserted preferably chronic catheter and has no issues with flow of the fluid. PD orders need to be individualized depending upon hemodynamic status of the patient, laboratory work, and volume status. PD orders need to be reviewed and written daily as patients with AKI usually fluctuate acid base and electrolyte balance daily

Nursing orders

Dialysis session length hours

Dialysis volume per exchange L

Dialysis dextrose concentration %

Inflow time min Dwell time min, Outflow time min

Vital signs q hours

Weigh patient q hours

Warm dialysate fluid to body temperature

Maintain strict intake and output

Additives to dialysate Heparin yes/no, Insulin yes/no, Potassium yes/no

Medication dose frequency

Vancomycin mg/L of exchange, Tobramycin mg/L of exchange other antibiotic mg/L

Catheter care and dressing change every day

Full chemistry panel including blood glucose level to be done every 12 hours each day during dialysis

Send 15 cc of dialysate fluid from catheter every morning during dialysis and send it for cell count with differential, gram staining, and culture and sensitivity yes/no

Renal Physician to be notified immediately for the following situations:

Poor dialysate flow

Severe abdominal pain or distention

Change in color of dialysate, bloody, or cloudy drainage

Dialysate leak or purulent drainage around catheter exit site

Patient hypotensive with systolic blood pressure of < mm Hg

Respiratory rate of \geq per minute or severe shortness of breath in non ventilated patient

Temperature of \geq C

Two consecutive positive exchanges

Single positive exchange balance (dialysate IN-dialysate OUT) of >1000 mL

If negative balance exceeds L over hours

Notification of abnormal laboratory values

procedure. Pain may be due to multiple factors such as low pH of PD fluid, low temperature, the jet flow from a straight catheter tip, or distension of the tissue around the catheter. This pain may be minimized by infusion of alkaline PD fluid with the addition of sodium bicarbonate and by raising the temperature of the PDF by warming or slowing down the rate of the infusion of fluid.

Perforation. Perforation of various abdominal viscera can occur during the insertion of the peritoneal dialysis catheter. Usual organs at risk of perforation are bowel and urinary bladder. Bowel perforation is manifested by severe abdominal pain, leak of intestinal contents, or urine in case of urinary bladder perforation through the catheter stylet. The diagnosis of the perforated organ may be evident immediately after the event or it may remain silent for some time, leading to other complications. Peritoneoscopic or surgical implantation of the catheter should reduce the incidence of perforation.

Blood in Dialysate. Bloody dialysate can occur due to a bleeding tendency in the patient's body. Bleeding can result from laceration of anterior abdominal wall vessels (i.e., inferior hypogastric artery) or less frequently, puncture of intraabdominal vessels. The treatment of bleeding depends on its severity. Usually, frequent exchanges and use of intraperitoneal heparin to prevent clotting are generally used until the effluent clears or surgical intervention is deemed necessary. Bleeding due to laceration of the abdominal wall can be controlled through ligation of the vessel through either laparoscopy or laparotomy.

Early Dialysate Leakage. Incidence of pericatheter leaks can vary from 0–40%. Pericatheter leaks may not be apparent in the immediate postinsertion period unless a full exchange is performed. Catheter leak usually occurs due to the presence of certain predisposing factors like old age, obesity, diabetes mellitus, chronic steroid use, and multiparity. It is usually avoided by using low fill volumes. The risk of leak is low in

supine position because intraperitoneal pressure is the lowest in this position as compared to sitting or standing. Catheter leaks can be prevented with use of tightly secured purse string sutures at the site of entrance of the catheter into the peritoneal cavity and by precisely placing the catheter cuffs. Sutures should never be placed at exit site skin to prevent leak.

Respiratory Insufficiency. Respiratory distress usually occurs due to abdominal distension as the instillation of peritoneal fluid causes a rise in intra-abdominal pressure. It can be prevented by careful observation to ensure complete emptying during the allowed drainage period.

Extravasation of Fluid in Tissue Compartments. Extravasation of fluid is usually in the abdominal wall. This sometimes presents as genital edema. It is usually due to peritoneal defects at the site of catheter insertion. It is suspected when there is a reduced amount of drainage volume, increased abdominal girth, and increased body weight without edema appreciated elsewhere in the body. Imaging studies are needed to diagnose the underlying cause of the extravasation.

Hydrothorax. PD-related Hydrothorax was first described in 1967 by Edwards and Unger [41]. The prevalence of Hydrothorax varies ranging from 1.6% [42] to 6% of adult PD patients [43]. Usually pleural effusion is transudate in nature, and it occurs usually immediately after starting PD or a few days later [44]. Hydrothorax is usually right sided and is due to the presence of a congenital diaphragmatic defect with a subsequent pleuroperitoneal communication, disorder of lymphatic drainage, and pleuroperitoneal pressure gradient [44–46]. The glucose concentration of the pleural fluid is usually greater than the glucose level in the serum although this is not always a consistent finding. Diagnosis of pleuroperitoneal communication may require use of radionuclide scanning with technetium. Severe cases may require cessation of PD and surgical closure of the communication, pleurodesis by talc insufflation, or video-assisted thoracoscopic pleurodesis.

7.3. Medical Complications

Fluid, Electrolyte, and Acid Base Disturbances. Complications related to fluid and electrolyte can be avoided by close monitoring of the changes in patient's body weight, documentation of dialysis regimen pertaining to dialysis exchange frequency, osmotic strength of fluid used, volume of PDF used per exchange, and ultrafiltration. Daily intake and nonurinary output records should be reviewed on a daily basis. Hyponatremia is usually caused by the sieving effect with ultrafiltrate being formed with much lower concentration of sodium than that of plasma. Hyponatremia usually can be alleviated by the use of glucose containing fluids. Lactic acidosis is rare except in patients with terminal liver failure. Lactic acidosis can be avoided by the use of bicarbonate containing peritoneal dialysis fluid in patients with terminal liver failure. Occasionally, severe lactic acidosis

can be due to ongoing bowel ischemia and should be excluded under relevant clinical conditions.

Hypervolemia and Hypovolemia. Volume changes can occur due to the use of either hyperosmotic fluid or due to ultrafiltration failure. This can be alleviated by adjusting the prescription of dialysis or in some situations may require temporary cessation of dialysis. Hypervolemia due to ultrafiltration failure is usually seen in high solute transporters. This particular ultrafiltration failure can be seen during episodes of acute peritonitis.

Hypoalbuminemia. Albumin loss is seen due to high protein losses in the dialysate especially during episodes of peritonitis. These losses can be as high as 10–20 grams a day and patients may require protein supplementation either orally or intravenously.

8. Outcome of Patients on Acute Peritoneal Dialysis

This section will review recent studies conducted in AKI patients treated with acute PD alone for dialytic therapy and the studies comparing acute PD with other modalities of renal replacement therapies. Two recent studies conducted in AKI patients using acute PD have given promising results. One prospective study [47] with 30 AKI patients was performed in Brazil. The purpose of the study was to explore role of high volume continuous peritoneal dialysis (CPD) in patients with AKI, analyzing metabolic abnormality, resolution of fluid balance, and patient outcome. All patients had AKI due to ischemic or nephrotoxic Acute Tubular Necrosis (ATN). Adequacy of dialysis was measured by formula Kt/V (where K is rate of urea clearance by peritoneal membrane in litres, t is the treatment duration (24 hours), and V is volume of body urea distribution in litres). The prescribed Kt/V value was 0.65 per session. In this study patients were assigned to high-dose continuous peritoneal dialysis (CPD) via a flexible PD catheter and automated PD with a cycler. PD exchanges were done with two liter peritoneal fluid using 35–50 minute dwell time with total of 36–44 Liters of PDF per day. Biochemical parameters (Urea, Creatinine, pH, Potassium and Bicarbonate) were measured twice daily. Patients received 236 CPD sessions resulting in normalized creatinine clearance and urea Kt/V values of 110 ± 22.5 and 3.8 ± 0.61 per week per 1.73 m^2 body surface area, respectively. After 4 days of CPD, patients had stable BUN value $<50 \text{ mg/dL}$ and creatinine at $<4 \text{ mg/dL}$. In this study, 57% of the patients died and 23% of the patients recovered their renal function. The authors concluded that high-dose CPD using flexible PD catheter and automated PD with a cycler was an effective therapy for AKI which provides appropriate metabolic and acid-base control as well as adequate dialysis dose and fluid removal.

Another prospective, randomized, crossover study [48] from India enrolled 87 hemodynamically stable patients with AKI (88% of AKI in this study was due to medical reasons). Two different modalities of PD, Tidal PD (TPD),

versus continuous peritoneal dialysis (CPD) were done in patients with mild to moderate hypercatabolism. Severely hypercatabolic and hemodynamically unstable patients were excluded from the study. Patients received either TPD or CPD after insertion of rigid peritoneal dialysis catheter. If there was a need to continue PD in patients with no recovery of renal function, patients were crossed over to other modality of PD after washout period of 14 hours. Total volume of PDF used daily was 26 L by using 2 L bags with dwell time of 210 minutes in CPD group and 10-minute dwell in TPD group. Patients completing at least one set of dialysis (CEPD + TPD or TPD + CPD) were included in final analysis. The study showed that different modalities of PD are adequate methods to maintain BUN levels at 65 mg/dL in mild to moderate hypercatabolic AKI patients from developing countries. Other studies done in the past in patients with AKI have shown similar results [24, 49].

Studies comparing acute PD to other modalities of renal replacement therapy are limited and the results of the conducted studies are conflicting. Phu et al. [50] performed an open, randomized comparison of pumped venovenous hemofiltration and peritoneal dialysis in patients with infection-associated AKI in an infectious disease referral hospital in Vietnam. The primary outcome in this study was to assess rapidity of resolution of metabolic abnormalities like correction of acidemia and creatinine level between the two modalities in patients with AKI. Secondary end points were death, need for further renal replacement therapy, incidence of serious complications, and cost of treatment. This study included patients with AKI due to sepsis (48 patients with severe *Falciparum Malaria*, 22 patients with sepsis). Children under age of 15 years, pregnant females, and patients who received renal replacement therapy previously were excluded from the study. This trial recruited 70 patients over a period of five years (1993–1998). PD was performed by use of rigid peritoneal catheter done under local anesthesia, and open drainage system was used with dwell time of 30 minutes. Daily PD fluid volume of 70 L was used. Hemofiltration was performed through insertion of femoral catheter at blood flow rate of 150 cc/min, and CVVH effluent rate was approximately 25 L/day. Renal replacement therapy was continued till attending physician decided that it was no longer indicated. Duration of Hemofiltration was half as compared to duration of peritoneal dialysis. Results of the study showed that rate of correction of metabolic abnormalities was twice as fast in Hemofiltration group as compared to patients on peritoneal dialysis. Mortality rate of patients (one of the secondary end points in the study) on Peritoneal Dialysis was 47% compared to 15% on CRRT. The need for further renal replacement therapy (another secondary end point) was higher in survivors of PD than those of Hemofiltration. This trial had a small number of patients in shock (3% versus 5% in PD and Hemofiltration group, resp.). However, use of intermittent PD with rigid catheters, an open drainage system, and manual exchanges may have led to inadequate solute clearance and hence high mortality rate in the PD group. Interestingly, the same authors had published another study in 1992 showing a significant reduction in mortality of AKI patients treated

with acute PD associated with malaria. In this study, PD was the only modality used as there was no other dialytic modality available in this tertiary care [51].

Another prospective, randomized, controlled trial from Brazil compared high volume Peritoneal Dialysis (HVPD) with daily Hemodialysis (DHD) in RRT of AKI due to ischemic ATN associated with sepsis in the majority of the patients [52, 53]. The primary outcome in this study was to compare patient outcome for mortality rate and recovery of renal function. Secondary end point was to examine the adequacy of HVPD and DHD in relation to metabolic control. In this study, intermittent Hemodialysis was given 6 days a week with targets Kt/V of 1.2 even though delivered dialysis dose was much lower in HVPD patient (weekly Kt/V = 3.6) as compared to DHD group (weekly Kt/V = 4.8). Peritoneal dialysis was performed 24 hours a day 7 days per week by using a flexible peritoneal dialysis catheter with 30–55-minute dwell time assisted with use of automated cycler. The prescribed Kt/V value was 0.65 in CPD group and total of 36–44 L per day of PD fluid was used. DHD was performed daily with at least 3-hour session six times a week using double lumen temporary dialysis catheter. A total of 120 patients out of 154 completed the trial from 2004 to 2006 with 60 patients enrolled in each arm of the study. 70% of the enrolled patients had hemodynamic instability. Mean number of sessions was 5.5 in HVPD and 7.5 in DHD group. Hospital mortality was 58% in patients who were treated with high volume peritoneal dialysis and 53% in patients who were randomly assigned to daily hemodialysis ($P = .71$). 83% of surviving patients in the peritoneal dialysis group recovered kidney function as compared with 77% in the hemodialysis group and time to renal recovery was shorter in HVPD group as compared to DHD (7.2 ± 2.6 versus 10.6 ± 4.7 days, $P = .04$). Rate of catheter-related infection was similar between the two groups. There was no significant difference in patient survival after 30 days of treatment (50% survival rate in each group). This outcome is different from the study mentioned earlier.

