Acute Renal Failure in the Intensive Care Unit

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ABSTRACT

Acute renal failure (ARF) is a common complication in critically ill patients, with ARF requiring renal replacement therapy (RRT) developing in ~5 to 10% of intensive care unit (ICU) patients. Epidemiological studies have demonstrated that ARF is an independent risk factor for mortality. Interventions to prevent the development of ARF are currently limited to a small number of settings, primarily radiocontrast nephropathy and rhabdomyolysis. There are no effective pharmacological agents for the treatment of established ARF. Renal replacement therapy remains the primary treatment for patients with severe ARF; however, the data guiding selection of modality of RRT and the optimal timing of initiation and dose of therapy are inconclusive. This review focuses on the epidemiology and diagnostic approach to ARF in the ICU and summarizes our current understanding of therapeutic approaches including RRT.

KEYWORDS: Acute renal failure, renal replacement therapy

EPIDEMIOLOGY OF ACUTE RENAL FAILURE

Acute renal failure (ARF) is an abrupt decline in kidney function that develops over a period of hours to days. Although simple to define conceptually, there is no consensus on an operational definition of ARF. Definitions that have been used in clinical studies have been highly variable. Some have been based on changes in the serum creatinine (Scr) concentration with wide variability in the relative or absolute magnitude of change, others on the presence of oliguria, and still others on the need for renal replacement therapy (RRT). This variation in definitions has confounded efforts to characterize the epidemiology of ARF. Interpretation and comparison of epidemiological studies must therefore take into consideration not only the characteristics of the patient population studied but also the particular criteria used to define ARF.

In two large European studies, the overall population-based annual incidence of ARF was 140 to 209 cases per million persons.[1,2] Other series have demonstrated community-acquired ARF in 0.4 to 0.9% of hospital admissions,[3] whereas hospital-acquired ARF developed during 4.9 to 7.2% of hospitalizations, with an apparent increase in incidence over a 2 decade interval.[4,5]

With a well-recognized relationship between severity of illness and risk for ARF, it is not surprising that the incidence of ARF increases dramatically in the intensive care unit (ICU) setting. Over a 10-month period spanning 1991 to 1992, Liano and Pascual studied the epidemiology of ARF in 13 tertiary-care hospitals in Madrid, Spain.[2] Of the 747 episodes of ARF that were identified, 253 (34%) occurred in ICU patients. In other studies, the prevalence of ARF in critically ill patients has ranged from 3 to 25%. In a large, multinational study published a decade ago, ARF, defined as an increase in Scr to more than 3.5 mg/dL or the presence of oliguria, was observed in 348 of 1411 ICU patients (24.7%).[6] Nearly half of these

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patients had primarily medical causes for ICU admission; however, in 25% of cases, ARF developed in the setting of trauma or during the postoperative period. In contrast, in a study of 17,126 patients in 30 Austrian ICUs, the incidence of ARF was only 4.9%, with ARF defined by the need for RRT.[7] Similarly, Uchino and colleagues reported a prevalence of severe ARF of 5.7% in 29,269 patients treated at 54 centers in 23 countries, using a definition of ARF based on the presence of oliguria or azotemia severe enough to warrant RRT.[8] Although the varying incidence of ARF in these and other studies almost certainly relates to the different criteria employed to define this syndrome, it is quite clear that ARF complicates the clinical course of a substantial proportion of patients requiring ICU care.

OUTCOMES OF ACUTE RENAL FAILURE

Much like efforts to describe the epidemiology of ARF, attempts to characterize outcomes associated with ARF are confounded by the different definitions that have been employed. A series of studies in demographically diverse populations have demonstrated in-hospital mortality rates in critically ill patients with ARF that range from ~35% to as high as 75%.[7,9–13] A variety of factors have been associated with mortality risk. In the recent multinational study by Uchino and colleagues, independent predictors of hospital mortality included use of vasopressors and mechanical ventilation, septic shock, cardiogenic shock, and hepatorenal syndrome.[8] Although the definition of ARF used in this study precluded an assessment of the effect of RRT on hospital mortality, this variable has emerged as one of the primary predictors of hospital mortality in multiple other studies of ARF in critically ill patients. Metnitz and colleagues found a fourfold higher mortality rate among patients requiring RRT for ARF than in patients without ARF (62.8% vs 15.6%; $p < .001$).[7] This excess mortality persisted after adjustments for illness severity, age, and treatment center. Similarly, in the Program to Improve Care in Acute Renal Disease (PICARD), a multicenter observational study of ARF in the United States, Mehta and colleagues also demonstrated markedly higher mortality rates in patients with ARF who required RRT than in those who did not (45% vs 24%).[14] Thus it appears that not only is ARF associated with increased mortality risk compared with other critically ill patients, but RRT is one of the strongest negative prognostic factors, although this may merely reflect RRT serving as a surrogate for severity of renal injury.

