Hospital-Acquired Acute Renal Failure

CHARLES R. NOLAN and ROBERT J. ANDERSON
Department of Medicine, University of Colorado Health Sciences Center and Denver Veterans Affairs Medical Center, Denver, Colorado.

Acute renal failure (ARF) is the abrupt loss of renal function sufficient to decrease urinary elimination of nitrogenous waste (urea nitrogen and creatinine). Although there is consensus about this general definition, few agree on the magnitude of the rise in serum creatinine necessary to ascribe a diagnosis of ARF (1,2). These differences in definition plus variances in methods of patient accrual, populations analyzed, and categorization of causes render development of a broad-based overview of ARF difficult. However, two generalizations about contemporary ARF are compelling. First, ARF is predominantly a hospital-acquired disorder (1-3). Second, the high mortality of patients with ARF is not explained entirely by comorbid conditions. Recent data indicate that ARF per se increases the risk of development of multiple nonrenal conditions that lead to death and disability (4). Thus, ARF should not always be considered a treatable condition that complicates advanced disease. Together, these two generalizations prompt this review, which focuses on the causes, diagnosis, prevention, and management of hospital-acquired ARF.

Causes and Clinical Settings of Hospital-Acquired ARF
Categorization of the cause(s) of hospital-acquired ARF has traditionally involved determining which general physiologic mechanism (prerenal, postrenal, or intrarenal) is responsible for the decline of glomerular filtration (Figure 1). This method has the advantage of providing a well accepted diagnostic framework that guides the clinician to comprehensively consider most potential causes of deteriorating renal function (1,5). Prerenal factors (e.g., extracellular fluid volume loss and/or sequestration and impaired cardiac function) contribute to 30 to 60% of all cases of ARF. Postrenal factors (e.g., intra- or extrarenal obstruction of urine flow) are much less frequently encountered causes of hospital-acquired ARF (1 to 10%) but are almost always amenable to therapy. When considering renal causes of ARF, it is helpful to think of each renal anatomic compartment (vasculature, glomeruli, interstitium, and tubules) as a potential contributor to the renal failure. Although acute vascular (e.g., atheroemboli, vasculitis, thrombosis), glomerular (e.g., glomerulonephritis), and interstitial (e.g., allergic interstitial nephritis) processes occasionally cause hospital-acquired ARF, the major cause is acute tubular injury. This tubular damage is most often due to either ischemia (e.g., prolonged prerenal insult) or a nephrotoxin. Sometimes acute tubular injury occurs in the setting of pigmenturia (e.g., myoglobinuria or hemoglobinuria).

A recent study by Liano and Pascual provides a reasonable overview of the causes of hospital-associated ARF (3). This experience was based on more than 740 cases of ARF that were either referred to or occurred within 13 tertiary care facilities in Madrid, Spain. Of these cases, 45% were attributed to acute tubular necrosis, 21% to prerenal causes, 10% to postrenal causes, 3% to renal vascular disorders, 3% to glomerulonephritis, and 2% to acute interstitial nephritis (3). In the study by Brivet et al. drawn from 20 French multidisciplinary intensive care units (ICUs), the type of ARF was prerenal in 17%, renal (usually acute tubular injury) in 78%, and postrenal in 5% (6).

From a more pragmatic standpoint, general hospital-acquired ARF is usually encountered within a relatively narrow context of settings. These settings include the postoperative state, advanced cardiovascular disease, neoplastic disease, HIV infection, multiple organ failure, systemic infection, and solid organ transplantation. The hospital-acquired ARF that occurs in these disparate settings is usually associated with one or more of three renal insults, including prerenal events (extracellular fluid volume defects and hemodynamic instability), exposure to nephrotoxins, and sepsis.

The postoperative period is currently one of the most prevalent settings of ARF. For example, 27% of the 748 cases of ARF reported by Liano and Pascual were encountered in the postoperative setting (3). Older studies by Charlson et al. indicated that 25% of elective, noncardiac surgical procedures were complicated by an acute rise in serum creatinine of 20% or greater (7). In 11% of these patients, a 50% decline in endogenous creatinine clearance occurred (7). More recent studies by Chertow et al., using Veterans Affairs patient databases, indicate that the development of ARF sufficient to require renal replacement therapy occurs in 0.4 to 7.5% of patients undergoing cardiac surgery and 0.6% of patients undergoing general surgery, and is dependent on a number of preoperative risk factors (8,9).

