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PERSPECTIVES IN RENAL MEDICINE

Treatment of acute renal failure

ROBERT A. STAR

Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Treatment of acute renal failure. Acute renal failure is a life threatening illness whose mortality has remained high since the introduction of hemodialysis 25 years ago, despite advances in supportive care. Acute renal failure is an extremely morbid and costly disorder with a significant proportion of patients progressing to end-stage renal disease requiring dialysis. To the nephrologist, acute renal failure remains an extremely frustrating disease, because the pathophysiology is not well understood and the limited therapeutic options force the nephrologist to sit on the sidelines and wait for renal function to return. For example, dialysis remains the only FDA-approved treatment for acute renal failure, but dialysis may also cause renal injury that prolongs renal failure. The purpose of this perspective is to understand the results of the recent, largely negative, clinical trials in view of recent advances in the epidemiology of ARF. This review will also discuss diagnostic tools, strategies for improved design of clinical trials, and other therapeutic interventions that will be needed to properly treat acute renal failure in the 21st century.

Acute renal failure is a life threatening illness whose mortality has remained high since the introduction of hemodialysis 25 years ago despite advances in supportive care. Acute renal failure is an extremely morbid and costly disorder with a significant proportion of patients progressing to end-stage renal disease requiring dialysis. To the nephrologist, acute renal failure remains an extremely frustrating disease because the pathophysiology is not well understood and the limited therapeutic options force the nephrologist to sit on the sidelines and wait for renal function to return. For example, dialysis remains the only FDA-approved treatment for acute renal failure, but dialysis may also cause renal injury that prolongs renal failure. Aspects of acute renal failure have been the subject of many recent excellent reviews [1–5] and an entire issue of *Kidney International* [6]. The purpose of this perspective is to understand the results of the recent, largely negative, clinical trials in view of recent advances in the epidemiology of ARF. This review will also discuss needed diagnostic tools, strategies for improved design of clinical trials, and other therapeutic interventions that will be needed to properly treat acute renal failure in the 21st century.

Key words: acute renal failure, creatinine, epidemiology, dialysis, clinical trials, end-stage renal disease.

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DETECTION OF ACUTE RENAL FAILURE

Acute renal failure is typically diagnosed by observing rises in BUN and plasma creatinine and decreases in urine flow rates over several days. Unfortunately, creatinine is a suboptimal indicator of renal function during acute renal failure because plasma creatinine is influenced by many non-renal events that regulate creatinine generation, volume of distribution, and creatinine excretion (Fig. 1). Each of these can be dramatically altered in acute renal failure. For example, patients with ARF are often edematous, which dilutes creatinine and slows recognition of ARF. Also, creatinine is excreted by glomerular filtration and tubular secretion. As GFR decreases, the amount of tubular secretion becomes an increasingly important fraction of creatinine excretion, such that creatinine clearance overestimates GFR by 50 to 100% once the true GFR is less than 15 ml/min [7]. The dynamic relationship between creatinine and GFR (Fig. 2) further erodes our ability to both detect and quantify renal dysfunction during ARF. Moran and Myers noted that a sudden fall in GFR to a constant low level causes a slow increase in plasma creatinine; the rate of rise depends on the new GFR but also on the rate of creatinine generation and the volume of distribution of creatinine [8]. A new steady state is reached when the creatinine generation equals creatinine excretion. During recovery from ARF, the reverse occurs. This dynamic relationship has several consequences. First, it is difficult to estimate GFR from plasma creatinine during these non-steady state conditions. The continued rise in plasma creatinine does not indicate that renal function has worsened; rather, it indicates that a steady state has not been achieved. GFR is a complicated function of the rate of rise of the plasma creatinine, the patient's baseline GFR, and the presence of edema and altered creatinine production. Second, large changes in GFR are initially manifested as small changes in creatinine in the first one to two days after renal injury. Since these changes are near the detection