There are no studies comparing the outcome of peritoneal dialysis as compared to alternate day intermittent hemodialysis in AKI. Hence, peritoneal dialysis remains an acceptable alternative to hemodialysis and CRRT especially in countries where technology for IHD and CRRT is not readily available.

9. Conclusion

Peritoneal dialysis has been in use since 1970 in patients with acute kidney injury especially those who are hemodynamically unstable or at risk of bleeding because of bleeding tendency, in pediatric patients with acute kidney injury, and in patients with vascular access failure.

Peritoneal dialysis remains an effective therapy which is simple and easy to use. This is especially the case for infants and children with AKI both in ICU and non-ICU settings, although its use is less preferable in western countries especially with advent of newer options available for CRRT like SLED and CVVDHF. It is a less effective modality

in certain clinical situations like patients with poisoning, hypercatabolic states, and pulmonary edema. There is a limited data concerning the effect on mortality of PD versus other RRT therapies like intermittent hemodialysis and other continuous renal replacement therapies in patients with acute kidney injury.

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Review Article

Citrate Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Patients: Success and Limits

Filippo Mariano,¹ Daniela Bergamo,¹ Ezio Nicola Gangemi,² Zsuzsanna Hollo',¹ Maurizio Stella,² and Giorgio Triolo¹

¹ Department of Medicine Area, Nephrology and Dialysis Unit, CTO Hospital, Via G. Zuretti 29, Turin, Italy

² Department of Plastic Surgery, Burns Unit, CTO Hospital, 10126 Turin, Italy

Correspondence should be addressed to Filippo Mariano, filippo.mariano@poste.it

Received 30 September 2010; Accepted 20 January 2011

Academic Editor: Michael Oppert

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Citrate anticoagulation has risen in interest so it is now a real alternative to heparin in the ICUs practice. Citrate provides a regional anticoagulation virtually restricted to extracorporeal circuit, where it acts by chelating ionized calcium. This issue is particularly true in patients ongoing CRRT, when the “continuous” systemic anticoagulation treatment is per se a relevant risk of bleeding. When compared with heparin most of studies with citrate reported a longer circuit survival, a lower rate of bleeding complications, and transfused packed red cell requirements. As anticoagulant for CRRT, the infusion of citrate is prolonged and it could potentially have some adverse effects. When citrate is metabolized to bicarbonate, metabolic alkalosis may occur, or for impaired metabolism citrate accumulation leads to acidosis. However, large studies with dedicated machines have indeed demonstrated that citrate anticoagulation is well tolerated, safe, and an easy to handle even in septic shock critically ill patients.

1. Introduction

Multiple technological advancements affecting continuous renal replacement therapy (CRRT) delivery to critically ill patients have been developed in the past twenty years. Dedicated CRRT equipment with better thermal control, more precise balances and volumetric control of infused and filtered fluids, and user friendly machines now allow a safe CRRT provision, which has become increasingly popular.

Generally speaking, the practical background of continuous treatment feasibility in critically ill patients, often hemodynamically unstable, septic, or suffering from trauma or recent surgery, is closed to the need for anticoagulation. In effect, systemic anticoagulation is still the main challenge in the application of CRRT, since it exposes the patient to a risk of active bleeding episodes.

Heparin, first adopted as an anticoagulant in the late 1920s, made feasible the patency of extracorporeal circuits, and nowadays it remains the most popular anticoagulant worldwide used in extracorporeal dialysis [1]. Heparin is the

drug of choice in chronic patients undergoing hemodialysis as well as in acute patients treated by CRRT. Heparin is efficient and instantaneous in its anticoagulation, quite safe and cheap so that heparin can be administered with ease to patients.

Bleeding is the main side effect of i.v. heparin administration for CRRT. The incidence of bleeding episodes considering all of the administration methods ranges from 10% to 50%, with a bleeding mortality rate as high as 15% [2–4]. Heparin is contraindicated in critically ill patients with active bleeding or at high risk of bleeding, as seen in such patients with extensive trauma, burns, or in surgery patients [2].

As alternative to heparin, several methods of systemic or regional anticoagulation have been proposed over the past 50 years, including low-molecular weight heparin, prostacyclin, the serine proteinase inhibitor nafamostat, hirudin, regional heparinization, saline flushes, and regional citrate anticoagulation. Among these, citrate anticoagulation has risen in interest so it is now a real alternative to heparin in the ICUs practice of CRRT.

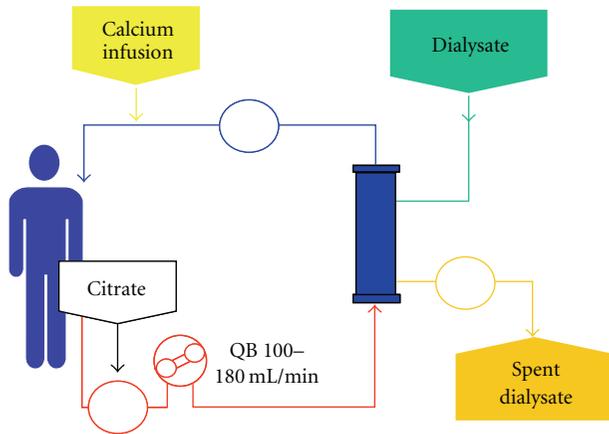


FIGURE 1: Scheme of standard citrate anticoagulation in CVVHDF.

2. Regional Citrate Anticoagulation as Alternative to Heparin

Citrate was first reported as an anticoagulant for hemodialysis in 1960s by Morita et al. [5] and as an alternative regional anticoagulation in patients ongoing CRRT in 1990 by Metha et al. [6]. Since then, citrate has gained more and more popularity. Regional citrate anticoagulation has been utilized in CRRT programmes based on its fundamental properties of avoiding a systemic anticoagulation. Citrate provides a regional anticoagulation virtually restricted to extracorporeal circuit, where it acts by chelating ionized calcium. This issue is particularly true in patients ongoing CRRT, when the “continuous” systemic anticoagulation treatment is *per se* a relevant risk of bleeding.

However, citrate use is not uniform, and it has been utilized mainly in North America and Europe CRRT programmes. For instance, anticoagulation with a regional citrate or systemic heparin standardized protocol for CRRT has been implemented since 1999 in all adult ICUs patients in Canadian Calgary Health Region [7]. Based on a North American survey, it has been estimated that a quarter of all patients suffering from acute kidney injury (AKI) are treated with CRRT, and regional citrate anticoagulation has been used as method of choice in only 13% of these patients [8]. In a recent survey on all ICUs practice in North-West of Italy (covering a population of 4.5 millions of inhabitants), in the vast majority of dialysis sessions done in 2007 unfractionated heparin was the anticoagulant of choice (5,296 out of 7,842 dialysis sessions, 67.5%). Interestingly, on patients at high risk of bleeding regional citrate anticoagulation was performed only in 18.0% of the cases, whereas the principle treatment modality remained that of a dialysis session without heparin, or at low heparin doses with saline flushes (77.6%) [9]. However, it is reasonable to presume that the use of citrate will grow in popularity in the near future. The inherent complexities of the method are now reduced since RRT dedicated monitor may indeed provide a safe and an easy-to-handle citrate anticoagulation protocol besides standard heparin anticoagulation [10].

3. Citrate Acts by Reducing Ionized Calcium (iCa^{++}) Concentration

As anticoagulant, citrate has been applied to hemodialysis, hemodiafiltration (in pre/postdilution), hemofiltration (in pre-postdilution), sorbent technology and in both continuous and intermittent treatments [4, 6, 7, 11–20]. By a Medline search more than 60 different systems for citrate administration can be found. Most of these systems have been home made with its specific composition of fluids, and its own rules to provide anticoagulation and titrate calcium administration. In the last years global citrate market has been deeply changing. Dialysis machines for CRRT have incorporated citrate anticoagulation in the soft- and hardware, as well as dedicated fluids have been certified and registered by industries.

However, as shown in Figure 1 all citrate systems present in the market work on few simple and shared modalities:

- (1) prefilter infusion of citrate, which acts as chelating ionized calcium (an iCa concentration below 0.35 mmol/L is required to inhibit coagulation);
- (2) dialysate (and predilution or postdilution if present) fluids are calcium free;
- (3) a replacement infusion of calcium at the end of extracorporeal circuit, in the blood line returning to patient.

As part of mechanisms operating during citrate anticoagulation, in the filter citrate-calcium complex and iCa^{++} are partially cleared by convection and/or diffusion, since membranes currently used in CRRT have a sieving coefficients near to unit for these small molecules. The remaining amount of citrate not cleared by filter enters the systemic circulation, and should be metabolized. As a consequence of the use of calcium free fluids, citrate anticoagulation leads to a net loss of calcium by filter. In the patient iCa^{++} rises again by replacement infusion of calcium at the end of circuit and the liberation of chelated calcium when citrate is metabolised.

4. Efficacy and Safety of Citrate

4.1. Circuit Survival. In respect to heparin, citrate is emerging as being similar or even superior as anticoagulant in terms of filter life and efficacy of anticoagulation. Factors influencing the circuit life reflect in part the coagulation capacity of the patient (procoagulant and/or anticoagulant factors due to acute illness, platelet count) and in part the technical aspects of dialysis (diffusion/convection modality, filtration fraction, pre- postdilution, vascular access quality, blood flow rate, nursing monitoring of dialysis).

In addition, citrate anticoagulation could be modulated by the target of citrate concentration reached in circuit blood (from 3 to 5 mmol/L of citratemia). As increased levels of anticoagulation could be obtained according to increased dose of heparin, a level of citratemia of 5 mmol/L (according to a concentration of iCa^{++} below 0.1 mmol/L) leads to a total and persistent inability of blood coagulation.

Most of studies reported longer circuit survival with citrate, but only few studies comparing citrate to heparin were randomized [13, 14, 21–23]. Circuit life was significantly longer with citrate [13, 14, 23], while circuit life was similar in the other 2 [21, 22]. As a matter of fact, blood citrate concentration of around 4 mmol/L is adapted to achieve excellent filter run times. Some trials who found that citrate did not achieve better filter run time used a blood citrate concentration of 3 mmol/L, and often did not control the ionized postfilter calcium values [21].

In a prospective, randomized clinical trial, Monchi et al. compared unfractionated heparin and regional citrate anticoagulation in 20 CVVH patients [13]. They found a median circuit life of 40 h with heparin and 70 h with citrate (heparin adjusted to get an APTT at 60–80 s, citrate infusion adjusted to maintain circuit $iCa^{++} < 0.3$ mmol/L). Similarly, a prospective randomized study involving 30 patients undergoing CVVHDF not at high risk of hemorrhagic complications showed a median hemofilter survival time of 124.5 hours in the citrate group and 38.3 hours in the heparin group ($P < .001$) [22]. Heparin dose was adjusted to obtain an APTT at 45–65 s, citrate infusion to maintain circuit iCa^{++} between 0.25–0.35 mmol/L. In a recent prospective randomized multicenter trial Hetzel et al. [23] compared in CVVHF in total predilution citrate with heparin. Mean hemofilter patency was significantly longer in the HF-Citrate group compared with the HF-bicarbonate group (37.5 ± 23 h versus 26.1 ± 19 h, $P < .001$, $n = 87/81$).

In contrast, in other 2 randomized trials citrate was not superior to heparin in circuit survival [21, 22]. In a large multi-center study involving seven USA centers, 138 patients and 442 CRRT circuits were studied to assess filter life span and anticoagulation complications with anticoagulation based on heparin, citrate, or with no anticoagulation [15]. Mean circuit survival was not different for circuits receiving heparin (42.1 ± 27.1 h) and citrate (44.7 ± 35.9 h), with similar clotting rates and without any significant difference by Kaplan-Meier analyses of survival between the two groups. Circuits without anticoagulation presented a significant lower survival (27.2 ± 21.5 h, $P < .001$).

In another study of 87 patients undergoing CRRT from the Calgary Health Region, Canada, 54 were initially treated with citrate (212 filters), 29 with heparin (97 filters), and 4 with saline flushes [7]. Median filter lifespan was significantly higher with citrate than with UFH (40 hours versus, 30 hours, $P < .001$) [7].

Finally, in 70 severe burn patients with septic shock treated by continuous or intermittent HDF with citrate or heparin anticoagulation, circuit survival was significantly longer with citrate on continuous treatment but not in intermittent modality [24].

4.2. Bleeding Complications. The primary reason to use citrate is that it leads to a regional anticoagulation, virtually restricted to extracorporeal circuit. Therefore, citrate anticoagulation does not increase patient risk of bleeding. In addition citrate is specifically indicated in patient at high risk of bleeding.

The 5 available randomized studies comparing heparin to citrate enrolled patients excluding those at high bleeding risk [13, 14, 21–23].

However, bleeding episodes were similar with citrate and heparin in two reports [13, 21] and reduced with citrate in other two [14, 22, 23]. No definite hemorrhage in the citrate group and seven instances in the heparin group and one occult hemorrhage in both citrate and heparin groups were observed [14]. After adjustment for antithrombin-III levels and illness severity score, the relative risk of hemorrhage with citrate anticoagulation was still significantly lower than that with heparin (0.14 versus 0.96). Even if citrate was used in presence of a lower systemic anticoagulation with heparin (at mean dose of 5,428 UI/day), bleeding complications episodes (5.7%) were significantly lower in comparison with heparin (14.5% episodes, at mean heparin dose of 13,174 UI/day) [23].

