Outcomes Research in Acute Renal Failure

By Ravindra L. Mehta

Acute renal failure (ARF) is associated with morbidity and mortality in excess of 50% in the intensive care unit (ICU) setting. A variety of outcome measures have been described in published reports of ARF, however, the studies often do not distinguish between clinical outcomes and surrogate endpoints. Multiple factors can influence these outcomes, including variations in practice. It is important to be aware of the potential effects of these factors when clinical trials are planned and executed for ARF patients. For any intervention trial, knowledge of the natural history of the disease and process of care informs the design and conduct of the trial. Standardization of a definition for ARF and of the criteria for initiation, frequency, duration, and withdrawal of dialysis support would be of great benefit. This article provides a critical appraisal of outcomes research in ARF and describes an approach for selecting appropriate endpoints for future clinical research in ARF.

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AN APPROPRIATE DEFINITION of relevant, measurable health outcomes is a common goal for all health care. To improve outcomes it is necessary to define those of most interest and identify the best tools to measure them. Standardized measurement of health outcomes permits assessment of the effects of different therapeutic interventions and associated conditions, standardizes comparisons, and supports cost effectiveness and benefit analysis. Although acute renal failure (ARF) is a common disease, there is limited information on outcomes from ARF. Uncomplicated ARF usually can be managed outside the ICU setting and generally has an excellent prognosis, with mortality rates less than 5% to 10%. In contrast, ARF complicating other organ failure in the intensive care unit (ICU) setting has a distinctly different outcome, with mortality rates of 50% to 70%. ARF requiring dialysis is associated with an even worse outcome. Over the past 2 decades, several observational studies and a few clinical trials have been published and have focused generally on survival as the main outcome measure. This discussion highlights the different outcomes of interest, describes the potential factors affecting outcomes, and provides an assessment of methods used to measure outcomes from ARF.

OUTCOMES FROM ARF: A CONCEPTUAL MODEL

A clinical outcome represents a measurable change in a patient’s status. Clinical outcomes generally represent an improvement in longevity, prevention of nonfatal events, and/or an improvement in quality of life. The clinical utility of an intervention often is measured by its effects on clinical outcomes; however, depending on the nature of the disease and the type of intervention, it may be difficult to determine these outcomes. Surrogate outcomes measures commonly are substituted for clinical outcomes because they provide measurable endpoints to monitor the effect of therapy and permit shorter time spans to assess the effects of an intervention. However, surrogate endpoints must be predictive of the relevant clinical outcome and must fully capture the effect of the intervention on the clinical outcome. Although useful for early phase research, surrogate endpoints are subject to a variety of problems that may contribute to the failure of a clinical trial. A SMART approach to outcomes definitions requires the measures to be Specific, Measurable, Acceptable, Realistic, and Time-related. Additionally, endpoints should be reproducible, sensitive, and responsive to an intervention. The time course of the unmodified disease and the effect of interventions need to be captured by the endpoint. Composite outcomes may include clinical events, specific measures such as disease-free survival and changes in physiologic parameters (eg, a change in blood pressure or serum creatinine level). Composite clinical endpoints provide a method to evaluate the effect of an intervention on several relevant events. The validity of a composite endpoint depends on its components. Selection of appropriate endpoints for any study requires that each intervention be matched with a relevant outcome. Generally, this...
requires an intimate knowledge of the natural history of the disease process and of the nature and timing of the intervention, as well as some knowledge of other factors that influence the course of the disease.

Myers\(^{17}\) has offered a classification previously describing the natural course of hemodynamically mediated postoperative ARF that represents the spectrum of disease likely to be seen (Table 1). It is apparent from their model that the abbreviated form of ARF is significantly different in its pathophysiology and course than the protracted form. A major distinction among the groups is the severity of renal dysfunction, requirement for dialysis, reversibility, and duration of ARF. Whether patients with nonoperative ARF follow similar patterns is not well described. It is evident that given the varying course of ARF, the nature and timing of various outcomes will likely differ. Figure 1 depicts process of care time points in the course of ARF in the ICU setting. These time points are affected by the natural history of ARF, but may not match the time sequence of the disease. It is important to recognize the relationship of the natural history of the disease (influenced by patient characteristics) and the patients’ course in the ICU (influenced by the process of care) to appropriately define endpoints for an intervention. To ascertain the true effect of an intervention, endpoints specific for disease severity and process of care should be selected.