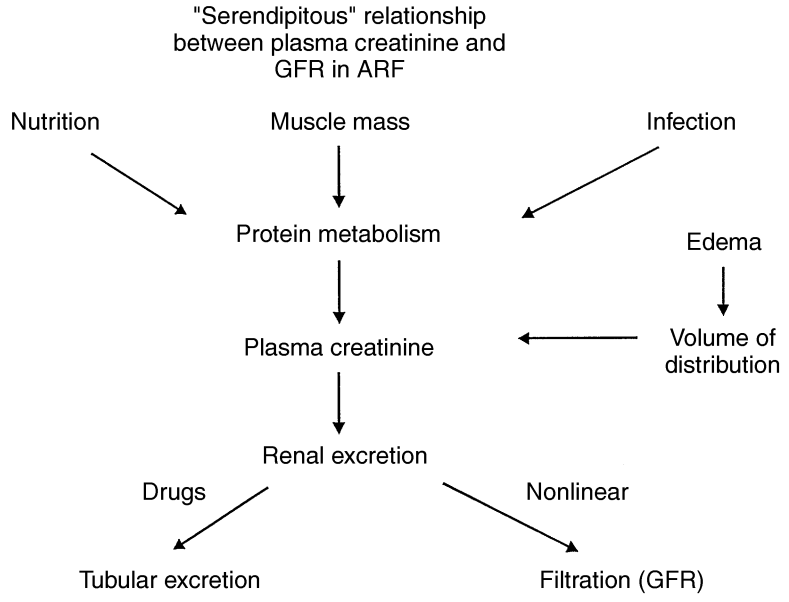

Fig. 1. Factors that influence steady state creatinine and glomerular filtration rate (GFR) in acute renal failure (ARF).

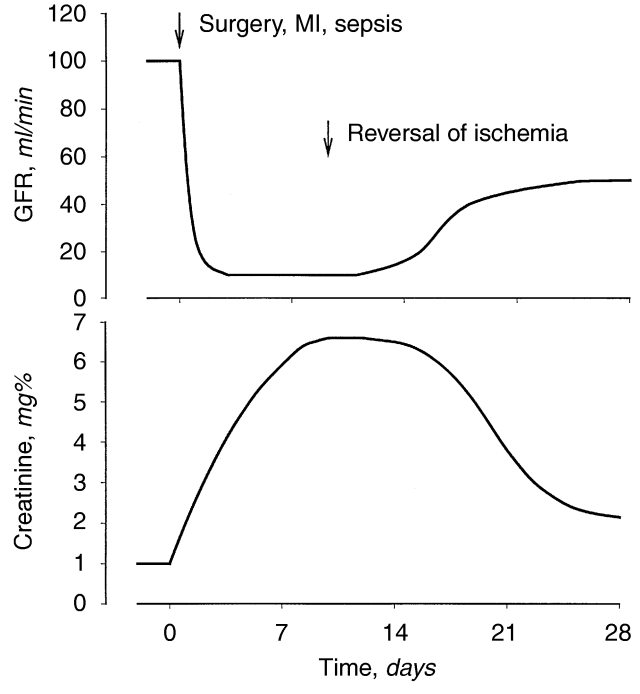

Fig. 2. Dynamic relationship between creatinine and GFR in ARF. Modified from Moran and Myers [8].

limits of a clinical laboratory, the diagnosis of ARF may be delayed, especially in the setting of malnutrition or edema. Third, the degree of renal dysfunction cannot be determined accurately until the new steady state is reached (creatinine is stabilized), which typically takes one week. Thus, both plasma creatinine and creatinine clearance are poor markers of renal function in the setting of acute renal failure. The early diagnosis of ARF would be aided by discovery of a serum marker akin to troponin for myocardial infarction, or a method that measures renal function more rapidly than a standard three-hour clearance study (Glofil).

EPIDEMIOLOGY OF ACUTE RENAL FAILURE

Incidence

In the past five years there have been major advances in understanding the epidemiology of ARF. This is no small feat, since we still lack a centralized registry of patients with ARF. The incidence of azotemia (including pre- and post-renal ARF), ascertained from DRG coding of hospital discharge summaries, is projected to be approximately 275,000 per year in 1997 and increasing at a rate of 16,000 patients per year according to the yearly National Hospital Discharge Survey. The incidence of ARF is harder to ascertain. Since ARF is present in about 42% of patients with azotemia [9], the incidence of intrinsic acute renal failure is about 115,000 cases/year. Thus, intrinsic acute renal failure qualifies as an orphan drug indication, which has important implications for future drug discovery.