Similarly, the number of transfused packed red cells per day with citrate was similar to those with heparin in 3 studies [14, 21, 22], whereas in CVVHF study by Monchi et al. [13] was significantly reduced (1.0 transfused packed red cells/day in heparin group and 0.2 in citrate group).

In the multi-center study involving 138 patients and 442 CRRT circuits, life-threatening bleeding complications as a result of the anticoagulant were shown in 9 patients in the heparin group and absent in citrate group [15]. In the same way, in a study of 87 patients undergoing CRRT from Calgary Health Region citrate anticoagulation was well tolerated, and no treatment was discontinued for hemorrhagic episodes [7].

In 70 severe burn patients with septic shock and AKI, and undergoing RRT, bleeding complications were significantly lower with citrate during CVVHDF, as well as the requirements of transfused packed red cells per day (1.76 transfused packed red cells/day with heparin group and 0.98 with citrate group) [24].

4.3. Citrate Anticoagulation in Critically Ill Patients Treated with Sorbent Technology. Sorbent technology is a promising tool for extracorporeal techniques targeted to remove detrimental substances present in blood of septic shock patients. Sorbents have specific characteristics, such as an access to substances bound to protein, a removal capacity of larger molecular weight toxins exceeding cut-off of dialysis membranes. In addition, in the future many advances in resin sorbent technology will come out.

As anticoagulant, citrate has been demonstrated to be safe and efficient in septic shock patients treated by sorbent technology [25]. In 13 severe burn and polytrauma patients at high risk or with active bleeding and treated with plasma adsorption, 58 sessions using systemic anticoagulation with heparin (mean heparin 741 U/h) were compared with 28 sessions using citrate regional anticoagulation (circuit citratemia at 4 mmol/L) evaluating efficiency and safety of the technique. Plasma filtration efficiency and number of used cartridges were similar, whereas the number of lost cartridges was significantly lower in the citrate patients [25].

5. Metabolic Consequences and Tolerance of Citrate

When administered intravenously in healthy subjects citrate is rapidly metabolized to bicarbonate by the tricarboxylic pathway in liver, kidney, and skeletal muscle. In addition, at high serum levels a substantial percentage of citrate is excreted unchanged in the urine [26]. Citrate can also be involved in many other biochemical pathways including amino acid synthesis and gluconeogenesis [26].

In presence of chronic renal failure citrate metabolism may be impaired. Both loss of metabolically active kidney mass and accumulation of soluble toxins can affect some metabolic pathways in extrarenal tissues. In addition, liver metabolism of gluconeogenic intermediates and the tricarbonic acid cycle are impaired in uremic state [27]. Investigating the metabolism of citrate in patients on regular hemodialysis and minimal residual renal function (urinary output < 400 mL/d), Bauer et al. [27] did not observe alkalization or pH variation after sodium citrate i.v. infusion.

When used for regional anticoagulation of the dialysis circuit in CRRT, the infusion of citrate is prolonged, and it may have some adverse effects. Citrate is an organic compound able to react with divalent cations such as magnesium and calcium. By chelating calcium citrate blocks coagulation activation in the dialysis circuit. As citrate is metabolized to bicarbonate, metabolic alkalosis may occur or, in contrast, if citrate is not metabolized and accumulates, acidosis can develop. Moreover, since citrate is usually applied as trisodium citrate it can lead to excessive sodium load and hypernatremia. Hypomagnesemia may be another consequence but, at our knowledge, no case of severe hypomagnesemia has been reported.

In 1997 Palsson and Niles [11] reported 2 cases of citrate accumulation and refractory systemic hypocalcemia using a simplified protocol with prefilter citrate infusion during CVVHF in 15 patients. More recently by using the same protocol as citrate as the only buffer substance Hetzel et al. [23] found equivalence of standard bicarbonate in groups HF-citrate and HF-bicarbonate from day 3 to day 11. However, more patients in the HF-citrate group needed additional bicarbonate infusions compared with the patients treated with heparin.

In a large single-center analysis of 209 patients (37 received citrate as sole anticoagulant, 87 low-dose heparin plus citrate, and 85 only heparin), a development of metabolic alkalosis in 50% of patients treated with citrate was observed [18], and all cases were solved by increasing the dialysate flow rate.

Three recently controlled large studies [7, 14, 15], involving a total of 251 patients and comparing citrate (121 patients) with heparin anticoagulation in CRRT in critically ill patients, confirmed the safety of the citrate. In 138 patients and 442 CRRT circuits, out of 37 patients treated with citrate, metabolic alkalosis was shown in 4 cases and citrate accumulation in 2 patients with liver failure but they were all managed by decreasing infusion rate of bicarbonate containing solution or of citrate [15]. Generally speaking, citrate anticoagulation was well tolerated, and no treatment

was discontinued for hypernatremia, metabolic alkalosis, hypocalcemia, or citrate accumulation. A safe and an easy-to-handle citrate anticoagulation protocol now commercially available has been recently validated in 162 patients [20]. This protocol provided an excellent acid base and electrolyte control in critically ill patients with acute renal failure, allowing a wide spectrum of treatment doses.

Liver is the most important organ in citrate metabolism. Kramer et al. [28] showed that in intensive care patients liver citrate clearance is decreased by approximately 50% in patients with cirrhosis compared with normal liver function. In cirrhotic patients impairment of citrate metabolism can cause citrate increase and hypercalcemia due to an accumulation of calcium-citrate complexes [28].

When citrate-calcium complexes increase in circulation, systemic iCa^{++} concentration decreases and the ratio between total to ionized calcium increases [29]. Ratio has been used as an indirect parameter of blood citrate increase. However, this ratio may not predict citrate accumulation in all cases [28, 30].

A recent study [24] involving 31 severe burn patients undergoing CVVHDF or SLED-HDF with citrate regional anticoagulation showed a good metabolic tolerance. Systemic arterial pH, Na^+ , K^+ , iCa^{++} , total Ca^{++}/iCa^{++} ratio and bicarbonates did not show any derangements over the period of observation. Citrate was determined directly dosing systemic citratemia and the levels of citrate in the ultrafiltrate. During the CRRT a high portion of the citrate-calcium complexes were lost in effluent (membranes currently used were highly permeable to free and calcium-bound citrate, with a sieving coefficients near to unit). The marked loss of citrate (up to 60% of the infused amount) directly correlated with effluent volume. By increasing dialysate flow rate, citrate loss could be increased [24] and decreased the remaining amount of citrate-calcium complexes returning to the patient.

Oudemans-van Straaten [21] recently compared the safety and efficacy of citrate with the nadroparin anticoagulation in 200 patients (97 treated with citrate) on CRRT. As it concerns tolerance citrate was superior to low-molecular weight heparin. Nadroparin patients more frequently developed metabolic alkalosis, hyponatremia and hyperlactatemia, whereas initial hypocalcemia was less often corrected in the citrate patients. Unexpectedly, citrate seemed to improve patient and kidney survival (three-month mortality was 48% with citrate versus 63% with nadroparin). Citrate appeared particularly beneficial in the subgroups of patients after surgery, with sepsis or with severe multiple organ failure [21]. However, favourable data about mortality are not confirmed in more recent multicenter randomized trial [23]. Sepsis was the predominant reason for death in both studies [21, 23], and exposure to citrate was considerably longer (8.5 days versus 2.7 days) in the trial without any favourable effect on mortality [23].

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Clinical Study

Comparison of Sustained Hemodiafiltration with Acetate-Free Dialysate and Continuous Venovenous Hemodiafiltration for the Treatment of Critically Ill Patients with Acute Kidney Injury

Masanori Abe,¹ Noriaki Maruyama,^{1,2} Shiro Matsumoto,¹ Kazuyoshi Okada,¹ Takayuki Fujita,¹ Koichi Matsumoto,¹ and Masayoshi Soma^{1,3}

¹ Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, Tokyo 173-8610, Japan

² Department of Internal Medicine, Nihon University Nerima Hikarigaoka Hospital, Tokyo 179-0072, Japan

³ Division of General Medicine, Department of Internal Medicine, Nihon University School of Medicine, Tokyo 173-8610, Japan

Correspondence should be addressed to Masanori Abe, abe.masanori@nihon-u.ac.jp

Received 1 September 2010; Revised 18 February 2011; Accepted 4 March 2011

Academic Editor: Michael Oppert

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We conducted a prospective, randomized study to compare conventional continuous venovenous hemodiafiltration (CVVHDF) with sustained hemodiafiltration (SHDF) using an acetate-free dialysate. Fifty critically ill patients with acute kidney injury (AKI) who required renal replacement therapy were treated with either CVVHDF or SHDF. CVVHDF was performed using a conventional dialysate with an effluent rate of $25 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, and SHDF was performed using an acetate-free dialysate with a flow rate of 300–500 mL/min. The primary study outcome, 30 d survival rate was 76.0% in the CVVHDF arm and 88.0% in the SHDF arm (NS). Both the number of patients who showed renal recovery (40.0% and 68.0%, CVVHDF and SHDF, resp.; $P < .05$), and the hospital stay length (42.3 days and 33.7 days, CVVHDF and SHDF, resp.; $P < .05$), significantly differed between the two treatments. Although the total convective volumes did not significantly differ, the dialysate flow rate was higher and mean duration of daily treatment was shorter in the SHDF treatment arm. Our results suggest that compared with conventional CVVHDF, more intensive renal support in the form of post-dilution SHDF with acetate-free dialysate may accelerate renal recovery in critically ill patients with AKI.

1. Introduction

Despite improved medical care, the mortality rate in critically ill patients with acute kidney injury (AKI) who require renal replacement therapy (RRT) is still high (>50%) [1–5]. Whether or not more intensive RRT improves the outcomes of patients with AKI is an ongoing debate; several studies have reported the benefits of frequent dialyses and/or high-dose regimens [6, 7], while others have reported no such benefit [8, 9]. The multicenter, prospective, randomized US Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network study recently investigated this issue and is the largest trial in this field to date [10]. The study found no significant difference between the intensive and less-intensive treatment groups with regard to death

rate by day 60, duration of RRT, rate of recovery of kidney function, rate of nonrenal organ failure, or proportion of patients who developed hypotension that required the discontinuation of one or more RRT modalities. Thus, there were no significant differences in the benefits of intermittent hemodialysis (IHD), sustained low-efficiency dialysis (SLED), high-dose ($35 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) CVVHDF, and standard-dose ($20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) CVVHDF.

We previously tested the hypothesis that more intensive RRT decreases mortality among critically ill patients with AKI to a greater extent than SLED or IHD [11]. In order to achieve clearance of small and medium molecular weight solutes, we tested a modified IHD protocol which we termed sustained hemodiafiltration (SHDF). SHDF is a form of

intermittent hemodiafiltration (IHDF) with extended (6–10 h) sessions, and regular blood and dialysate flow rates of 200 mL/min and 500 mL/min, respectively. In addition, the replacement fluid in SHDF is infused postfilter. The results of that study suggested that compared with conventional continuous RRT (CRRT) including high-dose CVVHDF, more intensive renal support in the form of postdilution SHDF could decrease mortality and accelerate renal recovery in critically ill patients with AKI.

The majority of maintenance hemodialysis (HD) patients in Japan are currently treated using an acetate-containing bicarbonate dialysate (acetate dialysate) with an acetate concentration of 48 to 60 mg/dL (8 to 10 mmol/L). Acetate may induce the production of cytokines and dilatation of vessels, but a small amount of acetate is necessary to maintain the pH of the dialysate at 7.1 to 7.6 to prevent precipitation of calcium and magnesium [12–14]. Although patients with acetate intolerance normally require acetate-free biofiltration, the standard dialysate still includes acetate. Therefore, critically ill patients with AKI who required acute RRT have been treated with acetate-containing dialysate. In the USA, although citrate dialysates (Citrasate® and DRYalysate®, Advanced Renal Technologies Co. Ltd, USA) may be used for maintenance of HD patients or critically ill RRT patients, those formulations still include a small amount of acetate [15]. Citrate dialysates are also commonly used as anticoagulants in cases when heparin cannot be utilized, such as in heparin-induced thrombocytopenia (HIT), high bleeding risk, trauma, and impending/postsurgical procedure, or in order to prevent the hemofilter clotting. Recently, the completely acetate-free bicarbonate dialysate Carbostar® (Ajinomoto Pharma, Tokyo, Japan) became available in Japan. However, as yet there are no reports which investigate the efficacy of acetate-free bicarbonate dialysate in critically ill patients with AKI.

In order to determine the impact of acute RRT strategies on patient outcomes, we conducted a prospective, randomized study comparing postdilution CVVHDF with an effluent rate of 20 to 25 mL·kg⁻¹·h⁻¹, with postdilution SHDF performed on a daily basis. Since there were no significant differences in the benefits afforded by high-dose (35 mL·kg⁻¹·h⁻¹) CVVHDF and standard-dose (20 mL·kg⁻¹·h⁻¹) CVVHDF in the largest previous ATN trial [10], CVVHDF was performed with the standard dose. CVVHDF was performed using acetate-containing dialysate and replacement fluid, and SHDF was performed using acetate-free dialysate.