Table 2 describes common outcomes that have been reported previously and are recommended for future studies in ARF\(^{16,18,19}\). Although helpful, this approach is limited in defining which endpoints should be used for specific studies. Table 3 further classifies various outcomes based on their specificity and relevance for different types of studies in ARF. Organ-specific measures are based on physiologic measurements (eg, changes in renal perfu-

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Insult</th>
<th>Marker Profile</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Abbreviated| Single well defined                                                     | Serum creatinine elevated but returns to baseline                             | 3-7 d        | Return to baseline renal function
Survival good |
| Overt      | Initial insult followed by additional injury (eg, postoperative hypotension followed by sepsis a few days later) | Serum creatinine elevated, level improves but following additional insult slow improvement to level above baseline | Days to weeks | Return to worse than baseline
Patients may survive |
| Protracted | Pre-existing renal dysfunction, primary insult, secondary insult from underlying poor disease state (eg, impaired cardiac function) | Serum creatinine elevated and remains high                                    | Several weeks | Continued renal failure; dialysis dependency until primary organ improvement
High mortality |

Data from Myers\(^ {17} \).
sion or renal function or urine output), and are ideal efficacy parameters to show the effect of an intervention on the kidney. Similarly, endpoints specific for the intervention (eg, changes in hemodynamic parameters related to use of a vasopressor agent), are a measure of the efficacy of an intervention. Disease-specific measures define the progress of the underlying disease and its effects on other organ function. For instance, disease-specific scoring systems (eg, sequential organ failure assessment [SOFA] scores), provide an estimate of disease severity and can be used as a measure of efficacy or effectiveness. Global outcome measures are likely to be influenced by several factors and consequently are best reserved as an effectiveness parameter. Organ, disease, and global outcomes reflect patient outcomes from ARF and should be distinguished from endpoints that reflect the efficiency of the intervention. For example, in a dialysis dose study for continuous renal replacement therapy (CRRT) the operational characteristics can be assessed by measuring the sieving coefficient of a solute at predefined intervals. Changes in the sieving coefficient are a specific marker for CRRT performance and strongly influence outcomes such as maintenance of a low steady state blood urea nitrogen (BUN) concentration, hemodynamic stability, and correction of acid-base balance. However, efficiency markers rarely are measured and generally not reported for ARF studies. For device studies, a measure of device efficiency should be incorporated as a component of the efficacy endpoint. Endpoints to show effectiveness and clinical use often are linked. In general, clinical utility endpoints should provide evidence of overall benefit to the patient for improved survival, reduction of morbidity, or improved quality of life. Benefit and cost-effectiveness analysis may be additionally helpful endpoints to show clinical utility for some interventions.

FACTORS AFFECTING OUTCOMES FROM ARF

Several factors can affect the outcomes from any intervention trial (Table 4). Broadly, these can be categorized as (1) patient characteristics contributing to the nature and severity of the underlying disease associated with ARF; (2) the effects of the process of dialysis for replacement of renal function; and (3) other factors, including practice variations and the impact of post-ARF interventions. Recognizing the contribution of each of these factors in determining each outcome helps in the selection process.

Patient Characteristics

Advanced age and male gender have been associated variably with adverse outcome for ARF in previous studies with ARF. It is well recognized that the development of ARF is associated with an increase in mortality. It also is known that patients with ARF as part of multiorgan failure (MOF) have a higher mortality than those with limited ARF. Clermont et al compared outcomes for ICU patients with and without ARF...
and ESRD patients admitted to the ICU in a single center and showed a significant increase in mortality for ARF patients. Dialyzed ARF patients had the worst outcomes. Metnitz et al. found a similar increase in mortality in dialyzed ARF patients, and using a case-control study, showed a significant increased risk for mortality attributable to the requirement of dialysis. Patients with ARF at admission to the ICU may have a better prognosis than those who develop ARF during the course of their ICU stay.28,29 In the French multicenter study of severe ARF,29 patients with ARF on ICU admission had higher severity of illness (APACHE II, SAPS, and OSF) scores at ICU admission than the patients who developed ARF in the ICU, however, by the time of enrollment into the study the 2 groups had similar scores. This suggests that development of ARF in the ICU is associated with a worsening organ failure. Despite the similarity in severity of illness in the 2 groups at enrollment, the mortality was significantly different. Other studies have failed to find a significant difference in out-