Etiology

Acute renal failure is caused by ischemic (50%) or nephrotoxic (35%) injury to the kidney. About 15% of acute renal failure is caused by acute tubular interstitial nephritis or acute glomerular nephritis [2]. However, 50% of hospital acquired acute renal failure is frequently multifactorial, for example, sepsis treated with aminoglycosides, radiocontrast in patients receiving angiotensin-converting enzyme inhibitors, or congestive heart failure patients who develop sepsis or are treated with non-steroidal anti-inflammatory agents. Studies from the 1980s found that the major risk factors for ARF are hypotension, congestive heart failure, septic shock, volume depletion in diabetic

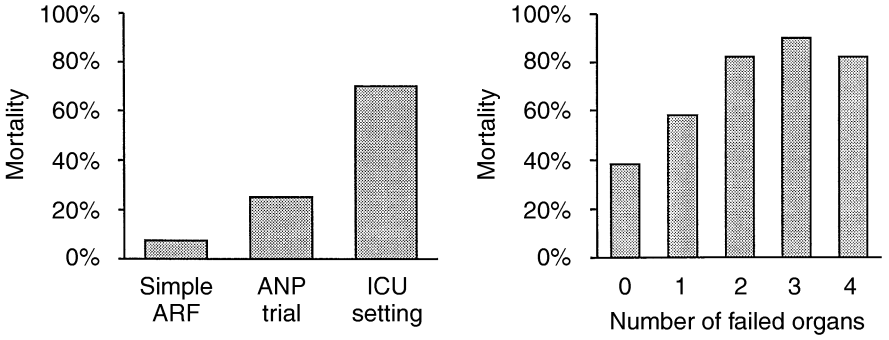

Fig. 3. Mortality of ARF partly depends on co-morbidity. Data taken from [2, 18–20, 22].

patients, aminoglycoside use, or radiocontrast procedures [10, 11]. Acute renal failure also occurs in about 15 to 25% of patients after renal transplantation despite careful attempts to optimize fluid status and increase renal perfusion [12, 13]. There is an increased risk of acute renal failure if the transplanted kidney is obtained from a marginal donor who is either hypotensive with a rising creatinine at the time of transplantation or is greater than 60 years old. Post-transplant acute renal failure has tremendous morbidity, since it prolongs the initial hospitalization and increases the risk of acute and subsequent chronic rejection [12]. If this acute renal failure could be prevented, it would be possible to transplant more kidneys from marginal donors and thus double the size of the donor pool [14]. This would dramatically decrease the waiting time for renal transplantation, which currently averages about three years.

Mortality

Acute renal failure is a devastating illness that is associated with a high risk of mortality. The mortality rate of ARF was 91% during World War II, 68% in Korea, and 67% in Vietnam. Most [15, 16] but not all [17] studies have shown a modest improvement in the mortality of ARF over the last 15 to 20 years; however, the rate is still unacceptably high. The mortality rate depends on underlying comorbid illnesses and, hence, location in the hospital (Fig. 3). For example, simple acute renal failure in the presence of no other underlying illnesses has about a 7 to 23% mortality, whereas the mortality of acute renal failure in an ICU setting is 50 to 80% [2, 18–21]. Liaño et al recently found that the morbidity of intrinsic ARF was 37% outside the ICU and 78% in an ICU setting [21]. Survival after acute renal failure is dramatically influenced by the severity of the underlying illnesses and number of failed organs. The mortality of ARF in patients on a ventilator is about 80%, and mortality dramatically increases with increasing numbers of failed non-respiratory organs [20]. The mortality of patients with ARF increases with the number of failed organ systems both in ICU and non-ICU settings [21]. In a recent trial of atrial natriuretic peptide (ANP), the average mortality was much lower at 26% [22]. The study excluded patients with severe non-renal illness, since treatment of the renal disease would not dramatically influence their outcome; hence, the study population was biased towards a less seriously ill population [23].