It had been widely believed that with the widespread availability of RRT to manage the uremic consequences of renal failure, patients with ARF died with, but not of, their renal failure. However, evidence accrued over the past decade suggests that this paradigm is incorrect. In the earliest of these studies, Levy and colleagues observed an independent mortality risk in patients developing radiocontrast nephropathy (RCN).[15] After adjustment for comorbidities, there was a 5.5-fold increased mortality risk associated with the development of ARF. The increased mortality risk was greatest in patients with the lowest levels of comorbid illness, and declined as the burden of comorbid conditions increased. Although this study was not restricted to critically ill patients, other studies restricted to critically ill patients have demonstrated a similar increased mortality risk. Using their database of patients treated in Austrian ICUs, Metnitz and colleagues compared survival in patients with and without ARF based on disease-specific observed to expected (O:E) mortality ratios.[7,16] Among patients with lower severity of illness, ARF was associated with a sevenfold higher O:E mortality ratio.[16] Differences in the more severely ill patients were less robust, suggesting that among the most critically ill, risk-adjustment for severity of illness becomes increasingly difficult, and extrarenal factors are progressively more important predictors of outcome. Similarly, Chertow and colleagues demonstrated a nearly eightfold increased mortality risk associated with ARF following open heart surgery.[17]

As part of a study addressing the effect of ARF in ICU patients, Clermont and colleagues prospectively tracked outcomes of 1530 ICU admissions at a single institution over a 10-month period, categorizing patients into three groups: patients with ARF, patients with end-stage renal disease (ESRD), and patients without evidence of renal failure.[9] Mortality among patients who developed ARF was double that observed among patients with ESRD and four times greater than that seen in patients without renal dysfunction (23% vs 11% vs 5%). Although Acute Physiology and Chronic Health Evaluation (APACHE) III scores were comparable in the ARF and ESRD cohorts, hemodynamic instability and leukocytosis were more common in patients with ARF and the study lacked a robust multivariable adjustment for confounding factors. Despite these limitations, the results of this study imply that the pathophysiological effects of ARF extend beyond the loss of organ function.

ETIOLOGIES OF ACUTE RENAL FAILURE

Early recognition of ARF and prompt determination of its etiology facilitate the institution of appropriate therapy and can potentially mitigate its severity. ARF can be broadly classified into prerenal, intrinsic, and postrenal etiologies. Prerenal azotemia, the most common form of hospital-acquired ARF, represents a decline in glomerular filtration rate (GFR) due to hemodynamic factors that diminish effective renal perfusion. The defining pathological feature in prerenal azotemia is the absence of histological damage to the renal parenchyma. The

Table 1 Laboratory Findings in the Syndromes of Acute Renal Failure

	BUN:Scr Ratio	U_{Na} (mEq/L)	FE_{Na}	Urinalysis	Other Findings
Prerenal ARF	>20:1	<20	<1%	Bland specific gravity >1.015	FE_{urea} <35% hyperuricemia
Intrinsic ARF					
ATN	10:1	>40	>2%	Granular casts specific gravity ~1.010	FE_{urea} >50%
AIN	10:1	Variable	Variable	RBCs, WBCs, WBC casts, eosinophiluria	Eosinophilia
GN	Variable	<20	<1%	RBCs, RBC casts	—
Intratubular Obstruction	Variable	Variable	Variable	Crystalluria or immunoglobulin light chains	Urine or serum monoclonal paraprotein
Vascular	Variable	Variable	Variable	Variable	Hematuria
Postrenal ARF	>20:1	Variable	Variable	Variable	Fluctuating urine output elevated postvoid bladder volume hydronephrosis

ATN, acute tubular necrosis; AIN, acute interstitial nephritis; GN, glomerulonephritis; BUN, blood urea nitrogen; Scr, serum creatinine; U_{Na}, urine sodium concentration; FE_{Na}, fractional excretion of sodium; FE_{urea}, fractional excretion of urea; RBC, red blood cell; WBC, white blood cell.

physiological response to diminished renal perfusion is an increase in renal tubular sodium avidity and urinary concentration. Clinically, the increase in sodium avidity is manifested by a urine sodium concentration less than 20 mEq/L and a fractional excretion of sodium less than 1% (Table 1). In patients on diuretics, urinary sodium may be increased as a result of pharmacological blockade of reabsorptive pathways. In such patients, a fractional excretion of urea of less than 35% is highly suggestive of a prerenal state. The hemodynamically mediated secretion of vasopressin increases urinary concentration, resulting in a urine specific gravity greater than 1.015 to 1.020 and urine osmolality greater than 300 mOsm/kg H_2O. Increased tubular reabsorption of urea in prerenal azotemia may result in a disproportionate elevation in blood urea nitrogen (BUN) concentration relative to Scr. Severe and protracted renal hypoperfusion can lead to ischemic injury to the renal parenchyma and can contribute to the development of acute tubular necrosis (ATN), making early recognition and treatment of prerenal azotemia essential. Prompt reversal of the abnormal hemodynamics will usually lead to full recovery of renal function.