2. Subjects and Methods

2.1. Study Design. This study was conducted in accordance with the Declaration of Helsinki (1996 amendment) and was performed at the Intensive Care Unit (ICU) of Nihon University Nerima Hikarigaoka Hospital, Tokyo, Japan, with the approval of the Clinical Research Ethics Committee of the same institution. All participants or their family members provided written informed consent prior to the commencement of the study. This study was designed

specifically for critically ill patients with AKI. All patients were admitted to the ICU of our hospital between April 2008 and October 2010. A total of 50 patients who had developed AKI that required RRT in the ICU were eligible for inclusion in this study. The main criterion for inclusion was a clinical diagnosis of AKI, defined by at least one of the following conditions: (1) volume overload despite diuretic administration, (2) oliguria (urine output <200 mL/12 h) in spite of fluid resuscitation and diuretic administration, (3) anuria (urine output <50 mL/12 h), (4) azotemia (blood urea nitrogen >80 mg/dL), (5) hyperkalemia (K value > 6.5 mEq/L), or (6) classification under the “R,” “I,” or “F” categories of the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) classification system [16]. The exclusion criteria for this study were the presence of end-stage renal disease requiring IHD, advanced chronic kidney disease (CKD) stages 4 and 5 (defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²) before admission, previous kidney transplant, an anticipated ICU stay of less than 48 h, or inability to provide informed consent. Severity of illness and hemodynamic instability were not used as exclusion criteria. All the patients were followed prospectively from the time of enrollment through discharge.

The type of treatment, effective duration of treatment, volume of ultrafiltrate and replacement fluid, episodes of hemofilter clotting, and number of episodes of catheter dysfunction were recorded for each treatment day. Acute Physiology and Chronic Health Evaluation (APACHE) II scores [17] and Sequential Organ Failure Assessment (SOFA) scores [18] were obtained at the time of initiation of RRT. The presence of pre-existing chronic kidney disease stage 3 was defined by a premorbid estimated glomerular filtration rate (eGFR) of 30–60 mL·min⁻¹·1.73 m⁻². The eGFR for Japanese patients was calculated using the following formula [19]: eGFR (mL·min⁻¹·1.73 m⁻²) = 194 × sCr^{-1.094} × Age^{-0.287} (×0.739 for women), where sCr was the serum creatinine concentration. Pre-ICU sCr values were used to calculate the proportion of patients who fulfilled the RIFLE categories of risk, injury, and failure at the time of ICU admission. Sepsis was diagnosed clinically by the attending clinician using published consensus criteria [20]. The indicators of kidney function (sCr, serum urea nitrogen, and urine output) were documented on ICU admission, on study enrollment, and on ICU and hospital discharge.

2.2. Treatment Assignments. On the initiation of RRT, the patients were randomly assigned to the CVVHDF or SHDF treatment arms by a computer-generated adaptive randomization scheme. An independent investigator, who had neither treated nor was aware of the profile of the subjects before the commencement of the trial, monitored randomization in the order of the entry of the subjects; then the particulars of the assignments were immediately delivered to the individual investigators. To ensure balanced randomization, the treatment assignments were stratified by sepsis and oliguria, because both of these parameters are independent predictors of patient survival [1, 21]. We used

the following stratification categories: (1) sepsis + oliguria, (2) sepsis + nonoliguria, (3) nonsepsis + oliguria, and (4) nonsepsis + nonoliguria.

Each patient was treated for 2 or more consecutive days. Heparin or nafamostat mesilate was used as the anticoagulant in all patients at doses of 6–13 U·kg⁻¹·h⁻¹ and 0.4–0.6 mg·kg⁻¹·h⁻¹, respectively. Vascular access was obtained by placing temporary dual-lumen catheters in the femoral or internal jugular vein. Hemofilters with a 1.0 m² polymethylmethacrylate (PMMA; Hemofeel CH-1.0; Toray, Tokyo, Japan) or polyester-polymer alloy (PEPA; FDY-100GW; Nikkiso, Tokyo, Japan) membrane were used in both treatment arms.

All medications and nutrition were ordered and administered by the primary caregivers in the ICU, who did not actively participate in the study. Interventions to maintain hemodynamic stability, including adjustment of ultrafiltration, administration of saline flushes, cooling of the dialysate, and sodium modeling, were performed as required. The requirement of pressor support was determined according to the status of the patient during each RRT session.

2.3. CVVHDF. CVVHDF was performed using Asahi ACH-10 hemodiafiltration equipment (Asahi Kasei Medical Co., Tokyo, Japan). Hemodiafiltration was accomplished using blood flow rates of 80–200 mL/min and postdilution administration of replacement fluid. Sublood-BS[®] (Fuso Pharmaceutical Industries Ltd., Osaka, Japan), a sterile bicarbonate solution containing acetate, was used as the dialysate and replacement fluid for CVVHDF. The ultrafiltrate was adjusted to achieve fluid balance in each patient, and fluid replacement and net ultrafiltration rates varied with the clinical status of the patient. In the CVVHDF modality, the “total convective rate” represents the product of the convective components, that is, the sum of the replacement fluid rate and the fluid removal rate, and does not include the rate at which dialysate is spent. The “total convective volume” represents the sum of the replacement fluid volume and the fluid removal volume. The actual delivered dosage, or total effluent flow rate (mL/kg/h), is the sum of the replacement fluid rate, fluid removal rate, and dialysate flow rate. CVVHDF was prescribed to provide a total effluent flow rate of 25 mL·kg⁻¹·h⁻¹, based on the patient’s weight before the onset of acute illness. This dosage was adjusted for body weight changes and hemodynamic instabilities throughout the treatment period. Every attempt was made to divide the rate of flow of the sterile bicarbonate solution equally between the replacement fluid rate and dialysate flow rate. The total time of actual CVVHDF treatment (min/24 h) was recorded daily, along with time spent on treatment of clots, procedures, or other events. The hemofilters were replaced every 24 h. Arterial blood gas analysis was performed before (post) and after (pre) hemofilter replacement at each treatment session.

2.4. SHDF. SHDF was performed with the Nikkiso DBB-02 (Nikkiso Co., Tokyo, Japan). All patients underwent SHDF during the daytime in the ICU for 6–8 h. The acetate-free

TABLE 1: Renal replacement therapy procedures.

	CVVHDF	SHDF
RRT equipment	ACH-10	DBB-02
RO equipment	—	NRX-20P PURESYSTEM
Hemofilter	PMMA, PEPA	PMMA, PEPA
Dialysate	Sublood-BS [®]	Carbostar [®]
Replacement fluid	Sublood-BS [®]	Sublood-BS [®]
Blood flow rate (mL/min)	80–200	80–200
Dialysate flow rate (mL/h)	300–2000	300–500
Replacement fluid rate (mL/h)	300–3000	300–3000

CVVHDF: continuous venovenous hemodiafiltration; PEPA: polyester-polymer alloy; PMMA: polymethylmethacrylate; RO: reverse osmosis; RRT: renal replacement therapy; SHDF: sustained hemodiafiltration.

bicarbonate dialysate (Carbostar[®]) was prepared in the ICU using reverse osmosis equipment (NRX-20P PURESYSTEM; Daicn Membrane-Systems Ltd., Tokyo, Japan). SHDF was accomplished using blood flow rates of 80–200 mL/min and postdilution administration of replacement fluid. The initial dialysate flow rate was 300 mL/min, and if the patients were hemodynamically stable, this was increased to 500 mL/min. Sublood-BS[®] was used as the replacement fluid for SHDF. The ultrafiltrate was adjusted to achieve fluid balance in each patient, and the fluid replacement and net ultrafiltration rates varied with the clinical status of the patient. Target replacement fluid volume was set to greater than 14 L/session, and SHDF was performed until this target was achieved. In the SHDF modality, the “total convective rate” represents the product of the convective components, that is, the sum of the replacement fluid rate and the fluid removal rate. The “total convective volume” represents the sum of the replacement fluid volume and the fluid removal volume. The total SHDF treatment time was recorded daily, along with time spent on the treatment of clots, procedures, or other events. Arterial blood gas analysis was performed before (pre) and after (post) each treatment.

RRT procedures and composition of acetate-free dialysate (Carbostar[®]) and sterile bicarbonate solution (Sublood-BS[®]) are listed in Tables 1 and 2, respectively.

Patients in both treatment arms were transitioned to conventional IHD at the discretion of the treating nephrologists. This usually occurred when the patient was still dependent on dialysis but had been transferred from the ICU to the ward, or when the patient was being mobilized in the ICU. The dosage and timing of IHD were determined by the treating nephrologists. Renal recovery was defined on the basis of Cr clearance, measured by 6-hour timed urine collections when urine flow increased to more than 30 mL/h or when there was a spontaneous fall in the sCr level. RRT was continued if the Cr clearance was less than 12 mL/min and was discontinued if the Cr clearance was greater than 20 mL/min; decisions regarding discontinuation of RRT for subjects with intermediate values of Cr clearance were left to the investigator.

TABLE 2: Composition of acetate-free dialysate (Carbostar®) and sterile bicarbonate solution (Sublood-BS®).

	Acetate-free dialysate	Sterile bicarbonate solution
Sodium (mEq/L)	140	140
Chloride (mEq/L)	111	111.5
Calcium (mEq/L)	3	3.5
Magnesium (mEq/L)	1.0	1.0
Potassium (mEq/L)	2.0	2.0
Glucose (mg/dL)	150	100
Bicarbonate (mEq/L)	35	35
Acetate (mEq/L)	0	0.5
Citrate (mg/dL)	12.8	0
Final pH	7.5–8.0	7.2–7.4
Osmolarity (mOsm/kg)	298	298

2.5. Outcome Measurements. The primary outcome measure was survival until discharge from the ICU or for 30 d, whichever was earlier. Secondary end points included renal recovery at the time of discharge from the ICU, renal recovery at the time of discharge from the hospital, ICU survival, hospital survival, length of ICU stay, and length of hospital stay.

2.6. Statistical Analysis. Data were expressed as mean \pm SD. Analyses were performed on an intention-to-treat basis. The primary analysis was the comparison of the proportion of patients in each study arm who survived until discharge from the ICU or for 30 d, whichever was earlier. The proportions were compared using Pearson's χ^2 test, or Fisher's exact test when the χ^2 test was not valid. The secondary analysis was the comparison of the following parameters between the two study arms: proportion of patients who recovered renal function at the time of discharge from the ICU and hospital, ICU survival, hospital survival, and length of hospital stay. The methods used to perform these comparisons were similar to those used in the primary analysis. Baseline characteristics and outcome measures were compared using the two-group *t*-test or Wilcoxon's rank-sum test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables.

The Kaplan-Meier method was used to estimate the hospital survival for the prescribed RRT, and the log-rank test was used to compare the survival curves of the two therapies. All statistical tests were two sided and were performed using a significance level of $P < .05$.

3. Results

A total of 50 patients were enrolled in the study and were randomly assigned to each treatment arm. The demographic data and clinical characteristics of the patients in the two arms are presented in Table 3. The baseline characteristics did not significantly differ between the two arms. In all,

18 patients were included in the sepsis + oliguria stratum, 7 in the sepsis + nonoliguria stratum, 12 in the nonsepsis + oliguria stratum, and 13 in the nonsepsis + nonoliguria stratum. The proportion of patients with oliguria, sepsis, and preexisting chronic kidney disease (defined as premorbid eGFR $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) was similar for both treatment arms.

The RRT parameters are described in Table 4. The number of treatments performed per patient was not significantly different between the two arms. The number of treatment hours per day was significantly less in the SHDF arm than in the CVVHDF arm. The dialysate flow rate and total dialysate volumes were significantly higher in the SHDF arm (dialysate volume, $9.6 \pm 1.6 \text{ L/session}$ in the CVVHDF arm versus $189 \pm 28 \text{ L/session}$ in the SHDF arm; $P < .0001$). The total convective rate was higher in the SHDF arm than in the CVVHDF arm; however, because the duration of SHDF treatment was shorter, the total convective volumes were not significantly different between the two groups. Accounting for the effect of postdilution fluid replacement on solute clearance, the mean actual delivered dosage was $26.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in the CVVHDF arm. There were instances in which RRT was interrupted by hemofilter thrombosis and catheter dysfunction; interruptions were observed significantly more frequently during CVVHDF (30.1% of sessions) than during SHDF (12.6% of sessions; $P < .05$). In 20 of the 203 CVVHDF treatments (9.8%), hypotension occurred that required discontinuation of the treatment (versus 12 of the 170 SHDF treatments [7.1%], $P = .32$). In 26 of the CVVHDF treatments (12.8%), initiation of vasopressor support was required (versus 18 for SHDF [10.5%], $P = .48$), and in 63 of the CVVHDF treatments (31.0%), other interventions were required because of treatment-associated hypotension (versus 44 for SHDF [25.8%], $P = .19$). As shown in Figure 1, the pH and HCO_3^- concentration of arterial blood was significantly increased after treatment compared to pretreatment in both arms. However, comparing between the two arms, pH and HCO_3^- concentration were higher in the SHDF arm compared to the CVVHDF arm both before and after treatment.