Independent risk of mortality

The studies cited above suggest that acute renal failure is merely an unfortunate complication that is a proxy for the severity of the other medical problems. However, a recent study found that the development of even mild acute renal failure itself increases morbidity (Fig. 4 [24]). Levy, Viscoli and Horwitz performed a cohort analysis study of over 16,000 patients undergoing radiocontrast procedures. They identified 183 patients who developed contrast nephropathy (defined as an increase in serum creatinine of at least 25% to at least 2 mg/dl), and matched them to patients of similar age and baseline serum creatinine who underwent similar contrast procedures without developing acute renal failure. This small 25% change in serum creatinine may reflect as much as a 50% reduction in GFR. Only 12% of the index patients needed dialysis. The mortality rate in patients without renal failure was 7% compared to 34% in the index patients. After adjusting for differences in comorbidity, renal failure was associated with an odds ratio of dying of 5.5 [24]. The innovative feature of this study was to perform the analysis in a relatively healthy population of patients. Thus, the high mortality rate is not explained by the underlying comorbid conditions alone. Acute renal failure should not be regarded as a treatable complication of a serious illness. Instead, changes in creatinine level, however small, should be taken seriously and trigger subsequent steps to determine the cause and specific treatment of the renal failure [24, 25].

Morbidity of acute renal failure

How does acute renal failure result in excess morbidity and mortality? A recent study of patients who died after developing acute renal failure found that the patients had complicated clinical courses characterized by sepsis, bleeding, delirium, and respiratory failure [24]. Many of these events occurred after the onset of ARF, implying that renal dysfunction results in a generalized disturbance. All of these events are well recognized complications of acute

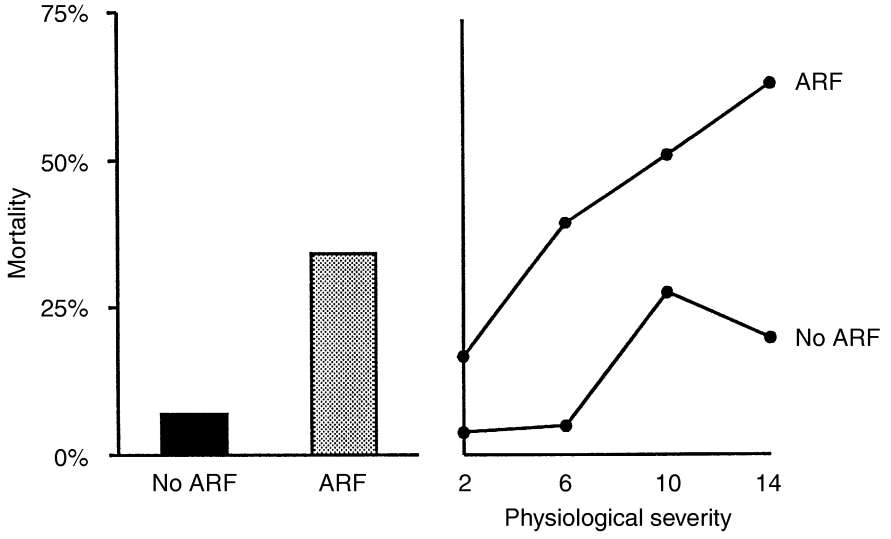

Fig. 4. ARF is an independent risk factor for death. Data taken from study of Levy et al [24].

renal failure that should in theory be well treated by effective control of uremia with dialysis. This study suggests that the recognition of patients at risk, prevention of acute renal failure, and early treatment of acute renal failure will be much more effective than treatment of established acute renal failure.

Severity of illness

Before discussing the treatment of ARF, one must have an index of the severity of renal and comorbid illnesses that is accurate in patients with ARF. One of the notable advances in the last five years has been the development of indices that accurately predict the severity or mortality associated with acute renal failure. These indices will become extremely important in the future to detect changing trends in acute renal failure as well as in the design of randomized clinical trials. APACHE II or III scores, which measure the severity of physiological impairment in ICU patients, underestimate the risk of mortality of patients with acute renal failure (Fig. 5) [26, 27]. APACHE scores do not work, perhaps because the proportion of the score allocated to renal failure is only 4%, which de-emphasizes the independent mortality risk of ARF [26]. Recently, ARF-specific severity of index scores have been developed for all patients with ARF [28, 29], and ICU patients with acute renal failure [27, 30–32]. For example, Liaño et al in Madrid have developed an accurate index that has been validated retrospectively and prospectively in several different patient populations (Fig. 6) [26, 29, 33]. The index accurately predicted overall mortality in ICU (actual 71.5%, predicted 65%) and non-ICU ARF (actual 31.5%, predicted 32%) [21]. This index represents an important advance, since previous indices worked quite well in the hospital in which they were developed, but failed when transported to other settings [27]. Renal dysfunction accounts for 21% of the index, and comorbid illnesses