Postrenal ARF results from anatomical obstruction to urine flow at the levels of the ureters or bladder outlet. Although obstructive disease may be unilateral, renal failure requires the presence of bilateral obstruction or unilateral obstruction of a solitary functional kidney. Postrenal ARF is usually readily diagnosed on the basis of bilateral hydronephrosis on renal ultrasound or the finding of an elevated postvoid residual bladder volume (>100 mL). Treatment of postrenal disease requires relief of the obstruction. In patients in whom the obstruction is at the level of the urinary bladder, improvement in renal function may be accomplished with simple placement of a bladder catheter. Among patients with upper tract obstruction, ureteral stenting or percutaneous nephrostomies are required.

Although pre- and postrenal ARF can cause or exacerbate a decline in renal function in critically ill patients, the most common etiology of ARF in the ICU is intrinsic ARF, most commonly due to ATN. In a prospective analysis of patients hospitalized in 28 ICUs in France, 83% of recorded cases of ARF were attributed to ATN, with 54% associated with ischemic renal injury, 8% from nephrotoxic injury, and 21% of mixed etiology.[11] Among 253 episodes of ARF in critically ill patients reported by Liano and colleagues, ATN accounted for 75.9% of episodes compared with 61.4% in non-ICU patients.[18] Prerenal azotemia was the second leading cause of ARF, with obstructive disease accounting for less than 1% of cases.

Unlike prerenal azotemia, ATN is defined by the presence of tubular epithelial cell injury, apoptosis, and necrosis, and is associated with the characteristic urinary finding of coarse granular "muddy brown" casts composed of sloughed epithelial cells and cellular debris. The resulting defects in renal tubular function generally result in impaired sodium reabsorption, a urine sodium concentration greater than 40 mEq/L, and fractional excretion of sodium greater than 2 to 3%. Defective urinary concentration and dilution are manifested by isosthenuric urine, with a specific gravity of ~1.010 and an osmolality of 250 to 300 mOsm/kg H_2O.

ATN may result from renal ischemia, endogenous or exogenous nephrotoxins, and/or sepsis. Although the pathophysiology of ATN remains incompletely understood, robust conceptual models of its pathogenesis have been developed. In ischemic ATN, the initial insult causes hypoxia of highly metabolically active tubular cells. Cells at the corticomedullary junction are particularly susceptible to ischemic injury due to their high basal oxygen demand and relatively low

regional oxygen delivery. Although ATN associated with sepsis has commonly been viewed as mediated primarily by ischemic injury, recent data suggest primacy of other pathophysiological processes.[19] Recent experimental animal models and limited human studies suggest that overall renal perfusion is preserved or even increased with sepsis, yet regional redistribution of blood flow within the kidney may shunt blood away from the corticomedullary junction.[20–22] Although specific mechanisms for deterioration in renal function in hyperdynamic sepsis remain unknown, recent work suggests that activation of cellular and humoral inflammatory mediators and of coagulation pathways play a central role.[23–27] In nephrotoxic ATN, direct cytotoxicity to tubular epithelial cells is the primary mechanism of renal injury. Epithelial cell injury leads to loss of polarity, activation of apoptotic pathways resulting in both apoptotic and necrotic cell death, and sloughing of both viable and dying epithelial cells into the tubular lumen. The associated fall in GFR that defines ARF is mediated by a combination of intratubular obstruction from the sloughed debris, backleak of glomerular filtrate across the denuded tubular basement membrane, and intrarenal vasoconstriction. Although the tubular epithelial cell injury has been the central focus of understanding ATN, the role of endothelial cell injury, generation of reactive oxygen species, and activation of inflammatory pathways have been increasingly recognized as critical to the pathogenesis of ATN.[28–31]

A variety of other intrinsic forms of ARF such as acute interstitial nephritis, acute glomerular disease, atheromboembolic disease, and tumor lysis syndrome account for some cases of ARF in critically ill patients. Nonetheless, the following discussion of the prevention and treatment of ARF will focus on patients with ATN because it is the predominant form of ARF in the ICU setting.