Although the length of ICU stay was not significantly different between the two arms, the length of hospital stay was significantly shorter in the SHDF arm than the CVVHDF arm (Table 5). The primary study outcome, survival until discharge from the ICU or for 30 d, whichever was earlier, was 76.0% in the CVVHDF arm and 88.0% in the SHDF arm (no significant difference). There was no significant difference in the ICU survival rate and hospital survival rate between the two arms (Figure 2). However, the total number of patients who showed renal recovery was significantly higher in the SHDF arm than in the CVVHDF arm, and significant differences were detected in the number of surviving patients showing renal recovery at the time of discharge from the ICU or from the hospital (Table 5). In addition, 16% of patients in the CVVHDF arm and 8% of those in the SHDF arm were transitioned to IHD while in the ICU (no significant difference).

TABLE 3: Baseline characteristics of patients.

Characteristic	CVVHDF	SHDF	P value
No. of patients (male/female)	25 (17/8)	25 (16/9)	NS
Age (years)	65.3 ± 13.1	66.5 ± 12.1	NS
Cause of acute kidney injury (%)			NS
Nephrogenic	20	24	
Sepsis	52	48	
Cardiogenic	12	12	
Postsurgical	8	8	
Drug induced	0	4	
Hepatic failure	4	4	
Other	4	0	
Presence of CKD on admission (%)	40	44	NS
APACHE II score	19.6 ± 3.7	20.0 ± 4.3	NS
SOFA score	8.1 ± 2.0	8.2 ± 3.2	NS
RIFLE classification			
R (%)	20	20	NS
I (%)	44	40	NS
F (%)	36	40	NS
Mechanically ventilated (%)	36	32	NS
Oliguric (%)	60	60	NS
Baseline systolic blood pressure (mmHg)	107 ± 32	110 ± 29	NS
Required vasopressors (%)	28	24	NS
Renal parameters at RRT initiation			
Serum urea nitrogen (mg/dL)	69 ± 26	68 ± 24	NS
Serum creatinine (mg/dL)	4.6 ± 2.3	4.8 ± 2.1	NS
Days from ICU admission to RRT	2.1 ± 1.3	2.1 ± 1.5	NS

APACHE: acute physiology and chronic health evaluation; CKD: chronic kidney disease; CVVHDF: continuous venovenous hemodiafiltration; ICU: intensive care unit; RIFLE: Risk, Injury, and Failure with the outcome classes Loss and End-stage kidney disease classification system; RRT: renal replacement therapy; SOFA: sequential organ failure assessment; SHDF: sustained hemodiafiltration.

TABLE 4: RRT characteristics by treatment group.

Characteristic	CVVHDF	SHDF	P value
Total number of treatment days/sessions	203	170	—
Mean treatment times (days or sessions) per patient	8.1 ± 3.5	6.6 ± 2.6	NS
Mean duration of daily treatment (h)	15.2 ± 3.8	6.0 ± 1.0	<.0001
Dialysate flow rate (mL/min)	10.8 ± 2.8	471 ± 27	<.0001
Total dialysate flow volume (L/session)	9.6 ± 1.6	169 ± 28	<.0001
Total convective rate (mL/h)	683 ± 159	2006 ± 826	<.0001
replacement fluid rate (mL/h)	549 ± 127	1696 ± 819	<.0001
fluid removal rate (mL/h)	134 ± 58	310 ± 70	<.0001
Total convective volume (L/session)	15.0 ± 4.5	12.0 ± 5.1	NS
Actual delivered dosage (mL/kg/h)	26.6	—	—

CVVHDF: continuous venovenous hemodiafiltration; RRT: renal replacement therapy; SHDF: sustained hemodiafiltration.

4. Discussion

We propose that the acetate-free dialysate may have improved circulatory dynamics during RRT due to the differences in glucose and bicarbonate levels from standard dialysate, a direct effect of citrate, and the absence of acetate in the dialysate. Acetate can induce the production of nitric oxide, a vasodilator [22] that can cause intradialytic cardiovascular instability [23, 24], and therefore

elevated acetate load might lead to hemodynamic instability. Following treatment with acetate-free dialysate, we found a significant increase in pH and HCO_3^- concentration, and these levels were significantly higher after treatment in the SHDF arm than in the CVVHDF arm. There was no significant difference in the requirement for vasopressors during RRT between the two groups.

Therefore, in contrast to CVVHDF, SHDF may be suitable for both hemodynamically stable and unstable subjects. It

TABLE 5: Outcome by treatment group.

Characteristic	CVVHDF	SHDF	P value
Total ICU days	18.8 ± 11.1	14.1 ± 7.2	NS
Total hospital days	42.3 ± 18.8	33.7 ± 18.8	<.05
Survival until discharge from ICU or for 30 d (%)	76	88	NS
ICU survival (%)	72	84	NS
Hospital survival (%)	64	80	NS
ICU renal recovery (%)			
All patients	20	44	<.05
Survivors	27.8	52.3	<.05
Hospital renal recovery (%)			
All patients	40	68	<.05
Survivors	62.5	85	<.05

CVVHDF: continuous venovenous hemodiafiltration; ICU: intensive care unit; SHDF: sustained hemodiafiltration.

is difficult to ascertain whether this finding can be attributed to the use of dialysate “without” acetate, which might cause vasodilation and hypotension, since we could not measure blood acetate concentrations in the present study to compare the two dialysates. Further studies would be needed to clarify the efficacy of completely acetate-free dialysate. Acetate-free dialysate has several advantages. Rapid correction of acidosis is possible because of the greater bicarbonate concentration. Also, acetate-free dialysate contains 12.8 mg/dL (667 μ mol/L) of citrate instead of acetate to adjust the pH. Citrate has a long history of use in medicine as an anticoagulant and has the ability to chelate calcium ions. The half-life of citrate is very short, allowing it to be rapidly metabolized by the liver. Indeed, the successful use of citrate dialysate in liver transplant patients and in high bleeding risk patients has been reported [15]. These advantages suggest that acetate-free dialysate may be suitable for critically ill patients with AKI, without precipitating metabolic acidosis. Although CVVHDF was continued for 15.2 h, the pH level and HCO_3^- concentration following CVVHDF treatment were similar to pre treatment in the SHDF arm. In the SHDF arm, diffusive transport was engendered by a dialysate flow rate of 471 mL/min, with an extended session duration (6.0 h). SHDF convective transport was characterized by post-filter infusion of replacement fluid and a total effluent volume of 12.0 L/session, which was not significantly different from the CVVHDF arm. Therefore, SHDF showed superior efficacy of diffusive transport and equivalent efficacy of convective transport to those reported in previous studies that used “more intensive CRRT.”

The present study has several limitations. Firstly, our study was performed on a small number of patients and was a single-center study. A randomized, prospective trial comparing SHDF with conventional CRRT in a large cohort of patients is necessary to determine the relative impact of SHDF on mortality. Secondly, severity as assessed by APACHE II and SOFA scores in our patients was mild compared to other trials because subjects with nephrogenic AKI, including acute tubular necrosis (ATN), were included,

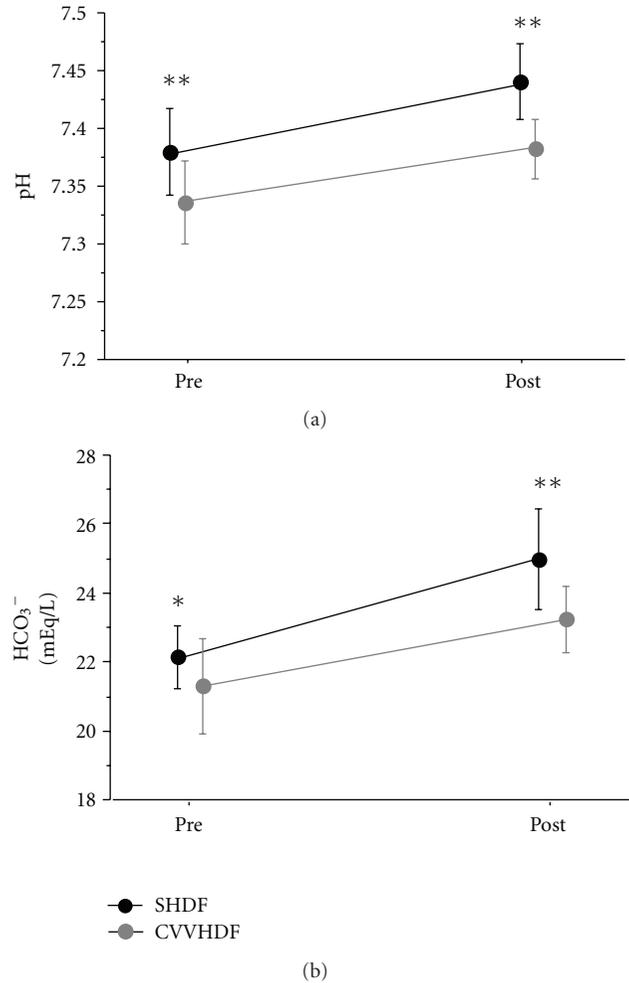


FIGURE 1: Changes in arterial blood pH and HCO_3^- concentration before and after treatment in the two treatment arms. * $P < .01$, ** $P < .001$ versus CVVHDF.

and so the survival rate was very high even in the CVVHDF arm. Thirdly, 16% of patients in the CVVHDF arm and 8% of those in the SHDF arm were transitioned to IHD while in the ICU (no significant difference). Therefore, in those subjects, there was the possibility that the efficacy of treatment could not be accurately assessed. Lastly, since the sterile bicarbonate solution (Sublood-BS®) used as replacement fluid in our SHDF contained a small amount of acetate, this method was not completely acetate-free. Therefore, in order to further validate the effectiveness of acetate-free SHDF for the treatment of critically ill patients with AKI, further studies are needed; these should involve a comparison of completely acetate-free dialysate and replacement fluid, with conventional dialysate and replacement fluid both containing a small amount of acetate.

5. Conclusion

Our results suggest that compared with conventional CRRT, a strategy of more intensive renal support involving daily

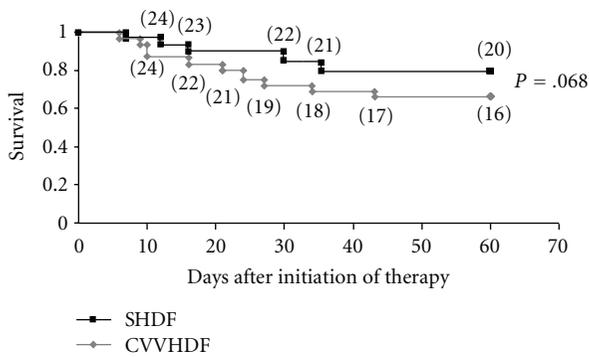


FIGURE 2: Kaplan-Meier analysis of hospital survival rates after CVVHDF versus SHDF. (): number of subjects alive.

postdilution SHDF with acetate-free dialysate may accelerate the recovery of kidney function in critically ill patients with AKI. The interruption of RRT by hemofilter thrombosis and catheter dysfunction was more frequent during CVVHDF than during SHDF. These advantages suggest that acetate-free dialysate may be preferable for patients with AKI. As this study was performed on a small number of patients in a single center, a randomized, prospective trial comparing the efficacies of acetate-free dialysate with conventional dialysate in a large cohort of patients is warranted in order to determine the relative impact of acetate-free dialysate and SHDF on mortality.

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Review Article

Renal Replacement Therapy in Austere Environments

Christina M. Yuan¹ and Robert M. Perkins²

¹*Nephrology Service, Department of Medicine, Walter Reed Army Medical Center, 6900 Georgia Avenue Northwest, Washington, DC 20012, USA*

²*Department of Nephrology, Center for Health Research, Geisinger Medical Center, MC 44-00, 100 North Academy Avenue, Danville, PA 17822, USA*

Correspondence should be addressed to Robert M. Perkins, rmperkins@geisinger.edu

Received 7 September 2010; Revised 8 February 2011; Accepted 22 February 2011

Academic Editor: Achim Jörres

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Myoglobinuric renal failure is the classically described acute renal event occurring in disaster environments—commonly after an earthquake—which most tests the ingenuity and flexibility of local and regional nephrology resources. In recent decades, several nephrology organizations have developed response teams and planning protocols to address disaster events, largely focusing on patients at risk for, or with, acute kidney injury (AKI). In this paper we briefly review the epidemiology and outcomes of patients with dialysis-requiring AKI after such events, while providing greater focus on the management of the end-stage renal disease population after a disaster which incapacitates a pre-existing nephrologic infrastructure (if it existed at all). “Austere” dialysis, as such, is defined as the provision of renal replacement therapy in any setting in which traditional, first-world therapies and resources are limited, incapacitated, or nonexistent.

1. Introduction

Austere renal replacement therapy (RRT) describes the provision of renal replacement therapy in any setting in which traditional, first-world therapies and resources are limited, incapacitated, or nonexistent. The provision of RRT in an austere environment is very different from that in a routine situation in a first-world country. In the latter case, the following apply (1) the environment is secure from violence and physical risk to the providers and patients; (2) the transportation infrastructure is functioning; (3) there are plentiful and stable sources of electricity, RRT supplies, and potable water; (4) engineering systems are in place for the production of pure water; (5) sophisticated equipment is available; (6) adequate equipment maintenance and nursing/technician staff support exist; (7) patient acuity and numbers are predictable and stable.