### Table 3. Classification of Outcomes for ARF

<table>
<thead>
<tr>
<th>Category</th>
<th>Organ</th>
<th>Disease</th>
<th>Global</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficiency</td>
<td>Alterations in markers for renal perfusion (RBF, RPF) or renal functional parameters (GFR, tubular function)</td>
<td>Changes in generic and disease-specific scoring systems of organ function (eg, SOFA scores)</td>
<td>Survival rates: Kaplan Meier or Cox survival analysis</td>
<td>Device specific (eg, membrane clearance of marker molecule such as urea nitrogen)</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Changes in renal functional markers (eg, creatinine, BUN, and other markers)</td>
<td>Incidence of new onset disease syndrome (eg, infections or sepsis)</td>
<td>Mortality rates at different points</td>
<td>Drug: endpoint specific for drug effect (eg, natriuresis from atrial natriuretic peptide)</td>
</tr>
<tr>
<td>Requirement for dialysis</td>
<td>Changes in generic and disease-specific scoring systems of organ function</td>
<td>Changes in generic and disease-specific scoring systems of organ function</td>
<td>Mortality rates at different points</td>
<td>Drug: endpoint specific for drug effect (eg, natriuresis from atrial natriuretic peptide)</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Return of renal functional status to baseline</td>
<td>Improvement in disease state and return to normal health</td>
<td>Survival, Dialysis Dependency, Composite outcomes: dialysis free survival or death or nonrecovery of renal function</td>
<td>Maintenance of target parameters influenced by device or drug within specified range (eg, acid-base balance, hemodynamic stability or fluid balance)</td>
</tr>
<tr>
<td>Clinical use</td>
<td>Return of renal functional status to baseline</td>
<td>Prevention of nonfatal events</td>
<td>Death</td>
<td>Benefit-cost and cost-effectiveness analysis</td>
</tr>
<tr>
<td>Safety</td>
<td>Direct nephrotoxicity</td>
<td>Changes in disease or organ dysfunction status attributable to intervention (eg, hypotension during dialysis)</td>
<td>Death</td>
<td>Adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teratogenecity</td>
<td>Frequency, duration, and relationship to intervention (eg, WHO-ART terminology for bleeding caused by anticoagulation)</td>
</tr>
</tbody>
</table>

Abbreviations: RBF, renal blood flow; RPF, renal plasma flow; GFR, glomerular filtration rate; BUN, blood urea nitrogen; QALY, quality of life years; WHO, World Health Organization; ART, adverse reaction terminology.
comes related to the timing of ARF. Sepsis-related ARF has a significantly worse prognosis, with sepsis contributing an independent effect on outcome. It also is recognized that untreated ARF may contribute to a higher incidence of new-onset sepsis.

The etiology and type of ARF may influence outcome. We recently reported our findings from a large prospective cohort of patients with ARF in the ICUs at 4 centers in Southern California. Patients with ARF secondary to multisystem disorders such as lupus nephritis had the lowest mortality, whereas the highest mortality was seen for ischemic acute tubular necrosis (ATN), with nephrotoxic ATN showing an intermediate mortality (multisystem 15.8%, nephrotoxic 42.9%, and ischemic 64.2%, respectively, \( P \leq .005 \)). Other studies have shown similar results. These data suggest that if the renal insult can be identified clearly or a specific therapeutic strategy (eg, use of steroids for lupus nephritis) is required, outcome is improved. It is well recognized that nonoliguric ARF carries a better prognosis than oliguric ARF and represents a less severe form of ARF. Two multicenter trials in ARF patients appear to support this notion; however, both trials combined ICU and non-ICU patients. Recent data suggests that nonoliguric ARF may in fact have a worse prognosis in the ICU patient. Myers has shown that although nonoliguria is associated with a good prognosis in the abbreviated form of ARF, it does not reflect outcome in prolonged ARF. Paganini et al. retrospectively analyzed a large cohort of ICU patients with ARF at the Cleveland Clinic and found that nonoliguric patients who required dialysis had a higher mortality than oliguric patients who required dialysis. A possible explanation is that nonoliguric states result in an overestimation of renal function leading to a delay in initiation of dialysis. In our study there was an 8-fold greater likelihood of oliguric patients being dialyzed.