PREVENTION OF ACUTE RENAL FAILURE

The morbidity and mortality associated with ARF have energized multiple efforts to identify strategies to forestall its development. Unfortunately, most episodes of ARF are unpredictable, and hence prophylactic interventions are impractical. There are, however, specific settings in which it is possible to identify high-risk patients and institute preemptive strategies to decrease the risk of ARF.

Radiocontrast Nephropathy

The administration of intravascular radiocontrast media represents one of the most important settings for such strategies (Table 2). RCN is one of the most common forms of ATN, accounting for ~10% of hospital-acquired ARF.[4] Many of the radiographic procedures that utilize intravascular radiocontrast, even in critically ill patients, are planned sufficiently in advance to permit the implementation of preventative measures. Factors that predispose to the development of RCN include preexisting renal insufficiency, diabetes mellitus, and effective intravascular volume depletion. The presence of one or more of these risk factors should prompt the institution of preventive interventions. The best validated of these strategies are the administration of intravenous (IV) fluids and discontinuation of diuretics to expand the intravascular space. Although initial regimens for fluid administration in the prevention of RCN employed hypotonic saline,[32] isotonic saline, infused at 1 mL/kg/h for 12 hours prior to and 12 hours following the administration of radiocontrast, provides greater protection than equal volumes of hypotonic saline.[33] More recently, Merten and colleagues reported an incidence of RCN of only 1.7% using isotonic sodium bicarbonate administered at 3 mL/kg/h for 1 hour prior to and at 1 mL/kg/h for 6 hours following radiocontrast administration compared with an incidence of 13.6% with equal volumes of isotonic sodium chloride.[34] Although these results are notable, the protocol for fluid administration was not comparable to that used in the majority of other studies. It is therefore not possible to establish the superiority of this regimen to more conventional regimens. In addition, the mechanism for the benefit associated with sodium bicarbonate is not well understood, although it is speculated that it may relate to decreased production of reactive oxygen species. Additional studies involving multiple centers and with larger numbers of patients are needed to validate the conclusions of this study. However, because the risks associated with isotonic sodium bicarbonate administration are

Table 2 Prevention of Radiocontrast-Induced Acute Renal Failure

Effective interventions
Volume expansion with isotonic saline solutions
Avoidance of high-osmolar radiocontrast agents
Minimization of volume of radiocontrast
Discontinuation of nonsteroidal antiinflammatory drugs
Potentially effective interventions
Sodium bicarbonate (as compared with sodium chloride)
N-acetylcysteine
Iso-osmolar radiocontrast agents (as compared with low-osmolar agents)
Theophylline
Ineffective or potentially harmful interventions
Dopamine
Fenoldopam
Atrial natriuretic peptide
Diuretics
Mannitol
Renal replacement therapy

minimal in the majority of patients, use of this agent is a reasonable alternative to infusions of isotonic saline.

The role of the antioxidant N-acetylcysteine in preventing RCN is controversial. Although the initial study describing its use suggested a marked benefit,[35] subsequent studies have reached conflicting conclusions.[36,37] Because this agent is both inexpensive and without significant side effects, its use is not unreasonable while awaiting more definitive data. Theophylline, an adenosine antagonist, has also been proposed as potentially beneficial in preventing RCN. In a meta-analysis of six published studies, the effect size observed was similar to that seen with N-acetylcysteine; however, this result did not reach statistical significance.[38] Given the potential for complications with this agent, particularly in patients with cardiac disease, it is a less attractive agent than N-acetylcysteine for use in the absence of a clear benefit. A variety of other pharmacological agents, including dopamine, mannitol, furosemide, atrial natriuretic peptide, and fenoldopam, have been shown to be ineffective, or even harmful, in preventing RCN and should not be used.[39]

The selection of radiocontrast agent is also an important consideration in preventing RCN. Low-osmolar radiocontrast agents are associated with a lower risk of RCN compared with the older high-osmolar agents, particularly in patients with underlying kidney disease.[40,41] In patients with both diabetes mellitus and renal insufficiency, iso-osmolar agents may be more beneficial than low osmolar agents.[42] Regardless of the class of radiocontrast, the volume administered should be minimized because volumes in excess of 250 to 300 mL are associated with increased risk of RCN.[43,44]

Rhabdomyolysis

Rhabdomyolysis is an important cause of ARF, especially in trauma patients. The sine qua non of this condition is an elevation in the creatine phosphokinase concentration. ARF results from the toxicity of myoglobin and other intracellular constituents released from damaged myocytes. The early and aggressive administration of IV fluids is well recognized as effective at preventing ARF in this setting.[45,46] In patients with crush injuries, fluid administration with 1 L/h of normal saline should be initiated promptly, even before extraction of the patient, if possible. Although urinary alkalinization with bicarbonate-containing fluids,[47] and forced mannitol diuresis[48] have been advocated, the benefit of these agents is uncertain.[49]