In an austere situation, some or all of these components may be inadequate or completely absent. If austere environment RRT is to be successful, the provider must identify the components that are lacking and attempt to offer reasonably safe and effective substitutes for them if they cannot be controlled or repaired. This requires flexibility,

the ability to triage, and a thorough understanding of the engineering and physiologic principals of RRT. Moreover, specific advance planning is necessary, especially in an environment or geographic area where certain disasters are likely to occur (particularly true for storms and earthquakes). Every dialysis unit should have a disaster plan. Moreover, it is important during planning and implementation not to allow (as in Voltaire’s aphorism) the “perfect” to become the enemy of the good. Ultimately, the optimal scenario for RRT provision after a disaster, or in an austere situation, is for RRT to be unnecessary or able to be delayed.

Others have provided expert opinion regarding the appropriate response to certain likely disasters (especially earthquakes and storms) for both providers and patients requiring both acute and chronic RRT [1–7]. Many recent reviews focus on the epidemiology and management of patients with acute kidney injury (AKI) due to crush injury sustained after earthquakes [2, 3, 7]. The Renal Disaster Relief Task Force (RDRTF) and European Renal Best Practice (ERBP) are currently developing comprehensive guidelines for the management of crush syndrome [8]. Therefore, in this paper, although we will discuss the situation of AKI due to crush injury as the paradigm for austere RRT, we

will focus more on general practical aspects of managing patients who require RRT in austere settings, regardless of the cause of renal failure. A particularly important group is patients with ESRD receiving chronic dialysis. Many such patients are likely to be encountered where chronic dialysis units have been incapacitated or resources are otherwise severely limited due to unanticipated disaster events. Lastly, it is important to remember that an “austere” RRT situation may exist where there are only a few patients to manage, and no “disaster” has occurred, but RRT provision is limited by logistical and equipment considerations alone.

2. Earthquake-Associated Crush Syndrome as a Paradigm for AKI after a Disaster

Although crush syndrome with resultant myoglobinuria and AKI due to acute tubular necrosis (ATN) is not the only type of renal failure requiring RRT seen under austere circumstances, it has received the most attention. Although most associated with earthquake events, it also may be seen in the setting of entrapment after building collapse due to any cause and was first described in 1941 in patients removed from beneath collapsed buildings during the aerial bombardment of London [9]. There was no RRT infrastructure in 1941 (dialysis had not yet been developed), and death due to hyperkalemia was the outcome for the patients described in this series.

Subsequently, much of the disaster nephrology literature has focused on preparing for and treating the influx of patients with ATN due to crush-related muscle injury after an earthquake event [7, 10, 11]. RRT management of such patients can be very resource intensive because of the associated muscle damage with resultant accelerated hyperkalemia, hypocalcemia, and acidosis. In addition, in situations where intravenous fluid resuscitation is available and employed, severe symptomatic “rebound” volume overload can occur in those who develop oliguria. Even with efficient, single-pass hemodialysis, RRT may be necessary more than daily, and dialysis dependence may last for weeks. Less efficient forms of RRT, such as peritoneal dialysis and continuous therapies, may not provide enough clearance to control the metabolic abnormalities (particularly hyperkalemia).

Although patients with myoglobinuric ATN require very resource-intensive RRT, the effects of the earthquake itself may significantly limit RRT delivery. After an earthquake, there may be prolonged interruptions of electricity and water delivery, transportation infrastructure and medical building may be severely damaged, and medical personnel themselves may be casualties. It is also difficult to predict the number and severity of casualties that may develop ATN and require RRT. The type of buildings in the area, the rapidity of rescue, the provision of intravenous (IV) fluid prophylaxis at the injury site, and the strength and timing of the earthquake can substantially affect the number of casualties with crush injury and subsequent ATN. For example, after the large California earthquakes of 1971, 1983, and 1989, crush injuries were small in number, but in situations where there are collapses of multistory stone or reinforced buildings (as seen in the

Armenian earthquake in 1988), there may be many [12, 13]. The damage can be so great that there are paradoxically few crush injuries and cases of ATN, because few persons are rescued or are able to access medical care. They simply die at the scene, as observed after the Haitian earthquake, as well as after the collapse of the World Trade Center in New York in 2001 [8, 14]. In another scenario, where buildings are small and constructed of relatively light materials, such as brick, wood, or adobe, there are few crush injuries because rescues are very rapid, and crush syndrome does not develop [15, 16]. Despite these observations, it is important to recognize that crush syndrome remains the second most likely cause of death in earthquake disasters after direct trauma and, unlike the latter, may be medically prevented [7].

The best treatment of crush injury-associated ATN is prevention. The pathophysiology of crush syndrome and rhabdomyolysis-associated ATN is complex and beyond the scope of this paper. Direct tubular toxicity due to heme iron released from myoglobin, other toxins released from injured muscle (to include uric acid), formation of obstructing myoglobin casts, volume depletion, free radical activation, reperfusion injury, cytokine release, and acidosis all appear to contribute to renal injury and development of ATN [17–19]. It has been shown in animal models as well as in humans that volume repletion, with increased glomerular filtration and tubular flow, prevents ATN, along with (and perhaps to a lesser extent) alkalization and administration of free radical scavengers (such as mannitol) [20]. This has been translated into the clinical practice of prophylactic isotonic IV fluid resuscitation to victims of crush injury in the field, in many cases while still entrapped—an intervention shown to be effective in preventing ATN [11, 21].

The RTRTF of the International Society of Nephrology (ISN) has developed a disaster plan and organized a response team to assist in the management of RRT for victims presenting with ATN after earthquakes [4]. They have reported extensively on their experiences with crush syndrome and management of AKI, after numerous large earthquakes [4]. It is noteworthy that crush syndrome casualties are proportionately few relative to the overall injured population, and even fewer require RRT [4]. Of those who do require RRT, mortality appears relatively low, and the majority who survive will regain renal function (Table 1). That being said, the burden of AKI requiring resource-intensive management will vary widely from one earthquake event to another, depending on a multitude of factors, only some of which are predictable prior the disaster event [22].

3. Defining the Disaster: RRT Demand and Capacity in Austere Situations

There are many other situations, besides earthquakes, when nephrologists may be called upon to manage an influx of patients requiring RRT, in an environment in which optimal physical and personnel resources are not available, or are severely compromised (Table 2). First, it is useful to summarize, in an orderly manner, the situations in which RRT may be required in an austere situation taking into consideration the capacity and demand for RRT.

(1) The most commonly described, and planned-for event is a disaster that results in an increased incidence of AKI, requiring an increased demand for RRT services. In this situation, the RRT infrastructure (capacity) may be in one of three states.

- (a) *Present previously and now severely damaged.* In this scenario, not only is there an influx of patients requiring acute RRT, but also there is a population of patients with pre-existing ESRD who are receiving either chronic hemodialysis or peritoneal dialysis. Examples of events that could cause such a situation include, but are not limited to, earthquakes and urban battlefields. Damage to infrastructure may vary considerably depending on the age, design, and location of the buildings housing dialysis units, and the size and intensity of the damaging event. This would be the situation predicted for the recent Chilean earthquake. However, there appear to have been very few cases of AKI after this event, and the major impact was on the patients with ESRD who were unable to receive care because of severe damage to their dialysis units [8].
- (b) *Previously nonexistent or negligible,* although other medical services may exist. In this scenario, there are few patients with pre-existing ESRD receiving chronic RRT, and the patients who require RRT largely have AKI. Events that could cause this situation include earthquakes, urban battlefields, infectious disease outbreaks associated with AKI (e.g., hantavirus-associated hemorrhagic fever, gastroenteritis-associated HUS), or wide population exposure to renal-toxins (e.g., melamine-contaminated infant formula) [38–40]. Earthquake events in third-world countries, such as the Haitian earthquake of 2010, are examples of this scenario [33]. One would presume, in this situation, that dialysis resources would have to be brought to the area, but this is not clear-cut. After the Haitian earthquake of 2010, although limited dialysis resources were “brought” to the area aboard the USNS Comfort, which had 2 standard hemodialysis machines and provided 15 treatments within the first 9 days [41], the ISN RDRTF repaired the existing infrastructure of the University Hospital dialysis unit in Port au Prince to support the care of both patients with AKI due to crush injury and 30 of the 100 Haitian chronic dialysis patients [8, 34].
- (c) *Present previously and now undamaged,* but insufficient to handle the influx (demand) of patients with AKI (and/or ESRD). This scenario is most likely to be seen in a refugee situation in areas adjacent to, but not affected by, an earthquake or war, after an isolated building collapse, or in the setting of large case numbers of AKI after an infectious outbreak or toxic release. A special case of this is when refugees with ESRD travel from a disaster site to an adjacent area with intact RRT infrastructure, as could be seen

after a devastating earthquake, storm, flood, or in the aftermath of a battle or terrorist attack. Excellent examples were the aftermath of Hurricane Katrina in 2005 and after the recent Chilean earthquake [1, 8].

(2) A less commonly discussed event is a disaster that does not produce an increased incidence of AKI or an influx of patients with ESRD, but results in inability of existing local ESRD patients to access dialysis due to disruption of transportation, damage to the dialysis infrastructure, or both. *The demand for RRT is unchanged, but the capacity to provide it is degraded.* The most common cause of such an event would be a weather emergency (such as a hurricane, tornado, flood, or blizzard), but civil unrest, war, and terrorist attacks could also be causes. This was the local scenario after Hurricane Katrina, but occurs to some extent quite commonly after local flooding or blizzards (as seen after the blizzards on the east coast of the US in early 2010) [1, 42].

If one considers the numbers of victims with AKI needing acute RRT after a disaster in the last several decades (Tables 1 and 2), it is striking how proportionately few were identified as having AKI, and then the fewer number who required dialysis. For instance, after the January 2010, Haitian earthquake in which over 200,000 people died, the dialysis response team dialyzed 19 patients with AKI, but also managed 30 patients with ESRD who were dialysis dependent before the earthquake [8]. In Chile, after the earthquake of February 2010, most fatalities were associated with the tsunami, and only 2 patients are reported as requiring RRT due to crush injury-induced AKI. However, there were over 2400 patients with ESRD on chronic dialysis—and their management after the destruction of many chronic dialysis units was the primary challenge facing the local nephrology community [8]. Evacuation to areas unaffected by the earthquake and adjustment of dialysis schedules at units within the earthquake zone that had survived were used to accommodate those patients whose dialysis units were nonfunctional. In the aftermath of Hurricane Katrina, the population of patients requiring chronic dialysis in Baton Rouge, LA increased by approximately 700 patients (the usual population was about 1000) due to the influx of refugees from areas of Louisiana affected by the hurricane [1]. Although there were no immediate deaths reported due to unavailability of dialysis services in this population, CMS data indicated that there was an increase in deaths among ESRD patients in the area within the first 180 days after the hurricane, although later data suggests that there was no significant change in mortality rate in the 6 months following the disaster, when compared to the 6 previous months [1, 43]. Thus, as ESRD services become more commonly available, even in countries which have relatively poor medical infrastructure such as Haiti, the management of patients with ESRD who are unable to access chronic dialysis after disaster may become the primary concern of local nephrologists and renal response teams, rather than RRT for AKI, even in the setting of very severe earthquakes [6].

TABLE 1: Earthquake-associated crush injury and outcomes after renal replacement therapy.

Author/year	Location	Year	No. deaths	No. requiring RRT*	Mortality after RRT*
Collins and Burzstein 1991 [23]	Mexico City, MX	1985	>3000	Unknown	Unknown
Tattersall et al. 1990 [13]	Northern Armenia	1988	Approximately 25,000	385	2 of 15 reported
Collins and Burzstein 1991 [23]	San Francisco, USA	1989	60	1	Not reported
Atef et al. 1994 [24]	Northwest Iran	1990	>40,000	154	23
Oda et al. 1997 [25]	Kobe, JP	1995	>5,000	8/8 reported	0
Vanholder et al. 2001 [26]	Northwest Turkey	1999	17,479	477	82
Sever et al. 2004 [27]					
Hwang et al. 2001 [28]	Central Taiwan	1999	>2,300	30	Not reported
Huang et al. 2002 [29]					
Viroja et al. 2003 [30]	India	2001	>20,000	33	6
Sever et al. 2006 [7]	Algeria	2003	2,266	15 (?)	unknown
Hatamizadeh et al. 2006 [31]	Iran	2003	25,514	126	19
Vanholder 2006 [32]	Pakistan	2005	74,968	77	11
Vanholder et al. 2010 [33]	Haiti	2010	>200,000	59	3 confirmed of 54 (5 lost to follow up)
Amundson et al. 2010 [34]	Haiti	2010	>200,000	Not reported	Not reported
Vanholder et al. 2011 [8]	Chile	2010	507	2	0

* Data reported is in many cases from single-center analyses; number requiring RRT and deaths therefore do not reflect total morbid burden for each event, rather the experience at a single center or regional area as reported in the referenced article.

TABLE 2: Reported nonearthquake disasters, requirement for renal replacement therapy, and outcomes.