### Process Factors

There is wide variation in the nondiagnostic and dialytic management of ARF across the world; however, there is limited information on the process factors that influence outcomes. Part of the problem lies in the absence of a uniform definition of ARF, making it difficult to compare findings across studies. Additionally, it often is difficult to recognize the effect of a process factor on an underlying patient characteristic. Several process of care factors affect the clinical course and should be considered.

#### Nondiagnostic Management

The conservative management of ARF commonly includes the frequent use of low-dose dopamine and diuretics to maintain urine output. Several studies and metanalyses have shown a lack of benefit for dopamine or diuretics in preventing ARF or modifying the disease course. The conservative management of ARF commonly includes the frequent use of low-dose dopamine and diuretics to maintain urine output. Several studies and metanalyses have shown a lack of benefit for dopamine or diuretics in preventing ARF or modifying the disease course. We recently evaluated data from a prospective cohort of 552 patients with ARF in the ICU and categorized them by the use of diuretics on the day of nephrology consultation and, in companion analyses, by diuretic use at any time during the first week after consultation. All-cause hospital mortality, nonrecovery of renal function, and the combined outcome of death or nonrecovery were used as outcomes. Fifty-nine percent of patients had received diuretics at the time of nephrology consultation.

### Table 4. Factors Affecting Outcomes from ARF in the ICU

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factors</td>
<td>Age, sex</td>
</tr>
<tr>
<td></td>
<td>Etiology and nature of ARF (eg, oliguria)</td>
</tr>
<tr>
<td></td>
<td>Timing of ARF</td>
</tr>
<tr>
<td></td>
<td>Nature of underlying disease</td>
</tr>
<tr>
<td></td>
<td>Severity of illness and associated organ system failure</td>
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<tr>
<td></td>
<td>Presence of sepsis</td>
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<tr>
<td></td>
<td>Nutritional status</td>
</tr>
<tr>
<td>Process factors</td>
<td>Nondiagnostic management</td>
</tr>
<tr>
<td></td>
<td>Dialysis issues</td>
</tr>
<tr>
<td></td>
<td>Timing of intervention with dialysis</td>
</tr>
<tr>
<td></td>
<td>Modality</td>
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<td></td>
<td>Membrane</td>
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<tr>
<td></td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>Frequency and duration of support</td>
</tr>
<tr>
<td>Other factors</td>
<td>Practice variations</td>
</tr>
<tr>
<td></td>
<td>Ancillary support</td>
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<tr>
<td></td>
<td>Post-ARF interventions</td>
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<tr>
<td></td>
<td>Fluid balance</td>
</tr>
<tr>
<td></td>
<td>Nutritional support</td>
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</tbody>
</table>
penalty scores, diuretic use was associated with a significant increase in the odds of death or nonrecovery of renal function (odds ratio [OR], 1.77; 95% confidence interval [CI], 1.14–2.76). The odds were magnified (OR, 3.12; 95% CI, 1.73–5.62) when patients who died within the first week after consultation were excluded. Although a causal association cannot be established, this study highlights the importance of adjusting for process factors when outcomes are evaluated.53

**Dialysis Process Factors**

Over the past decade intervention trials have compared different modalities of dialysis, assessed the potential benefit of different components within a single mode of dialysis, and compared modifications in dialysis dose.21,22,41,54 Additionally, the need for dialysis has served as a surrogate outcome for other interventional trials in ARF.55–58 The majority of trials have encountered problems in the design and implementation of the interventions that are instructive for future trials. There are several steps in the process of renal replacement for ARF that are affected by different factors. For instance, the timing of intervention, the amount and frequency of dialysis, and the duration of therapy all affect the eventual outcome.59–61 In practice, these issues are based on individual physician preferences and experience; no set criteria are followed, thereby making comparisons between any 2 centers or even 2 patients at the same center difficult. Dialytic intervention in ARF usually is considered when there is clinical evidence of uremic symptoms or biochemical features of solute and fluid imbalance. Patient characteristics tend to influence the decision to dialyze, particularly in the presence of oliguric ARF. The majority of trials performed to date have not addressed these issues in the trial design and consequently trial implementation has been affected. It is not evident from the published literature which components in the process influence outcomes, and there are no specific guidelines for the use of dialysis in this setting.62–64 Published trials in dialysis have not been standardized for the indications or for the time point at which therapy is initiated.