Postsurgical Acute Tubular Necrosis

The incidence of ARF following cardiac and vascular surgery is significant, with some series demonstrating that up to 40% of patients manifest a perioperative decline in kidney function.[50] The implications of this are significant because even small changes in Scr are associated with increased postoperative mortality,[51] whereas postoperative ARF severe enough to require the use of RRT is associated with an approximately eightfold increased risk of death after adjusting for comorbidities.[17] Factors predisposing to the development of ARF following cardiac surgery include preoperative renal insufficiency, decreased left ventricular ejection fraction, and valvular surgery.[52] Although high-risk patients can be identified preoperatively, interventions to prevent postoperative ARF have not been effective. In a randomized, controlled trial, prophylactic administration of dopamine did not decrease the risk of ARF, whereas furosemide increased its incidence.[53] Although earlier studies of atrial natriuretic peptide did not demonstrate a benefit, a recent small study of low-dose recombinant human atrial natriuretic peptide reduced the need for dialysis in patients manifesting a 50% increase in Scr following cardiac surgery.[54] This suggests a potential benefit, but additional evaluation will be necessary for confirmation. The potential benefit of off-pump coronary artery bypass graft (CABG) surgery in decreasing the risk for renal injury compared with on-pump CABG is controversial. Although case series have suggested a decreased risk of ARF,[55,56] no benefit in renal outcomes was reported in a more recent prospective observational study.[57]

TREATMENT OF ESTABLISHED ACUTE RENAL FAILURE

Pharmacological Therapy

Multiple pharmacological agents including dopamine, the dopamine receptor agonist fenoldopam, loop diuretics, atrial natriuretic peptide, insulin-like growth factor-1 (IGF-1) and thyroxine are effective for the treatment of ARF in animal models. However, similar success has not been observed in human studies. No pharmacological agents have been clinically validated for the treatment of established ARF.

DOPAMINE AND FENOLDOPAM

When dopamine is administered in low doses (0.5–2.0 μg/kg/min), renal plasma flow and GFR rise, and urinary sodium excretion increases.[58,59] Based on these physiological effects, low-dose dopamine has been, and continues to be, used in critical care settings to attenuate the clinical impact of ARF and augment urine output. However, its use is not supported by clinical studies. In the largest prospective trial, Bellomo and colleagues randomized 328 critically ill patients with early ARF to infusions of low dose dopamine or placebo.[60] There was no benefit with regard to duration of ARF, need for RRT, or mortality associated with

dopamine. In a meta-analysis of over 60 published studies, Friedrich and colleagues also found no benefit of low dose dopamine on mortality or need for dialysis, although there was a small benefit in terms of urine volume excreted on the first day of therapy. However, even this benefit was not sustained beyond the first day.[61] Given the lack of benefit and the recognized complications, most notably cardiac arrhythmias, associated with this agent, there is no role for low-dose dopamine in the management of ARF.

The dopamine-receptor agonist fenoldopam has been evaluated in a small pilot study for the treatment of ARF. In 155 critically ill patients with early ARF randomized to fenoldopam or placebo, fenoldopam was associated with a trend toward decreased need for dialysis and improved survival, although these findings did not reach statistical significance.[62] Further evaluation using a larger patient sample will be necessary to adequately assess the potential role for this agent.

LOOP DIURETICS

Loop diuretics inhibit sodium transport in the loop of Henle through inhibition of the Na-K-2Cl cotransporter. It has been hypothesized that, by decreasing metabolic demand in this nephron segment, increasing urine flow, and washing out intratubular debris in more distal tubular segments, loop diuretics may be beneficial in patients with ARF. Moreover, based on the observation that patients with nonoliguric ARF have a better prognosis than patients with oliguric ARF, loop diuretics have been used in attempts to convert patients from an oliguric to a nonoliguric state. Unfortunately, clinical trials have failed to support the utility of loop diuretics in the treatment of ARF. In studies that are over 2 decades old, the use of furosemide to increase urine output had no impact the requirement for dialysis, recovery of ARF, or mortality.[63,64]

A more recent observational study used propensity scoring to adjust for factors leading to diuretic use.[65] Diuretic use was associated with an adjusted odds ratio for mortality of 1.68 (CI, 1.96–2.64), for nonrecovery of renal function of 1.79 (CI, 1.19–2.68), and for a composite end point of death or nonrecovery of renal function of 1.77 (CI, 1.14–2.76), suggesting potential harm with diuretic use. However, analysis of data from a multinational study of 1743 critically ill patients with ARF did not reproduce these findings.[66] Because all of the increased risk in the initial study was attributable to the diuretic-unresponsive patients, it has been suggested that the adverse impact of diuretic therapy may result from a delay in instituting RRT while using escalating doses of diuretics.