What underlies the relatively high frequency of ARF that occurs in relation to elective surgical procedures? In many cases, underlying comorbidity (diabetes mellitus, chronic hypertension, vascular disease, congestive heart failure) leads to diminished baseline GFR and reduced renal reserve (7-9). With this background, the "surgical experience" appears to
control study identified sepsis as the single factor associated with the greatest risk of developing hospital-acquired ARF (15), and sepsis was the most common factor (48% of cases) predisposing to development of ICU-associated ARF in the study of Brivet et al. (6). Not only is hospital-acquired sepsis often linked to ARF, but community-acquired sepsis is also commonly associated with ARF (16). The experience of Rayner et al. found that 24% of 239 patients with community-acquired bacteremia doubled their serum creatinine concentrations (16).

In every analysis, nephrotoxic agents have been found to contribute to hospital-acquired ARF (1–4,17). The number of potential nephrotoxins is large, and the mechanisms by which nephrotoxins contribute to ARF are diverse (Figure 2). Moreover, new agents (e.g., protease inhibitors, immune globulin, tacrolimus) are continually being added to the ever-expanding list of foods, plants, animal venoms, and diagnostic and therapeutic drugs capable of inducing ARF, emphasizing the need for a comprehensive review of medication/exposure history in each case (1,17,18).

**Diagnosis of Hospital-Acquired ARF**

The time-honored approach to evaluating a patient with ARF is to exclude prerenal and postrenal causes and then, if necessary, initiate an examination to determine potential renal etiologies. We favor a four-step approach to this process, as outlined in Figure 3. In our experience, the cause(s) of ARF is usually apparent after step 1. A thorough review of the medical record is mandatory to identify potential nephrotoxic drugs or other insults, such as volume depletion, hypotension, radiocontrast studies, or surgical interventions. A careful historical and physical examination for clues to volume status is imperative, because prerenal azotemia is a correctable condition, and careful volume repletion may be of value even in established ARF. Occasionally, hemodynamic monitoring, i.e., noting changes in cardiac output, capillary wedge pressure, or urine output in response to a trial of either volume expansion or inotropic agents, may be useful in the process of excluding prerenal azotemia.

Urinalysis performed by the physician is usually a key tool in the diagnostic evaluation of ARF. A normal urinalysis is most compatible with pre- or postrenal forms of ARF. Numerous pigmented granular casts or the finding of abundant tubular epithelial cells helps support a diagnosis of ischemia/nephrotoxin-induced ARF. The detection of heme-pigment by dipstick screening, which is out of proportion to the number of erythrocytes on microscopic examination, suggests the presence of pigmenturia due to rhabdomyolysis or intravascular hemolysis. Significant proteinuria, hematuria, or the finding of red blood cell casts suggests an underlying glomerulonephritis or vasculitis. White blood cell casts may be seen in the setting of acute pyelonephritis, interstitial nephritis, or glomerulonephritis.

The finding of eosinophilia by Hansel's stain suggests that the ARF is not due to acute tubular injury. However, in the absence of systemic signs of an allergic reaction (fever, rash, peripheral eosinophilia), the finding of eosinophilia is suggestive, but clearly not diagnostic, of drug-induced acute

---

**Figure 1. Acute renal failure.**

Potentially induce afferent arteriolar renal vasoconstriction and diminished GFR (10,11). If an additional renal insult is encountered, clinical ARF occurs (7–9). These additional renal insults are often referred to as "second hits" and include reoperation, sepsis, nephrotoxin exposure, circulatory/volume deficits, and heart failure (7–9).

A high percentage of contemporary hospital-acquired ARF occurs in patients in the ICU. For example, 27% of the 748 cases of ARF reported by Liano and Pascual were encountered in the ICU (3), and the frequency of ARF in patients admitted to ICUs ranges from 6 to 23% (reviewed in reference 1). In most cases of ICU-acquired ARF, the ARF occurs in the setting of multiple organ failure. For example, more than 90% of cases of ICU-acquired ARF have failure of one or more additional organ systems, and the failure of these other systems nearly always precedes the development of ARF (reviewed in reference 1). In the recent ICU experience of Brivet et al., failure of another organ system was nearly uniformly present in patients with ARF (6). In all series of ICU-associated ARF, hemodynamic instability, nephrotoxins, and sepsis are comitantly present in more than two-thirds of all patients (1–3,6).