The prescription of dialysis is even more variable. There are no guidelines for the dose of dialysis required to treat ARF.43,65,66 There is evidence from studies in ESRD that there is a reciprocal relationship between dose of dialysis as assessed by urea kinetic modeling–derived Kt/V and mortality up to a Kt/V of 1.5.67 Most nephrologists now use these methods for prescribing dialysis for ESRD.68 However, there is no equivalent strategy for ARF. Recent evidence suggests that the dose of dialysis also may influence outcome in ARF patients. There was a difference in the delivered dose of dialysis in survivors (Kt/V 1.09) and nonsurvivors (Kt/V 0.89) in ARF patients treated with equivalent prescriptions of dialysis (similar membrane, blood flow rate, time).41 The presence of hemodynamic instability, inadequate extracorporeal anticoagulation secondary to bleeding, blood recirculation, and a high catabolic rate may account for the discrepancy between prescribed and delivered dose of dialysis.69,70 Ronco et al22 have shown that large volumes of ultrafiltration in continuous venovenous hemofiltration (CVVH) provide a survival benefit for ARF patients. However, subsequent studies of high-volume hemofiltration have not shown a convincing benefit.71–73 The role of aggressive dialysis on outcome from ARF has been addressed in recent studies. A small randomized controlled study performed over 2 decades ago failed to show any difference in outcome in patients dialyzed daily to maintain BUN levels under 60 mg/dL in comparison with those dialyzed to BUN levels of 100 mg/dL.74 A subsequent study in trauma patients showed an improved trend for survival for patients started on hemofiltration early in the course.75 However, another study on high-volume hemofiltration started early did not show any benefit over low-volume hemofiltration.73 A retrospective analysis of ARF patients showed a mortality rate of 74.8% in patients dialyzed once, 66.7% and 50% in those dialyzed between 2 to 10 times and 10 to 20 times, respectively.76 Patients dialyzed more than 20 times had an increase in mortality to 61.5%. Other studies have found an improved survival with higher serum creatinine levels,77 whereas some had better outcome with lower predialysis creatinine values.78

The type of dialysis modality (intermittent versus continuous) also may influence outcome from ARF. Because intermittent techniques result in rapid shifts of fluid and solute, hemodynamic instability often is present. It has been felt that these episodes of hypotension may represent new ischemic insults to the kidney and may prolong the time to recovery.79 Although there is evidence that continuous dialysis provides a greater amount of
dialysis as judged by urea Kt/V and is associated with greater hemodynamic stability, it is unclear if CRRT techniques improve outcome from ARF. In a randomized controlled trial of CRRT versus intermittent hemodialysis (IHD), we were unable to show a survival benefit from CRRT but showed the association between underlying severity of illness and outcomes. Several additional studies have analyzed data comparing CRRT with IHD and have shown several important concepts. Martin et al have shown recently that the choice of CRRT itself influences outcomes because this modality likely is offered preferentially to patients with marked hemodynamic compromise. It is evident from the data described earlier that future studies need to define the influence of variations in the dialysis process on outcomes and these factors should be controlled for in future trials.

Practice Variations and Post-ARF Interventions

Management of ARF is multidisciplinary, involving nephrologists, intensivists, surgeons, and internists variably. There is wide variation in the approach to ARF and this may contribute to outcomes. Some of the factors that have been related to outcomes are described later.