In summary, diuretic therapy is not associated with an alteration in the clinical course of ARF. In diuretic-responsive patients, their use may facilitate volume management; however, it is uncertain whether the use of diuretics to delay the initiation of RRT is associated with benefit or harm.[67]

GROWTH FACTORS

Growth factors accelerate recovery of renal function in experimental models of ATN. In human trials, similar benefit has not been observed. IGF-1 did not hasten recovery of renal function, decrease the need for dialysis, or alter mortality.[68] Not only did thyroxine not improve renal recovery, it was associated with increased mortality.[69,70]

Renal Replacement Therapy

TIMING OF INITIATION

RRT is the primary means for managing severe ARF, especially when complicated by hyperkalemia, severe metabolic acidosis, volume overload, or overt uremic symptoms. Although the recognition of these clinical indications for renal support is relatively straightforward, there is uncertainty regarding the optimal time to initiate RRT in the absence of these complications. Advocates for the early initiation of RRT argue that RRT should be provided as soon as it is clear that the patient has sustained a significant and persistent reduction in GFR in order to maintain as normal a metabolic milieu as possible. The argument against early initiation is that it will subject some patients to the risks of RRT who, if managed conservatively, might recover renal function without requiring renal support. In addition, there is, at best, only limited data suggesting an outcome benefit associated with early initiation of therapy.

The debate regarding timing of initiation of RRT extends back to the early 1960s when Teschan and colleagues, and Easterling and Forland reported benefits to "prophylactic" dialysis, initiated prior to uremic symptoms, in uncontrolled case series of patients with ARF.[71,72] During the next decade, a series of retrospective studies supported the conclusion that earlier initiation of dialysis, prior to the development of advanced azotemia, was associated with improved survival.[73–75] The first prospective analysis of this issue was a study of 18 consecutive patients assigned in an alternating fashion to an early dialysis regimen (to maintain the BUN < 70 mg/dL and the Scr < 5 mg/dL), or late dialysis (BUN ~ 150 mg/dL, Scr ~ 10 mg/dL, or clinical symptoms) published by Conger in 1975.[76] Survival among patients receiving the intensive regimen was superior to that observed in the nonintensive cohort (64% vs 20% $p < .01$), and the frequency of gram-negative sepsis and gastrointestinal hemorrhage was diminished. In a subsequent study, Gillum and colleagues[76a] randomized 34 patients to receive either intensive dialysis (maintaining the BUN < 60 mg/dL and

the Scr < 5 mg/dL) or nonintensive dialysis (BUN ~100 mg/dL and Scr ~ 9 mg/dL). Mortality was higher (59% vs 47%), although hemorrhagic and septic complications were less frequent in the intensively treated patients; yet these differences did not achieve statistical significance. These data form the basis for the conventional teaching that dialysis should be initiated when the BUN approaches 100 mg/dL and that no further benefit is seen with earlier initiation of therapy. This dictum, however, is subject to the inherent limitations of retrospective analyses and underpowered prospective studies.

More recent investigation into the timing of RRT has focused on continuous RRT (CRRT). Gettings and colleagues retrospectively compared outcomes among 100 adults with posttraumatic ARF who were initiated on CRRT when their BUN was < 60 mg/dL (early) or > 60 mg/dL (late).[77] The early group was initiated on CRRT an average of 9 days before the late group (10 ± 15 days vs 19 ± 27 days, $p < .0001$) and had a substantially lower BUN at the time of initiation of therapy (43 ± 13 mg/dL vs 94 ± 28 mg/dL, $p < .0001$). Survival was 39% in the early group compared with 20% in the late initiation group ($p = .041$). Although the two groups had similar levels of acuity of illness, the retrospective design of the study does not eliminate the possibility that differences in outcomes were related to unrecognized differences in the clinical characteristics of the two groups. Similar findings have also been observed in a recent retrospective study of CRRT following cardiac surgery.[78] In the only prospective study evaluating timing of initiation of CRRT, Bouman and colleagues did not observe improved outcomes with early initiation of therapy, although the study is notable for its small sample size and an overall patient survival that suggests a lower acuity of illness than most studies of ARF in critically ill patients.[79] Thus, to date there are inadequate data to permit consensus on the optimal timing of initiation of RRT. Resolution of this question will require adequately powered randomized, controlled trials because this question cannot be adequately answered using retrospective or observational data.