ARF is commonly encountered in patients with HIV infection (12). Valeri and Neusy found that more than half of 246 HIV-infected patients had one or more episodes of a rise in serum creatinine of 0.3 mg/dl or greater (12). The causes of ARF in the HIV population are diverse and include prerenal conditions, postrenal failure (due to either intratubular microcrystallization from sulfa drugs/protease inhibitors or ureteric obstruction from lymphoma), and renal disorders, including thrombotic microangiopathy, HIV-associated nephropathy, glomerulopathy, interstitial nephritis, and acute tubular injury occurring in the setting of sepsis and/or nephrotoxins (12,13).

Patients with neoplastic disease are also at high-risk for hospital-acquired ARF (1,14). The frequency of development of ARF in patients with hematologic malignancies may be up to 40% in some series (14). Sepsis, tumor-lysis syndrome, hypercalcemia, hyperuricemia, nephrotoxins, and prerenal factors are the predominant causes of ARF in patients with malignancies. Less commonly encountered causes include tumor infiltration, obstructive uropathy, and glomerulopathy.

Two of the most common conditions predisposing to hospital-acquired ARF are sepsis and nephrotoxin exposure. A case-
interstitial nephritis (19). Moreover, the finding of eosinophiluria in a patient with ARF after an arteriographic procedure or in patients with severe peripheral vascular disease supports a diagnosis of atheroembolic renal disease, which should prompt investigation for systemic evidence of atheroembolism (livedo reticularis, purple toes, or Hollenhorst plaques) (see reference 1).

Urinary diagnostic indices have become a standard tool in the evaluation of patients with acute azotemia (Figure 4) (reviewed in reference 1). Patients with oliguria due to prerenal azotemia tend to have intact tubular function, whereas patients with established acute tubular injury typically have urine indices compatible with diminished tubular reabsorption of selected solutes and water (1). However, the term “urinary diagnostic indices” is a misnomer because urinary electrolyte results are often indeterminate, and the results must always be interpreted in light of the clinical situation. For example, patients receiving diuretic therapy, i.e., patients with either bicarbonaturia or an osmotic diuresis induced by glucose, urea, or radiocounter agents, and patients with primary adrenal insufficiency may have prerenal ARF with elevated FENa despite profound volume depletion. Likewise, patients with chronic renal insufficiency or interstitial disease may be unable to conserve sodium despite volume depletion with superimposed prerenal azotemia. Also, low urinary indices do not always indicate reversible prerenal azotemia. For example, early in the course of intrinsic renal damage due to radiocontrast agents, rhabdomyolysis, or sepsis, urinary indices often suggest intact tubular function. Urinary diagnostic indices are not reliable in patients with urinary tract obstruction, glomerulonephritis, or acute interstitial nephritis, and these disorders must be excluded on other grounds.

**Prevention of Hospital-Acquired ARF**

Because contemporary hospital-acquired ARF is associated with substantial mortality and morbidity, major efforts should be directed toward prevention. Potential preventive strategies are outlined in Table 1. A high percentage of hospital-acquired ARF occurs in the context of nosocomial infection with sepsis (1–3,15). Thus, although not always germane to the consultant nephrologist, maneuvers designed to prevent hospital-acquired infection (Table 1) are common sense, low-cost, low-tech maneuvers that potentially decrease the frequency of sepsis-related ARF.