Timing of Consultation

In most ICUs in the United States, ARF patients are managed by intensivists, often with consultative assistance from nephrologists. In contrast, ARF patients in Europe and Australia are managed predominantly by intensivists. The frequency and timing of consultation for nephrologists varies greatly. In 4 centers in California, we examined the relationships of time of consultation to outcomes from ARF to test the hypothesis that increased time to consultation is associated with worse outcomes. Nephrology consultation was delayed (≥48 h) in 61 of 215 (28%) patients (median time to consultation: 4 d). Lower serum creatinine level (P < .0001) and higher urine output (P = .002) were associated significantly with delayed consultation. Delayed consultation was associated with increases in mortality for dialyzed (31 of 42 [74%] versus 50 of 103 [49%], P = .006) and nondialyzed (10 of 19 [53%] versus 11 of 51 [22%], P = .01) patients, and increases in median lengths of hospital (19 versus 15.5 d, P = .02) and ICU stay (17 versus 6 d, P < .0001). The association between delayed consultation and mortality was attenuated by covariate adjustment, and was no longer statistically significant after adjustment with propensity scores. A possible explanation for these findings is that a delay in recognition of the severity of ARF and institution of corrective measures influenced the outcome. Patients who were delayed had a greater number of organs failing at consultation (3.6 versus 2.8 P ≤ .002) and stepwise logistic regression showed that delay had an independent effect on hospital mortality controlling for the level of organ systems failing (adjusted OR for delay, 4.98; CI, 1.99–12.55).

Concurrent Care

Intervention trials attempt to control for nonmeasured variables by randomization, under the assumption that random allocation will adjust for differences in patients’ characteristics. Unfortunately, randomization may not always control for process factors that may be random. For instance, ensuring concurrent care for critically ill patients is essential in any intervention trial. One factor that influences the level of care is the code status of the individual. Often decisions for do not resuscitate (DNR) status are made even before nephrology consultation. We found that approximately 10% of our study patients had chosen DNR even before the nephrologist was consulted. It has been shown previously and recently confirmed that the DNR status in the ICU setting affects the level of care administered and eventual outcome. In our study, patients who were delayed in consultation had a significantly higher rate of being made DNR after renal consultation, reflecting the perception that MOF was irreversible. It is interesting that there is often a dichotomy in the minds of the primary caregivers (intensivist, surgeon) in terms of level of interventions permissible. For instance, a DNR patient may not be a candidate for surgical intervention to drain an abscess but would be felt to be appropriate to receive dialysis. It is thus important to ascertain the code status of the patient in clinical trials for ARF because interventions targeted only at ARF are unlikely to compensate for other organ failure, which influences outcome.

Fluid Balance

A particular area for concern in ARF is fluid management. Although there has been an increased tendency to use aggressive volume resuscitation to
achieve and maintain supranormal oxygen delivery, in MOF there recently has been concern that these methods may not be without deleterious effects.\textsuperscript{91} Lowell et al.\textsuperscript{92} described a strong association of fluid overload and mortality. Similarly, Paganini et al.\textsuperscript{43} reported that nonsurvivors from ARF had a greater weight than survivors. CRRT techniques are particularly suited to allow fluid management in this setting, however the continuous nature of the therapy permits interference from multiple individuals who may not be trained in the procedure. As a consequence, an adverse outcome may result from misuse of the technique. There is limited information in this regard in the literature. Barton et al.\textsuperscript{77} found a relationship between improved survival and the number of years of experience with CRRT techniques.

**Nutritional Support**

The nutritional status of and nutritional support provided to ARF patients is an additional factor contributing to morbidity and mortality. Bartlett et al.\textsuperscript{93} have shown previously the effect of calorie deprivation on outcomes from ARF. Similarly, other studies in ICU patients suggest a strong effect of malnutrition on outcome.\textsuperscript{94} Unfortunately, there is no consensus on the amount of nutrition that is optimal for the ARF patient.\textsuperscript{95} Bellomo et al.\textsuperscript{96} were unable to show any additional benefit on outcome with an aggressive nutritional regimen. At the other extreme, it is not uncommon to withhold nutritional supplementation to reduce the likelihood of dialytic intervention.\textsuperscript{97} It is clear that nutrition is an important area that is prone to significant practice variations and has an effect on outcome, but additional research is needed to determine how nutritional support should best be provided.

**Post-ARF Interventions**

Finally, the effect of interventions after ARF is established is rarely considered.\textsuperscript{34,35,98} For instance, angiographic or surgical procedures, and use of nephrotoxic agents and antibiotics, all may impact on the duration of ARF, recovery of renal function, and mortality.\textsuperscript{99} Time to renal recovery was used as an outcome measure in studies comparing biocompatible with bioincompatible membranes in ARF, however it is unclear whether the number of interventions post-ARF were similar in the 2 groups.\textsuperscript{41,54} Co-interventions may be especially important with regard to morbidity outcomes (eg, using radiocontrast might not be associated with death, but might be associated with nonrecovery of renal function). It is thus important to track these factors in future clinical trials.