Author/year	Event and location	Date	No. deaths	No. requiring RRT	Mortality after RRT
Bywaters and Beall 1941 [9]	Crush injury after bombing and building collapse, London	1941	4	NA	NA
Bentley and Jeffreys 1968 [35]	Crush injury after mine collapse, United Kingdom	1968	1	2 of 3	1 of 2
Goldfarb and Chung 2002 [14]	World Trade Center collapse after terrorist attack, New York City	2001	2,752	1	None
Altintepe et al. 2007 [36]	Building collapse, Konya, Turkey	2004	92	2	None
Kutner et al. 2009* [37]	Hurricane, New Orleans, LA	2005	1,836	Unknown	No excess mortality risk identified

* Retrospective cohort study examining mortality rates after Hurricane Katrina among patients with end-stage renal disease receiving dialysis therapy in the New Orleans area.

4. Disaster Planning for the ESRD Population: The Nephrologist's Perspective

How then does an individual nephrologist or chronic dialysis unit prepare for and respond to a disaster that may result in an austere RRT environment? In the United States, the Center for Medicare and Medicaid Services (CMS) requires that dialysis facilities must develop written policies and procedures for emergencies. The Kidney Community Emergency Response Coalition (KCERC), formed in the US after Hurricane Katrina, has published a set of guidelines for emergency planning [1]. Although many of the recommendations apply to federal, state, and local emergency providers, effective strategies are available for patients and providers. The KCERC "Time-Line to Safety" is a helpful, general

resource for patients, local dialysis units, and providers in developing a disaster plan, especially for disasters that are predictable (such as weather emergencies). The copy of the CMS publication "Preparing for Emergencies: A guide for people on dialysis" should be available to all patients [5].

The first step is to identify the disasters most likely to occur. Regardless of the type of disaster event, there are several planning recommendations that nephrologists, dialysis directors, nursing staff, and local policy makers should consider in localities with an existing dialysis infrastructure and many dialysis-dependent patients with ESRD.

(1) Assess and implement measures that will keep the dialysis facility functional and safe during and after a disaster event. Simple measures are important, such as knowing where utility shut-off valves are located [1].

(2) Educate patients about modifications to chronic diet and fluid intake in the event of a disaster. Fasting should be avoided, because of the risk of hyperkalemia. Volume overload and hyperkalemia are the most likely complications to “force” RRT treatments [6]. The CMS publication “Preparing for Emergencies: A guide for people on dialysis” contains a detailed 3-day diet plan and food supply list [5].

(3) Provide medications which may delay the need for dialysis to patients before a predictable disaster (such as a hurricane or snowstorm). The most common would be sodium polystyrene sulfonate for control of hyperkalemia. High-dose loop diuretics may increase urine output and kaliuresis in patients with residual renal function. Explicit instructions should be given to the patient on when to begin such medications, and these instructions should be reviewed at regular intervals with all chronic dialysis patients [5, 6].

(4) Ask patients to maintain updated lists of medications, allergies, health problems, and contact information for his/her providers and local dialysis unit, and to carry these records with them in the event of travel out of a disaster area. Medical records, electronic or otherwise, may not be accessible during an emergency. In fact, it should be assumed that communication systems will be nonfunctional for a period of time, and advance planning should focus on optimizing self-sufficiency for each patient as much as possible [1, 5].

(5) Develop emergency evacuation plans—at both the unit and individual ESRD patient levels—that provide for efficient, practical, and safe egress for both patients and staff. It is crucial that this planning incorporate both on-site and from-home scenarios. These plans should be routinely practiced by both staff and patients during scheduled and unscheduled drills. Home dialysis patients, especially PD patients, should not be forgotten, and specific guidelines exist for them with regard to infection control management [5, 43]. These plans require frequent review and training for both patients and staff. At the local and regional levels, policy leaders need to incorporate planning for the orderly and timely evacuation of the chronic dialysis population to areas unaffected by a disaster event.

(6) Anticipate that providers may also be affected by the disaster. Nurses and physicians themselves may be injured, be unable to travel to the facility, and may have personal responsibilities that are equal to their professional ones. Development of a defined and flexible coverage plan for staff during the first days of a disaster should be in place.

5. RRT in the Austere Environment: Practical Considerations

5.1. RRT Equipment. Any successful plan for managing RRT in the event of large-scale resource incapacitation will need to incorporate several key elements, regardless of the type and number of patients being managed. A disaster management plan should be as follows.

(1) Conserve resources (e.g., supplies, transportation, purified water, and staff). A dialyzer reuse plan, plans

for limitation of water use (decrease of dialysate flow rate), shortening of dialysis times, and reduction of supply consumption all should be considered. Available supplies (especially dialyzers) may not be the type used before the disaster, or may be in short supply. Dialyzer reuse may not be feasible or safe in many situations, but in scenarios where patient numbers are low, and resupply is totally disrupted, reuse should be considered [34].

(2) Determine thresholds for RRT initiation and frequency. At the height of the disaster, with its attendant difficulties of transportation and resource access, the presence of acute indications for dialysis and the catabolic state may determine which patients receive dialysis treatments, and standard treatment schedules may need to be abandoned. As the situation improves, accepted standards of RRT adequacy should guide treatment decisions regarding both ESRD and AKI patients, although this may be constrained by available resources.

(3) Provide flexibility. Single-pass hemodialysis with dialysate water delivered by a state-of-the-art portable or fixed water treatment plant may not be possible. Alternate RRT modalities must be considered, and each hemodialysis center should plan for the provision of an alternative means of renal replacement therapy should the pre-disaster, existing infrastructure be rendered nonfunctional. None is perfect—and none will be successful with all patients. Many of the same resource constraints are likely to apply to these as to conventional dialysis. Realistically, the modality that can be made to work in the existing environment is the one preferred! Alternatives include the following [44–49].

- (a) Peritoneal dialysis [6]: Peritoneal dialysis is an attractive alternative in settings where the electrical supply and the water plant are disrupted. Drawbacks include the need for peritoneal catheter placement, the risk of peritonitis, the need to obtain (or make) large volumes of appropriate sterile dialysate, and difficulty of metabolic control in the severely hypercatabolic patient.
- (b) CAVH/D and CVVH/D using replacement fluid/dialysate from readily available commercial IV crystalloid solutions: CAVH/D and CVVH/D have the disadvantage of requiring large volumes of replacement fluid/dialysate and may also be resource intensive from the standpoint of personnel. CAVH requires arterial access, and use of upper extremity AV fistulae/grafts may be difficult with CVVH. Clearance is inefficient over a short period of time. A distinct advantage is the limited electrical power requirements (CAVH requires none), and there is no need for water purification.
- (c) Isolated ultrafiltration for volume control, which does not require dialysate or a functioning water treatment plant and may even be achieved with dedicated slow continuous ultrafiltration devices used for management of congestive heart failure (Aquadex ref). Although this approach can control volume, there is no solute clearance [6, 50].

- (d) Alternative devices developed for home hemodialysis based on either sorbent or CVVH technology [51, 52]: because these devices have been developed for the home market, they are simple to use and quite robust. Existing chronic dialysis access can be used, and water treatment capacity is not necessary, as they either use a sorbent column or premixed replacement fluid.

(4) Plan for the production of “safe enough” water. Knowledge of water preparation and monitoring for dialysis—not only among nursing and technical staff, but among physicians—is essential. Because chloramines may be increased in potable water after a disaster to prevent water-borne illness, they may need to be monitored with greater frequency. Water may need to have more contact time with activated carbon filters. If possible, product water should be carefully monitored, especially if preparation is by mixed bed deionizer. Product water may need to be stored in tanks, rather than continuously made [8, 34, 48].

(5) Provide for electrical back-up systems/generators, which should be considered and in place before the disaster, with a plan for fueling them.

(6) Include an infection control plan, especially for patients who may be infected with tuberculosis or hepatitis B [1, 34].

5.2. Planning for RRT in Military Situations. The United States military medical services have well-described protocols for the provision of RRT to casualties in theater [46, 48]. The Army has planned to provide RRT to field hospitals via a dialysis “augmentation team” consisting of two dialysis technicians, a nephrologist, and an ICU nurse. The dialysis machine specified for use, until recently, was the REDY 2000, a sorbent-based system, which required 6-7 liters of potable water to manufacture dialysate for a 3-4-hour dialysis treatment. However, because of the success of aeromedical evacuation systems in rapidly removing casualties with AKI from theater, deployment of this augmentation team was never required [48], and the REDY 2000 is no longer manufactured. There have been occasions when alternative, short-term solutions, including peritoneal dialysis, CVVH, and CAVH, have been used in austere conditions to manage individual patients presenting acutely who could not be evacuated in a timely manner [47]. The US Navy maintains a state-of-the-art dialysis facility on the USNS Comfort, which uses single pass dialysis machines that one might encounter in a tertiary care medical center. This ship assisted with the dialysis needs of patients in Haiti after the earthquake in 2010 [34].

5.3. RRT Triage and Prescription. The management of RRT for AKI/ESRD under austere conditions can be conveniently divided into management of crush syndrome patients (and, more generally, any patient in a hypercatabolic state) versus those patients with AKI or ESRD who are not hypercatabolic and may require less intense dialysis. For hypercatabolic patients, single-pass hemodialysis is the most efficient method of managing the hyperkalemia and acidosis which

are immediately life-threatening, and other modalities (such as CRRT and PD) may not be adequate to prevent life-threatening hyperkalemia. However, such modalities may be tried in settings where single-pass hemodialysis is not feasible, and they may be effective [44–48, 53].

In patients with AKI who are not hypercatabolic and in patients with ESRD, in settings where resources are limited, an effort should be made in the early period after a disaster to triage patients on the basis of their acute need for RRT [1, 48]. This approach to provision of RRT is supported by experience with AKI at the very beginning of the dialysis era. As early as the 1950s, it was well recognized that patients with ATN more-or-less followed a defined course, and that nonoliguric patients had better outcomes than oliguric patients. If an acute event could be avoided (i.e., fatal hyperkalemia, acidosis, volume overload, and life-threatening uremia), patients could be expected to recover, and acute dialysis (which was technically very complex and difficult) was reserved only for these potentially fatal events. Using this approach, mortality in AKI (even trauma-associated AKI) was reduced to approximately 50–60% from the previously near-universal fatality rates which accompanied the most severe AKI [54, 55].

Studies of dialysis withdrawal in well-dialyzed ESRD patients have shown that with aggressive volume restriction and judicious use of kaliuretics and potassium-binding resins, routine dialysis may be delayed for several days before the classic signs and symptoms of uremia develop or a life-threatening electrolyte imbalance occurs [6, 56]. Isolated ultrafiltration, which does not require the use of dialysate, may be helpful to those in whom volume overload is the only indication for RRT and is resource friendly in conditions where supplies are constrained [6].

Screening for the need for acute dialysis can be done simply and requires little in the way of laboratory support [33]. A physical examination and history assessing for symptoms and signs of severe uremia (pericardial friction rub, asterixis, vomiting/severe nausea, neurologic instability) can be done. Solid-state, hand-held blood analyzers may be invaluable in assessing for hyperkalemia and acidosis and may also be used to check the electrolyte content of dialysate [40]. Life-threatening hyperkalemia may also be assessed by ECG [1].

With screening, dialysis treatments may be reserved for patients who are in acute need of them, thus directing scarce resources to those most likely to benefit. Resources may be limited, and “optimal” RRT therapy, as defined in a nondisaster setting, may be impossible to deliver. However, difficult to recognize, it is important for patients and direct providers to remember that in large-scale disaster events, there are likely to be many more victims/refugees who will not require RRT services than those who will, and that there are likely to be other resource-intensive injuries present. Emergency providers must therefore focus on the principals of triage, a systematic patient-prioritization technique whereby decisions regarding care, medical evacuation, or any other resource-intensive intervention of limited supply are made based on a combination of factors to include illness or disease severity, likelihood of survival within the constraints

of the resources available, and the number of casualties relative to the resources at hand. The process might be best summarized as an attempt to achieve “the greatest good for the greatest number” [57]. In the mass casualty situation, this can be difficult, as in rare cases decisions to withhold available care to the most severely injured may be necessary in order to save others.

Applying the concepts of triage to decisions regarding maintenance hemodialysis therapies to chronic ESRD patients in a disaster setting may require that the nephrologist set aside his or her standard approaches and adherence to dosing and management guidelines in order to maximize outcomes for the greatest number of individuals. The underlying chronic illness burden and the age of the ESRD patient must be taken into account, as well as adherence to diet and volume restriction, overall dialysis adequacy prior to the disaster, and the likelihood of evacuation. In a situation of fixed and inadequate/barely adequate RRT capacity, it may not be possible to intensify RRT for a particularly fragile or non-dietary-compliant ESRD patient at the expense of dangerously decreasing RRT therapy intensity for others overall. In more extreme situations, especially those involving a mix of ESRD, AKI, and highly catabolic AKI patients, even more difficult RRT triage decisions may be required. Helpful reviews and guidelines are available for those medical personnel involved with disaster planning who may be less familiar with these important concepts [58–60].

The experience of others would support the notion that triage concepts can be applied successfully to the management of ESRD patients after natural disasters: Sever et al. have reported on the successful management of ESRD patients using a reduced dialysis schedule at seven dialysis centers in Turkey after the Marmara earthquake. In their report, an approximate 50% reduction in functional capacity contributed to a 3-fold increase in the number of once-weekly dialysis treatments. Despite this, interdialytic weight gain and blood pressures remained relatively stable, likely due to successful self-management of fluid intake and dietary restriction [61].

Disclaimer

The views expressed in this paper are those of the authors and do not reflect the official policy of the Department of Army, the Department of Defense, or the US government.