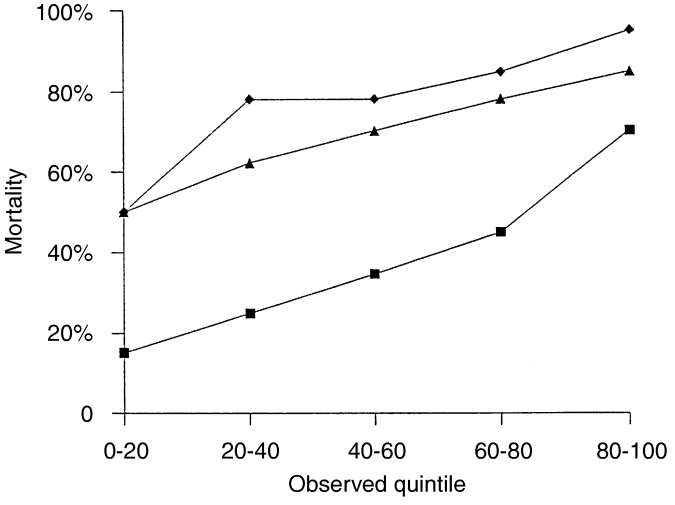

Fig. 5. Traditional indices of ICU mortality (APACHE III) underestimate the risk of death in patients with ARF, whereas the Liaño Severity of Illness score is accurate. Symbols are: (♦) observed; (▲) Liaño; (■) APACHE III). Data are taken from [26, 27].

account for the remainder [26]. This index is quite interesting because it indicates the individual contributions of oliguria, hypotension, jaundice, coma, and assisted ventilation. The largest contribution is assisted ventilation, which agrees with previous studies that have indicated the 80% mortality of those developing acute renal failure while on a ventilator. Some of these indices may eventually be useful in evaluating the futility of treatment in severely ill patients; however, patients with a Madrid ARF Study Group severity of illness score greater than 0.9 have survived [21].

As discussed above, the overall mortality rate of ARF has only modestly improved over the last several decades, despite the provision of better supportive care. Several explanations for this lack of dramatic improvement have been proposed: worsening comorbidity, dialysis-induced

Add		Subtract	
Constant	21	Pure nephrotoxic	11
Age	3* decades	Alert	15
Female	9		
Oliguria	11		
Hypotension	12		
Jaundice	12	Total = Expected % mortality	
Coma	15		
Assisted ventilation	18		

Fig. 6. Components of Liaño ARF Severity of Illness score [26, 29, 33].

morbidity, more invasive surgery in sicker patients, and older patients. Are these explanations correct? McCarthy at Mayo Clinic found that overall hospital morbidity decreased from 68% to 48% during the years of 1977 to 1979 and 1991 to 1993, respectively [16]. While the mean APACHE II score was similar in both study periods, the more recent group was older and had more points for chronic health problems. Stratification by APACHE II scores showed a dramatic improvement in mortality in patients with low (36% to 11%) or moderate (75% to 35%) APACHE II scores, with little change at high APACHE II scores (100% to 85%). Despite the shortcomings of the APACHE II score in ARF, the data suggest that advances in patient care have had an impact on the treatment of patients with ARF, despite an older population who typically have more chronic health problems and more risk factors for the development of ARF. It would be interesting to see a similar analysis using a renal severity of illness score.

Risk stratification

While the major risk factors for ARF are well known (ischemia, nephrotoxins, sepsis, etc.), the risk in individual patients is not well characterized. For example, after cardiac surgery, ARF requiring dialysis develops in 1 to 5% of patients and is strongly associated with peri-operative mortality and morbidity. Can this event be predicted? Chertow and colleagues recently collected prospective data from 43,600 patients from 43 VA hospitals during the years 1987 to 1995 [18]. The overall risk of ARF requiring dialysis was 1.1%. The development of ARF requiring hemodialysis increased the 30 day mortality by 15-fold, from 4.3% to 63.7%. They used the elegant statistical technique of recursive partitioning to allocate the patients into several distinct risk groups (Fig. 7), which allows the patients to be given more accurate prognostic information before surgery. It is hoped that similar analyses will be carried out for other procedures associated with a high risk of ARF.