**SELECTING THE RIGHT OUTCOME: STRATEGIES FOR FUTURE STUDIES**

Selecting appropriate endpoints for a clinical trial is an important component of study design. To determine which outcomes are appropriate for a particular study, it is helpful to map patient characteristics, the natural progression of the disease and the process of care, identify the points of intervention, and select endpoints that provide the information most relevant to the outcome. A key concept here is to distinguish the contributions of patient characteristics (eg, age and sex) that cannot be modified from those of process variables that could be altered (eg, dialytic support). Recognition of and adjustment for the effects of process variables that are not the focus of the study (eg, concurrent care), is an additional necessary step. A final consideration reflects the need to focus on outcomes that are relevant and reflect the primary goal for the study.

The focus of the study influences the choice of outcomes. For example, for early phase clinical trials, safety and efficacy parameters are the main determinants, whereas for phase III and phase IV trials, showing effectiveness and clinical use are important. Similarly, prevention trials will have different outcomes in contrast to intervention trials for established disease. The matrix shown in Table 2 provides a framework to guide selection of various outcomes for ARF studies. For instance, a study to prevent ARF could show a reduction in the incidence of ARF, a modification of the time course of renal dysfunction if it occurs (shortened time of renal dysfunction), or an enhancement of complete renal functional recovery. Each of these events can be linked to a target parameter that reflects renal functional change (eg, change in GFR as measured or estimated from serum creatinine level). Unless the drug directly influences the GFR in a dose-responsive manner, a change in the incidence of renal dysfunction is a surrogate marker for drug efficacy and is subject to the limitations for surrogate endpoints discussed earlier. Often the practicality of measurement can determine feasibility of using a particular endpoint (eg,
iothalamate GFR measurements in the ICU setting are impractical whereas serum creatinine level is measured routinely but its sensitivity and specificity as a marker for GFR is influenced by other factors such as the volume status of the patient).

Therapeutic trials for established ARF have different constraints wherein the timing of intervention in the course of ARF is an important factor. Figure 2 depicts the relationship of various outcomes to the process of care elements. These sequential events in the natural course of ARF identify time points for clinical management decisions. From a practical perspective, this approach helps determine the appropriate decision points at which therapeutic interventions will influence outcomes. For instance, nondialytic management of ARF is most likely to affect the need for dialysis before influencing mortality. The need for dialysis, time to dialysis, and dialysis-free survival have been endpoints in previous clinical trials, however, these outcomes are based on the assumption that the initiation of dialysis represents a common level of severity of renal disease. As discussed earlier, these endpoints are subject to wide individual variation and in the absence of predefined criteria for initiation of dialysis they should not be used. Efficacy endpoints for therapeutic intervention trials use physiologic measures as surrogate endpoints and are subject to the same limitations as outlined for prevention studies. Effectiveness measures for therapeutic trials should show an improvement in the burden of disease. Improved survival, changes in nonfatal events (eg, requirement for chronic dialysis or composite endpoints such as dialysis-free survival) are relevant outcomes. After the initiation of dialysis, renal function may improve enough to allow withdrawal of dialysis, as is likely in the overt form of ARF in the Myers model, or the patient may be dialysis dependent. Long term functional status and resources used provide additional measures of effectiveness and clinical use.

The influence of ARF on the length of stay in the ICU and the resultant costs are of obvious additional interest.

**SUMMARY**

ARF continues to be a significant disease contributing to morbidity and mortality in the ICU. Several measures are available to monitor the course of patients with ARF and can serve as endpoints for studies. Each endpoint has advantages and limitations that should be considered in the interpretation of any trial. Global outcomes are less specific but have greater clinical use than disease- and organ-specific endpoints. Surrogate measures should be selected with care to ensure that they are in the path of the disease and are affected by the intervention. Specific efficiency endpoints should be incorporated in device studies to monitor the performance of the device. Preven-
tion studies require showing a beneficial effect on organ-specific endpoints whereas therapeutic interventions should differentiate the effects on organ-specific, disease-specific, and global endpoints. Future research should define the effect of patient characteristics and process factors on various outcomes in ARF.

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