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Clinical Study

Acute Renal Replacement Therapy in Children with Diarrhea-Associated Hemolytic Uremic Syndrome: A Single Center 16 Years of Experience

Silviu Grisararu, Melissa A. Morgunov, Susan M. Samuel, Julian P. Midgley, Andrew W. Wade, James B. Tee, and Lorraine A. Hamiwka

Division of Pediatric Nephrology, Department of Pediatrics, Alberta Children's Hospital, University of Calgary, 2888 Shaganappi Trail NW, Calgary, AB, Canada T3B 6A8

Correspondence should be addressed to Silviu Grisararu, sgrisaru@ucalgary.ca

Received 31 August 2010; Revised 18 January 2011; Accepted 23 March 2011

Academic Editor: A. Davenport

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Acute kidney injury (AKI) is becoming more prevalent among hospitalized children, its etiologies are shifting, and new treatment modalities are evolving; however, diarrhea-associated hemolytic uremic syndrome (D+HUS) remains the most common primary disease causing AKI in young children. Little has been published about acute renal replacement therapy (ARRT) and its challenges in this population. We describe our single center's experience managing 134 pediatric patients with D+HUS out of whom 58 (43%) required ARRT over the past 16 years. In our cohort, all but one patient were started on peritoneal dialysis (PD). Most patients, 47 (81%), received acute PD on a pediatric inpatient ward. The most common recorded complications in our cohort were peritoneal fluid leaks 13 (22%), peritonitis 11 (20%), and catheter malfunction 5 (9%). Nine patients (16%) needed surgical revision of their PD catheters. There were no bleeding events related to PD despite a mean platelets count of $40.9 (\pm 23.5) \times 10^3/\text{mm}^3$ and rare use of platelets infusions. Despite its methodological limitations, this paper adds to the limited body of evidence supporting the use of acute PD as the primary ARRT modality in children with D+HUS.

1. Introduction

The incidence of acute kidney injury (AKI, previously called acute renal failure) in children is not well defined, however, a number of recent studies suggest that it is increasing. This observation may be related to the changing etiology of AKI in children particularly in the tertiary care pediatric care hospital setting. Primary renal disease used to account for the majority of hospitalized children with AKI, whereas now the leading cause for AKI in this population is multifactorial including ischemic/hypoxic and nephrotoxic injury secondary to primary conditions such as prematurity, postcardiac surgery, or bone marrow transplantation. The lack of a well-accepted universal definition of AKI has been one of the major hurdles for researchers trying to establish incidence and etiology of AKI in children, however, the recent validation of the pediatric RIFLE criteria promises to

offer a solution to this problem. RIFLE criteria (*R* risk for renal dysfunction, *I* injury to the kidney, *F* failure of kidney function, *L* loss of kidney function, and *E* end-stage renal disease) is a standardized classification method for AKI in adults which has been adapted for and validated in pediatric patients as pRIFLE [1–3].

Despite the shift in the most common etiologies for AKI in hospitalized children from primary kidney disease to injury secondary to nonrenal diseases, diarrhea-associated hemolytic uremic syndrome is still considered the most common primary disease causing acute kidney injury in young children [4]. Currently, there is no effective preventive or specific treatment for this disease leaving symptomatic and supportive treatments as the main management options for children with D+HUS [5, 6]. Acute renal replacement therapy (ARRT) is frequently required in the acute phase of D+HUS. Older published series have reported that ARRT

is needed in up to 100% of patients; however, more recent studies report that it is required in about 40%–60% of children with D+HUS [5, 7]. All available ARRT modalities are considered equally effective in the management of children with D+HUS although peritoneal dialysis (PD) has been mentioned to potentially enhance clearance of plasminogen activator inhibitor 1, therefore facilitating renal recovery [8]. Available literature supporting any one specific AART modality and even sharing practice experience performing ARRT in children with D+HUS is very limited.

We recently reviewed patients treated for D+HUS in our center to calculate the incidence of childhood D+HUS in Southern Alberta, a region previously shown to be endemic for D+HUS (in press). The objective in this current paper is to summarize and share our single center's experience with ARRT in children with D+HUS over the past 16 years.

2. Methods

2.1. Patient Recruitment and Inclusion Criteria. Institutional ethics approval was obtained for this study from the University of Calgary. Alberta Children's Hospital (ACH) is a sole tertiary care pediatric referral center providing care for 1.6 million inhabitants of Southern Alberta, Canada.

An electronic database search for all cases of D+HUS documented at ACH from March 1st, 1994 to March 31st, 2010 was conducted. Charts of identified patients were reviewed to confirm the diagnosis of D+HUS based on the following criteria: history of diarrhea-associated with intravascular hemolytic anemia (hemoglobin <105 gm/L with schistocytes), thrombocytopenia (platelets <150 × 10⁹/L), and evidence of renal injury (serum creatinine concentration above the 95th percentile for age or >10 erythrocytes per high-power field on light microscopy of a urine sample). Chart documentation of all 3 criteria was required to confirm a case of D+HUS. Patients younger than 18 years at diagnosis were included. Patients with atypical hemolytic uremic syndrome (HUS) such as inherited forms of HUS and HUS secondary to organisms other than Shiga-like toxin producing *E.coli* (STEC) were excluded.

2.2. Acute Renal Replacement Therapy. The need for ARRT was assessed by the attending nephrologist in a case-by-case manner for each one of the patients included in this cohort. Nonspecific indication for ARRT in the context of AKI were applied, the most common being progressive oligoanuria and rapid metabolic deterioration secondary to AKI (rapidly raising urea, creatinine, potassium, or progressive metabolic acidosis). While these indications are nonspecific and strict parameters have not been adopted, the general consensus in our center is that ARRT should be offered early. In cases where patients were not offered ARRT during their acute illness, the attending nephrologist felt that there was no need for it based on the general criteria mentioned above.

Acute renal replacement modalities available in our center include PD, intermittent hemodialysis (IHD), or continuous venovenous hemofiltration with or without dialysis (CVVH ± D). The preferred choice for D+HUS patients in

our center is PD however the choice is made by the attending pediatric nephrologist in a case by case manner. Cook spiral double cuffed Tenckhoff peritoneal dialysis catheters are usually used in our center; however, straight and other types of catheters are available. An omentectomy is not routinely performed at the initial insertion of a Tenckhoff catheter but is always done during catheter revisions performed due to technical failure of PD. The preferred access for CVVH in our institution is a temporary internal jugular line usually placed by the ICU attending physician or occasionally by the interventional radiologist. Urgently needed permanent hemodialysis lines for IHD are usually placed by the attending general surgeon or the interventional radiologist in the operating room.

PD is routinely performed on the general pediatric inpatient ward by appropriately trained nurses, whereas CVVH requires admission to the ICU. IHD can be performed in the hemodialysis unit; however, during the acute phase, patients with D+HUS are frequently hemodynamically or neurologically unstable enough to require ICU care.

2.3. Data Collection. Data was obtained from medical charts of identified patients and included age at presentation, gender, highest creatinine level, lowest platelet count, ARRT modality, duration of anuria, duration of ARRT, technical challenges, and complications related to ARRT. Outcome data collected included documentation of residual chronic renal failure, proteinuria, and hypertension at last follow-up visit. Patients were followed for a minimum 1 year and up to 14 years after presentation.

3. Results

After completion of the chart review, 134 children were confirmed to have been treated for D+HUS at the Alberta Children's Hospital from April 1994 to March 2010; fifty eight of them (43%), required ARRT in the acute phase of their management. Characteristics of these patients as well as the rest of the patients and ARRT details are presented in Table 1. Outcome parameters for patients who required ARRT and those who did not are shown in Table 2.

Fifty four patients (93%) of the total 58 who required ARRT were managed exclusively by PD. The remaining 4 patients were managed with PD and an additional modality: one patient who was septic and hemodynamically unstable on admission was started on CVVH in the ICU and then transitioned to PD after 5 days. The other 3 were initiated on PD but were temporarily switched to CVVHD or IHD due to severe peritoneal fluid leak, bowel necrosis, and development of a pleura-peritoneal communication with a pleural effusion.

One patient was diagnosed with bowel perforation while on PD due to feculent PD effluent. An urgent left hemicolectomy and resection at the hepatic flexure was performed after which CVVH was attempted but failed because of an inability to establish adequate vascular access. The patient successfully resumed PD and received intraperitoneal antibiotics for treatment of peritonitis caused by the bowel perforation.

TABLE 1: Patient characteristics and ARRT details.

Number of patients (<i>n</i>)	58
Male/Female	25/34
Highest creatinine, mean (\pm SD), μ mol/L	261.3 (\pm 240.1)
Lowest platelet count, mean (\pm SD), $\times 10^3/\text{mm}^3$	40.9 (\pm 23.5)
Patients that received platelets transfusion	3 (5%) Mean
duration of anuria (\pm SD), days	8.47 (\pm 8.9)
Duration of RRT (\pm SD), days	20 (\pm 32.4)
Duration of admission (\pm SD) days	23.8 (\pm 11.6)
Peritoneal fluid leak	13 (22%)
PD catheter malfunction	5 (9%)
Pleuro-peritoneal communication and leak	2 (3%)
PD catheter surgical revisions	9 (16%)
Bleeding events	0
Patients treated for suspected peritonitis	11 (20%)
Patients that required ICU admission	11 (20%)
Mortality	1 (2%)

TABLE 2: Outcomes after ARRT for D+HUS.

Number of patients (<i>n</i>)	58
Patients with GFR < 80 mL/min/1.73 m ²	7 (12%)
Patients with GFR < 40 mL/min/1.73 m ²	1 (2%)
Hypertensive at followup	3 (5%)
Proteinuria	18 (31%)

Among the 4 patients who were managed by CVVH or IHD in our cohort, 3 vascular access catheters clotted or did not function after insertion. The only death among the patients who required ARRT, and in fact among all 134 patients with D+HUS, was caused by an episode of massive gastrointestinal bleeding due to bowel necrosis.

4. Discussion

Diarrhea-associated hemolytic uremic syndrome is the most common primary disease causing acute kidney injury in children and among hospitalized children; it is second only to ischemic/nephrotoxic injury as a cause for acute kidney injury [4].

The prognosis of D+HUS has improved dramatically since the disease was first reported mostly due to the now widespread availability of acute renal replacement therapy in children [7]. Indications for initiation of ARRT in children with D+HUS are nonspecific, for the management of oligoanuria, metabolic acidosis, and electrolyte abnormalities. Effective management of these complications can be achieved by all available methods of ARRT, including hemodialysis and hemofiltration; however, PD is in many centers the preferred ARRT modality for children with D+HUS [6, 8]. Our experience reported here supports this practice by demonstrating that the vast majority of children with D+HUS requiring ARRT can be safely and successfully managed with acute PD performed on a pediatric ward after surgical insertion of a PD catheter. The most common

technical difficulty associated with this modality in our cohort was peritoneal fluid leaking around the catheter followed by catheter malfunction which did not always require surgical revision of the catheter. In the majority of cases, these complications did not result in discontinuation or change of modality. Peritoneal fluid leaks, for example, were in most cases successfully managed by temporarily reducing the dwell volumes.

Despite the profound thrombocytopenia experienced by the majority of the patients, platelets transfusion were almost never used, and bleeding events associated with the surgical insertion of the PD catheter did not occur. This was also shown by a recent retrospective study, which found no bleeding after insertion of PD catheters in children with D+HUS, with or without platelets transfusions [9].

Sepsis and severe gastrointestinal injury such as bowel perforation in patients with D+HUS have been mentioned as possible indications for selecting a different modality of ARRT [10]. One patient from our cohort was successfully managed with PD even after bowel perforation requiring emergency hemicolectomy. In fact, PD allowed for a very rapid diagnosis of the perforation, prompt surgical management, resumption of PD, and antibiotic treatment of the intra-abdominal infection. Two additional patients in our cohort that were on PD when they developed bowel obstruction secondary to intestinal strictures were managed conservatively without changing their ARRT.

Patients who are slow to recover their kidney function or require chronic dialysis can choose to continue with home PD using the original PD catheter that was inserted during the acute phase of their D+HUS. In our cohort, there were two such patients that continued on chronic home PD for 93 and 240 days, respectively, before regaining enough function to be able to come off dialysis.

Most of our patients did not require admission to the ICU and were managed on a regular pediatric ward by nursing staff that had previous training in PD. In our center, selection of other ARRT modalities would have led to many more days spent in the ICU. The availability of IHD and CVVH \pm D in children has been facilitated by significant technological advances leading to increasing popularity of these methods among pediatric nephrologists and intensivists, while the use of acute PD for children needing ARRT is declining [4, 11]. However, there is currently no evidence to support superiority of any specific ARRT modality in children with D+HUS.

The outcome data shown in Table 2 illustrates the excellent renal recovery which ultimately occurs in most patients as previously shown by many investigators [7]. The data also demonstrates that residual proteinuria is a frequent complication, suggesting that these patients have suffered significant renal injury with potentially long-term consequences and, therefore, need careful followup.

This study is limited by its retrospective descriptive methodology as well as the biased preference for PD in our center. However, despite these limitations, we believe that the experience reported here represents a worthy addition to the currently modest body of evidence supporting the use of PD in children with D+HUS needing ARRT.

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