Taken together, the recent advances in the epidemiology of acute renal failure are beginning to permit an accurate prediction of outcome based upon the nature and severity of the renal insult, and the severity of the non-renal illnesses. This tie between incident population and predicted outcome is key to the success of future clinical trials, since who to treat may be as important as how to treat.

PATHOPHYSIOLOGY

The pathophysiology of acute renal failure is quite complex and not well understood. The pathophysiology is generally viewed from several different viewpoints, or paradigms, which have been the subject of several recent reviews [2, 34]. The paradigms are summarized here to show how they have impacted on the choice of drugs that have been tested in clinical trials.

Hemodynamic paradigm

The hemodynamic paradigm, developed in the 1960s and 1970s, views the nephron as a series of pipes: the blood enters, is filtered, and then the glomerular filtrate is processed by the nephron [35]. As such, acute renal failure, that is, the failure to produce good urine, could be produced either by vasoconstriction of the supplying vasculature, impairment of the filtration process, obstruction of the tubules, or backleak of urine into the interstitium. This paradigm led to the testing of vasodilators (ANP, dopamine), diuretics (furosemide, mannitol), and anti-obstructive agents (integrins) to prevent acute renal failure [36–38].

Cell fate paradigm

The cell fate paradigm, developed in the 1980s and early 1990s, focuses on the fate of an individual polarized tubular cell after it is injured [34]. After injury the cell becomes stunned and loses its polarity. This stunned cell can either undergo necrosis or apoptosis, or the cell can initiate a repair program that would return the cell to its normal polarized state. This paradigm assumes that repair follows developmental pathways. Hence, researchers have focused on the use of growth and differentiation factors elaborated by the developing nephron (that is, IGF-1, HGF, EGF) in animal studies. IGF-1 has been tested in clinical trials.

Interactive cell biology paradigm

In the early 1990s, it became apparent that these paradigms ignored the anatomical complexities of the kidney. Tubule cells act as immune cells and actively participate in