One or more nephrotoxins potentially contribute to at least 25% of all cases of hospital-acquired ARF (1–6,15–17,20,21). The best strategy is avoidance. For example, there are currently multiple antimicrobial alternatives to potentially nephrotoxic aminoglycosides. Although recent studies suggest low nephrotoxic risk from nonsteroidal anti-inflammatory drugs in the postoperative state (22), the potential renal vasoconstrictive effect of these agents should be kept in mind in selected patients, such as those with sepsis, heart failure, cirrhosis, nephrosis, volume depletion, and hypoalbuminemia (1,20).
Many nephrotoxins exert dose-dependent toxicity. This appears particularly true for radiocontrast agents, aminoglycosides, cisplatin, and amphotericin B. Thus, for radiocontrast agents, carefully limiting the dose given appears to be the best means of prevention of nephrotoxicity (23). Alterations in dosing strategy may also affect nephrotoxicity of selected agents such as the aminoglycosides. Animal studies demonstrate equivalent antimicrobial efficacy with lower renal tissue levels and less nephrotoxicity when aminoglycosides are given once daily as opposed to multiple times a day. Meta-analysis of human studies also demonstrates a small effect of single daily dosing of aminoglycosides to decrease nephrotoxicity (20,24). Formulation and structure modifications of potential nephrotoxins might also reduce ARF. The two best examples are nonionic contrast agents and lipid emulsified amphotericin B, which may be associated with reduced nephrotoxicity (25,26). In selected cases (e.g., radiocontrast agents, amphotericin B, cisplatin, and drugs that induce crystalluria) (Figure 2), modest
volume expansion appears on the basis of substantial retrospective and anecdotal observations to protect against the development of nephrotoxicity (17,20).

Another approach to prevention of nephrotoxin-induced ARF is the use of modern information systems that link laboratory and pharmacy databases (27). In a recent prospective study, electronic mail notification of clinicians regarding mild rises in serum creatinine in their patients on either a potential nephrotoxin or a renally excreted agent resulted in a faster response time to stop the drug and lessened the frequency of development of severe ARF (27). This low-cost method could be even more effective in the context of a more powerful intervention (e.g., mandatory clinician notification and/or automatic drug stop order).

Pharmacologic manipulations to prevent hospital-acquired ARF, with the exception of modest volume expansion, have, in general, not met with great success. From a medical perspective, use of furosemide, mannitol, dopamine, and atrial natriuretic peptide to prevent contrast-associated ARF has been disappointing (28,29). From a general surgical perspective, intraoperative diltiazem and alpha-adrenergic antagonists can reduce the modest intraoperative fall in GFR that accompanies cardiac surgery, but these maneuvers have not yet been demonstrated to prevent ARF (10,11). To date, the effective use of low-dose dopamine to prevent ARF in several operative settings, including intrarenal aortic clamping, elective major vascular surgery, and biliary tract surgery, has not been demonstrated (reviewed in reference 1).

One pharmacologic intervention of great interest and promise in the prevention of ARF is the use of growth factors. To date, substantial experimental evidence on the use of growth factors to accelerate recovery from ARF is available. In the only reported study carried out in humans (n = 54), in which a growth factor has been used, insulin-like growth factor I exerted a modest but significant effect to prevent the fall in GFR in high-risk suprarenal aortic and renal artery surgery (30). For example, a smaller percentage of treated patients (22%) had a postoperative decline in creatinine clearance than did untreated patients (33%). Whether such therapy prevents postoperative ARF, however, remains to be determined.

With regard to high-risk surgical candidates, Berlauk and colleagues found that preoperative optimization of hemodynamic parameters, guided by Swan-Ganz catheterization, was helpful in patients undergoing limb salvage vascular surgery (31). In this small prospective study, mortality, graft loss, and frequency of development of postoperative ARF were diminished by the optimization procedure (31). Confirmation of these results and delineation and definition of high-risk populations for which this strategy is potentially helpful are needed.

With regard to other critically ill patients, it has been suggested that fluid volume and pharmacologic therapy designed to increase cardiac index and delivery and consumption of oxygen to supranormal levels can prevent tissue hypoxia. From a very simplified perspective, this enhanced oxygen delivery might protect end organs from ischemic injury. At least five prospective randomized trials have been undertaken to test this hypothesis (outlined in reference 1). Improved survival and decreased frequency of ARF have been seen in some, but not all, studies. Compelling data that this strategy will have a major impact on prevention of hospital-acquired ARF remain to be established.

### Treatment of Hospital-Acquired ARF

Treatment of hospital-acquired ARF starts with the provision of excellent general supportive care. The key aspects of supportive care include careful, sequential clinical and biochemical monitoring to detect complications; frequent surveillance of the medication lists to eliminate unnecessary drugs and to adjust, when appropriate, the dosage of drugs excreted by the kidneys to reduce drug-associated morbidity; minimization of the use of invasive lines to avoid nosocomial infections; and provision of adequate nutrition to optimize general health and recovery. These aspects of ARF care have been reviewed in detail elsewhere and will not be discussed in this review. Recent advances in two other areas of ARF therapy, i.e., pharmacologic manipulations to attenuate ARF and the use of renal replacement therapy, have drawn some controversy and thus merit further discussion.