MODALITY OF RENAL REPLACEMENT THERAPY

Over the past 2 decades there has been a rapid expansion of the modalities of RRT available for the management of ARF. Although the options were once limited to intermittent hemodialysis (IHD) and peritoneal dialysis, the current armamentarium of therapies includes multiple variants of CRRT and the more recently introduced "hybrid" therapies, such as sustained low-efficiency dialysis (SLED) and extended daily dialysis (EDD), which combine the machine technology of conventional IHD with the extended duration of CRRT. Unfortunately, despite the growing number of options, objective data to guide the selection of modality are limited.

CRRT is an umbrella term used to describe a family of therapies that provide slow continuous removal of solute and fluid. The variants of CRRT differ with regard to the mode of vascular access for the extracorporeal circuit [arteriovenous (AV) or venovenous (VV)] and the mechanism of solute removal (hemodialysis, hemofiltration, or hemodiafiltration).[80,81] When CRRT was first introduced, arterial cannulation was utilized, with the gradient between mean arterial pressure and central venous pressure providing the driving force for blood flow through the extracorporeal circuit. Although the use of an AV circuit provided for technological simplicity without the need for a blood pump or pressure monitors, reliance on the AV pressure gradient limited the blood flow through the extracorporeal circuit. Moreover, prolonged arterial cannulation was associated with unacceptably high complication rates.[82] For these reasons, pump-driven VV modalities are now nearly universally used.

Solute removal during CRRT can be provided by either diffusion or convection. In continuous hemodialysis, diffusive solute transport predominates; in hemofiltration, convective transport predominates; and in hemodiafiltration there is a combination of both mechanisms. Theoretically, convective clearance allows for greater removal of middle and higher molecular weight solutes. It has been postulated that the potentially greater removal of inflammatory mediators using hemofiltration favors this technique over purely diffusive therapies. In one study, lower tumor necrosis factor-alpha (TNF-α) levels were achieved during continuous VV hemofiltration (CVVH) than during continuous venovenous hemodialysis (CVVHD).[83] However, no difference in clinical outcomes based on modality of CRRT has been reported.

From a conceptual standpoint, it seems logical that the use of CRRT with its gradual fluid and solute removal would be superior to the rapid volume and solute flux associated with IHD in the critically ill patient with hemodynamic instability. However, clinical trials have not demonstrated outcome benefits associated with CRRT. The majority of studies comparing these modalities have been fraught with problems related to disparities in disease severity because more seriously ill patients are more likely to receive CRRT. Additionally, nonrandomized and/or retrospective study designs have confounded these comparisons. In a single-center retrospective comparison, Swartz and colleagues observed a twofold greater mortality in patients treated with CVVH compared with patients whose ARF was managed using IHD.[84] After adjusting for the greater burden of comorbid conditions in the patients managed using CVVH using two separate multivariate models, no difference in the odds of death was observed between modalities. Similar

results were observed in a prospective, multicenter, observational study by Guérin and colleagues.[85] In this series, mortality was 79% in 354 patients managed with CRRT and 59% in patients managed with IHD. However, after performing logistic regression to adjust for comorbidities, modality of RRT was not independently associated with outcome.

In a randomized, controlled trial of 166 patients with ARF conducted by Mehta and colleagues, ICU and hospital mortality rates were 59.5% and 65.5%, respectively, in patients randomized to CRRT and 41.5% and 47.6%, respectively, in patients randomized to IHD ($p < .02$).[86] Unfortunately, the randomization in this study was imbalanced, resulting in higher APACHE III scores and a higher prevalence of liver failure in the patients randomized to CRRT. After adjusting for the differences between groups using either logistic regression or proportional hazards regression, there was no difference in mortality attributable to modality of RRT. Two meta-analyses have attempted to compare outcomes between these modalities.[87,88] One meta-analysis that included both randomized and nonrandomized studies concluded that weakness in study quality significantly limited comparison between modalities, although there was a suggestion that CRRT might be potentially superior when studies were weighted based on assessment of study quality.[87] The second meta-analysis restricted the included studies to six randomized trials, only one of which, the study by Mehta and colleagues already discussed, was designed to evaluate mortality as an outcome and had been published as a peer-reviewed manuscript.[88] This meta-analysis found no difference in survival associated with modality of RRT.

An additional randomized, controlled trial comparing IHD to CRRT was published subsequent to these two meta-analyses.[89] In this study of 80 patients, acuity of illness was similar between the two treatment arms. Although CRRT was associated with greater net volume removal during the first 72 hours of therapy and greater hemodynamic stability than IHD, there was no observed difference in mortality between the two treatments.

It has been suggested that, despite the absence of a survival benefit with CRRT, recovery of renal function may be more likely with this mode of therapy.[86,90,91] The clinical mechanism postulated for this benefit is the lesser degree of hemodynamic instability with CRRT compared with IHD, leading to fewer episodes of intradialytic hypotension and associated renal ischemia. Although greater recovery of renal function has been observed in surviving patients in these studies, limiting the analysis to surviving patients fails to account for the competing risk of mortality. When analyzed using the combined end point of death or nonrecovery of renal function, no difference in outcome can be ascribed to modality.[92]

The data comparing other modalities of RRT are limited. One randomized, controlled trial demonstrated CVVH to be superior to peritoneal dialysis in infection-associated ARF.[93] The generalizability of this study is limited, however, by the predominance of malaria as the underlying etiology of ARF. No studies have directly compared outcomes with "hybrid" therapies to either IHD or CRRT, although these therapies have been shown to provide similar hemodynamic stability and metabolic control to CRRT.[94]

In summary, current data are inadequate to guide selection of modality of RRT in ARF. Issues associated with study methodology, lack of comparability of treatment groups, and inadequate sample size limit the interpretation of studies that have attempted to address this question. The choice of modality of RRT should therefore be dictated primarily by local expertise and availability of equipment and personnel.

DOSE OF RENAL REPLACEMENT THERAPY

Guidelines for the dosing of dialysis for patients with ESRD are well established. Unfortunately, similar guidelines for the dose of RRT for patients with ARF do not exist. When determining the dose of IHD for patients with ARF, both the frequency and the dose of each treatment session need to be considered. Only one study has evaluated the effect of IHD frequency on outcomes among patients with ARF. In this study, Schiffl and colleagues assigned 160 critically ill patients with ATN in an alternating fashion to daily or alternate day dialysis.[95] Patients who received daily dialysis had decreased mortality 14 days after discontinuation of RRT (28% vs 46%, $p = .01$), and shorter duration of ARF (9 ± 2 vs 16 ± 6 days, $p = .001$). Although these results are striking, concern has been raised that the dose of dialysis delivered to the alternate-day treatment group was exceptionally low, resulting in a markedly elevated time-averaged BUN in these patients and a high incidence of uremic complications, including gastrointestinal bleeding, altered mental status, and infections.[96] Thus, although demonstrating that increasing the dose of dialysis from a very low level of alternate-day therapy is associated with improved outcomes, this study does not provide convincing evidence that increasing the frequency of therapy provides added benefit to patients receiving an "adequate" delivered dose of therapy on an every other day or three-times per week schedule.

There are only limited data to establish what the "adequate" dose of therapy should be. In a retrospective study, Paganini and colleagues evaluated survival as a function of the delivered dose of dialysis in critically ill patients with ARF.[97] Although the dose of therapy appeared to have no impact on outcome among patients with either very high or very low acuity of illness, in patients with intermediate severity of illness, doses of dialysis above the 50th percentile were associated with

improved survival compared with patients who received lower delivered doses of therapy. However, the median dose of therapy was substantially lower than what would be deemed appropriate in the chronic setting. In the absence of other studies establishing a relationship between dose and outcome, a consensus panel convened by the multinational Acute Dialysis Quality Initiative (ADQI) concluded that the patients with ARF should receive at least the same minimum dose of dialysis that is considered appropriate for patients with end stage kidney disease.[98]

The data regarding dosing of therapy in CRRT are slightly more robust. Ronco and colleagues randomized 435 patients to one of three doses of CVVH, defined by ultrafiltration rates of 20 mL/kg/h, 35 mL/kg/h, and 45 mL/kg/h.[13] Survival was markedly higher in the intermediate and high dose arms (57% and 58%, respectively) compared with the low dose arm (41%, $p < .001$). In a subsequent study, however, Bouman and colleagues observed no such advantage with higher doses of CRRT.[79] However, the overall survival of greater than 70% in this study suggests that the enrolled patients may not have been representative of the majority of critically ill patients with ARF. Therefore, although definitive recommendations cannot be made, the data suggest that CRRT should be dosed to provide an ultrafiltration rate of at least 35 mL/kg/h. Several large randomized controlled trials are under way in the United States and elsewhere to better define the optimal dosing of RRT in ARF.[99]

SUMMARY

ARF is common in the ICU. Preventive strategies should be utilized in patients at high risk for RCN or rhabdomyolysis. RRT remains the mainstay of supportive care for the critically ill patient with established ARF because no effective pharmacological therapy is available. The high prevalence of ARF in the ICU setting necessitates a firm understanding by critical care providers of the salient issues related to timing of initiation of RRT, choice of modality, and optimal dose, all of which remain subjects of substantial debate and active clinical investigation.

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