Pharmacologic manipulation to either attenuate the severity of ARF or to hasten recovery have centered on mannitol, loop diuretics, dopamine, and atrial natriuretic peptide. To date, randomized trials have failed to establish that mannitol prevents postoperative ARF (32). On the basis of clinical experi-
ence and retrospective studies, however, many experienced nephrologists continue to use mannitol in an effort to attenuate ARF, especially pigment-associated ARF (1). With regard to loop diuretics, prospective randomized trials, undertaken in patients with advanced, well established ARF, fail to demonstrate a beneficial effect on duration of azotemia, dialysis requirement, or mortality (32,33). Although some of these studies demonstrate that loop diuretics increase urine output, it is not clear whether oliguric ARF patients with a loop diuretic-induced increase in urine flow have the same, more favorable prognosis than do ARF patients that are spontaneously nonoliguric. Nonetheless, because of the generally low complication rate associated with loop diuretics, many clinicians administer loop diuretics to patients with ARF who continue to be oliguric despite optimization of renal perfusion and exclusion of post-renal factors.

Low-dose (<3 to 5 μg/kg per min) dopamine is widely used in ARF, especially in oliguric patients. A large study, using each patient as his or her own control, has clearly established that low-dose dopamine can render many oliguric patients nonoliguric (34). This nonoliguric state, however, does not necessarily appear to reflect a rise in GFR. In a recent analysis of 256 patients with ARF in which dopamine was administered nonrandomly at the discretion of the treating physician, the relative risk of death or dialysis associated with low-dose dopamine administration, after adjustment for several variables, was 0.95 (95% confidence interval, 0.58 to 1.58; reference 35). Because there was no statistically significant difference in outcome in patients treated with low-dose dopamine, the authors concluded that the routine use of low-dose dopamine in ARF should be discouraged until a prospective, randomized, placebo-controlled trial establishes its safety and efficacy. Other researchers, however, believe that the documented potential diuretic effect and nonthreatening side-effect profile of low-dose dopamine mandate its continued use, especially in oliguric ARF.

Atrial natriuretic peptide is known to increase GFR by dilation of afferent arterioles and constriction of efferent arterioles. Several experimental and uncontrolled clinical trials suggest clinical benefit from both intrarenal and intravenous atrial natriuretic peptides in established ARF. In a recent multicenter, randomized, double-blind, placebo-controlled clinical trial of anaritide in 504 critically ill patients with acute tubular necrosis, patients received a 24-h infusion of either anaritide (0.2 μg/kg per min) or placebo (36). The primary end point was dialysis-free survival for 21 d after treatment. The rate of dialysis-free survival was not significantly different between the two groups (47% in the placebo group and 43% in the anaritide group, $P = 0.35$). However, in a subgroup of 120 patients with oliguria, dialysis-free survival was 8% in the placebo group (five of 60 patients) and 27% in the anaritide group (16 of 60 patients, $P = 0.008$). Anaritide-treated patients who became nonoliguric after treatment seemed to benefit the most. A subsequent, similarly designed study that enrolled only patients with oliguric acute tubular necrosis failed to demonstrate a benefit of anaritide administration. Drug company development of anaritide, however, has been suspended. The suspension was prompted by a low probability that a positive outcome could be obtained with respect to the primary clinical end point of dialysis-free survival (Robin Allgren, personal communication).

There are several arguable issues regarding renal replacement therapy (RRT) for ARF. These issues include: when to begin, what membrane and modality to use, and what level of intensity is sufficient? With regard to commencement of RRT, there has been a general trend in recent years toward earlier initiation. This aggressive approach does not necessarily equate with an improvement in therapy. To our knowledge, no study in the modern era has adequately addressed timing of initiation of RRT. One study of 132 critically ill ARF patients found an inverse relationship between serum creatinine concentration at initiation of hemodialysis and mortality (37). Although these data are subject to at least two interpretations (early dialysis is deleterious versus patients dialyzed earlier are sicker with more fluid overload and electrolyte disturbances), they do raise concerns. Moreover, intermittent hemodialysis may be associated with hemodynamic instability, which, with potential impairment of renal autoregulatory responses that can occur in ARF, may lead to enhanced ischemic injury (38). Few would argue that volume overload and hyperkalemia refractory to medical therapy, as well as uremic symptoms and complications, merit RRT. As far as the level of azotemia is concerned, little data support prophylactic RRT for blood urea nitrogen (BUN) levels <200 mg/dl (37).

The choice of RRT modality is also a subject of debate. One issue involves the type of membrane. It has recently become apparent that biocompatibility of dialysis membranes may be an important determinant of survival and recovery of renal function in patients with ARF (39,40). The polysaccharide structure of cellulosic (bioincompatible) membranes provides a trigger for complement activation via the alternative pathway, which leads to the liberation of anaphylotoxins and activation of leukocytes. The potential induction of a systemic inflammatory reaction during each dialysis treatment with bioincompatible dialysis membranes could conceivably cause further ischemia or inflammatory changes within the previously injured renal microcirculation.

In a recent study of 72 patients with ARF, patients were randomized to intermittent dialysis treatment with either bioincompatible Cuprophane dialysis membranes, which activate the complement system and leukocytes, or to dialysis with a bio compatible membrane composed of polymethyl methacrylate, which has a less marked effect on complement and leukocytes (39). The two dialysis membranes chosen for the study had similar clearance and ultrafiltration characteristics and the patient groups were similar. Fifty-seven percent of patients on dialysis with bioincompatible membranes survived, compared with 37% of those dialyzed with Cuprophane membranes ($P = 0.11$). Recovery of renal function occurred in 62% of those dialyzed with a bioincompatible membrane, compared with 37% of those who underwent dialysis with Cuprophane membranes ($P = 0.04$). The time to recovery of renal function after initiation of dialysis was also significantly shorter in the bio compatible membrane group compared with the Cuprophane.
group: five dialysis treatments over 11 d versus 17 dialysis treatments over 33 d, respectively. Subgroup analysis revealed that the benefits of biocompatible membrane dialysis were evident only in patients who were nonoliguric before the initiation of dialysis. These results suggest that use of the biocompatible dialysis membrane increases the likelihood of recovery of renal function and survival of patients with ARF. Other studies have confirmed and extended these observations to include other biocompatible dialysis membranes, including polysulfone and polyacrylonitrile membranes (40). However, this issue may not be quite as clear-cut as these two studies suggest. For example, in the most recent prospective randomized study (n = 133) of patients with severe ARF who were concomitantly undergoing mechanical ventilation and continuous, high-flux dialysis, the type of membrane did not influence survival in those patients undergoing continuous high-flux dialysis (41).

The modality of RRT for ARF is also debatable, with proponents of both intermittent hemodialysis (IHD) and continuous modes of RRT (CRRT) (42,43). Surveys of nephrologists in the United States reveal that IHD is the most common modality used for treating ARF, followed by CRRT and then peritoneal dialysis (43). The IHD modality has been widespread use for the past four decades for the treatment of ARF. In recent years, the development of bicarbonate-based dialyzer and volumetrically controlled machines for precise control of ultrafiltration has made IHD a safer procedure in the hemodynamically unstable ICU patient with multiorgan failure. In most centers in the United States, the standard approach to IHD for ARF uses moderate blood flow rates (200 to 250 ml/min) and dialysate flow rates of 500 ml/min. In contrast to the situation for treatment of chronic renal failure, there are no well-established guidelines for defining IHD adequacy in ARF. Dialysis frequency and intensity are usually determined empirically based on the patient's volume status, associated clinical events, BUN levels, and other blood chemistries.

The most common reasons cited for preferential choice of IHD are efficacy, ease of use, and familiarity of the dialysis and ICU nursing personnel with the procedure. CRRT tends to be reserved for patients who are hemodynamically unstable or hypercatabolic, or for those with large fluid burdens due to aggressive nutritional support (42). The minority of nephrologists who administer peritoneal dialysis cited the absence of a need for anticoagulation and better hemodynamic stability as the main reasons for using this technique. For rapid correction of life-threatening electrolyte or acid-base disorders, IHD is probably the best choice, given both the efficacy and rapidity of response. On the other hand, if fluid removal is the primary objective, hemodynamic instability may limit aggressive ultrafiltration during a 3- to 4-h IHD treatment. Thus, for hypercatabolic patients receiving nutritional support with a high nitrogen content, even daily hemodialysis may provide inadequate urea clearance. CRRT modalities, especially hemofiltration techniques that combine dialysis with significant ultrafiltrate volumes to enhance solute clearances, may provide the more intensive treatment necessary to control azotemia in catabolic ICU patients receiving high protein content nutrition (42). The major disadvantage of CRRT is the need for well-trained ICU nursing personnel to perform the procedure. A lack of detailed understanding of the CRRT flow sheets and the computations necessary to determine replacement fluid volumes can lead to disaster due to significant volume depletion. Occasionally, lactate-based replacement fluid may result in lactate accumulation and worsening acid-base status if the patient has liver disease and is unable to metabolize lactate as a source of base. On-site formulation of custom bicarbonate-containing replacement fluid is costly and time consuming. Ambulation and physical therapy may be difficult while the patient is receiving CRRT.

The issue of dialysis intensity in ARF also remains controversial. In one study, patients with ARF were matched by etiology and randomly assigned to either an intensive treatment group (dialysis to maintain BUN <60 mg/dl and creatinine <5 mg/dl) or to a nonintensive group (dialysis to maintain BUN <100 mg/dl and creatinine <9 mg/dl; reviewed in reference 37). Seven of 17 (41%) patients in the intensive group survived compared with nine of 17 (53%) in the nonintensive group. Complications such as hemorrhage (24% versus 59%) and septicemia (47% versus 65%) were less common in the intensive treatment group. Although none of the differences between groups reached statistical significance, this study has been criticized because of insufficient power to detect a difference in survival (37). It has been postulated that a randomized clinical trial capable of identifying an absolute risk reduction of 10% would require a sample size in excess of 750 matched patients (37). In general, once RRT is initiated, most nephrologists aim to keep BUN and serum creatinine at levels <80 to 100 and 8 to 10 mg/dl, respectively.

### Outcome of Hospital-Acquired ARF

The outcome of hospital-acquired ARF depends on the site (ward or ICU), comorbidity, cause, and severity of the renal failure. As a general estimate, contemporary survival of hospital-acquired ARF severe enough to be dialyzed averages 10 to 50% (1). The development of even mild hospital-acquired ARF sufficient to cause a 25% increase in serum creatinine at least 2 mg/dl increased mortality fivefold in a recent case control cohort analysis of contrast-associated ARF (4).

New developments have been reported in three areas with regard to ARF outcome. First, some analyses suggest that the outcome of severe hospital-acquired ARF, although generally dismal, may be improving. An excellent retrospective study found that ICU-associated ARF is associated with significantly lower mortality in the more modern era versus two decades ago despite comparable or more severe comorbidity (44). In the Mayo Clinic study, there was a 20% increase in hospital survival and a 9% increase in 1-yr survival when ICU patients with ARF who required dialysis from the period 1977 to 1979 were compared with comparable patients from the period 1991 to 1992 (44). Second, substantial effort is being placed on the application of existing severity of illness and outcome prediction models, as well as the development of new models, to patients with ARF (reviewed in references 1 and 45). These prediction models are useful to stratify and assign patients for
prospective studies, as well as to compare risk-adjusted outcomes across several sites. However, to date, they remain insufficiently predictive to be routinely used in clinical decision-making with regard to level of care in many cases.

Finally, reasonable cost-effectiveness analyses are being done regarding RRT in critically ill patients with hospital-acquired ARF (46). A recent prospective cohort study from five geographically diverse teaching hospitals included 490 patients with ARF requiring dialysis (46). Median survival was 32 d, and 27% survived 6 mo. Survivors were dependent for at least one activity of daily life (bathing, moving, toileting, feeding, or dressing), but 62% rated their quality of life as good. The estimated cost per quality-adjusted life-year saved by initiating dialysis was $274,100 for the 103 patients in the worst prognostic category and $61,900 for the 94 patients in the best prognostic category. These costs somewhat exceed $50,000 per quality-adjusted life-year, which has been arbitrarily defined as the threshold for cost-effective care.

References
34. Flanbaum L, Choban PS, Dasta JF: Quantitative effects of low