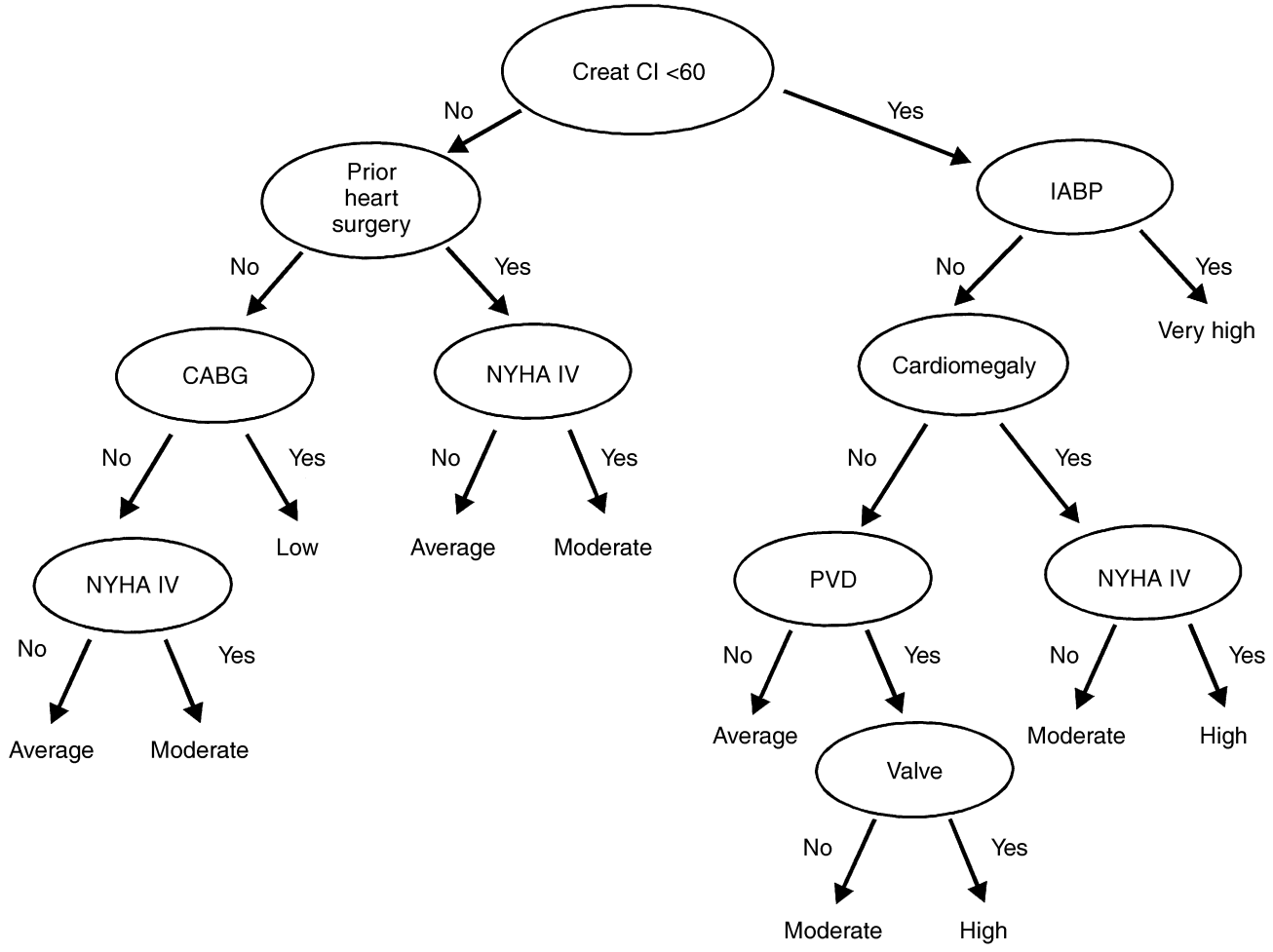

Fig. 7. Risk of ARF requiring hemodialysis in patients after cardiac surgery. Ovals represent important patient characteristics selected by recursive partitioning analysis. Abbreviations are: Creat Cl, creatinine clearance; CABG, coronary artery bypass grafting only (without valve replacement); IABP, intra-aortic balloon pump; PVD, peripheral vascular disease. Mortality rates: low (0.4%); average (0.9 to 1.4%); moderate (2 to 2.8%); high (5 to 6.1%); very high (9.5%). Modified from [18].

immune and inflammatory events surrounding them. Cells interact with each other and release inflammatory mediators and cytotoxic substances into their local environment. The ischemic kidney produces a variety of inflammatory mediators, including tumor necrosis factor-α (TNFα), interleukin (IL)-1, IL-8, and macrophage chemoattractant protein-1 (MCP-1) [39]. The kidney also synthesizes cytotoxic agents that injure tubular cells, including superoxide and, more recently discovered, nitric oxide [40–42]. There is good evidence for inflammation in animal studies, although the human data are less certain. The animal studies quite convincingly show that neutrophil infiltration during the recovery phase causes a no-reflow phenomenon. The neutrophils plug the blood vessels, prevent red cells from passing, and thus increase the amount of ischemic damage. This paradigm is supported by the ability of anti-neutrophil agents, such as neutrophil depletion and anti-ICAM-1 antibodies, to decrease injury following ischemia reperfusion [39, 43, 44]. This paradigm is supported by human data, which show that dialysis membranes that activate neutrophils prolong the course of acute renal failure [45] and accelerate the decline in residual renal function in patients newly started on chronic hemodialysis [46]. Animal studies have shown that activated neutrophils deposit in the kidney, where they increase renal damage [47]. This paradigm has led to the testing of anti-platelet agents, anti-inflammatory agents (such as α-MSH [42, 48] or IL-10 [49]) and nitric oxide inhibitors in animal studies. For example, we have shown that the anti-inflammatory cytokine α-melanocyte-stimulating hormone (α-MSH) prevents renal ischemic injury even when started six hours after ischemia, and is effective even in the absence of neutrophils [42, 48]. While none of these agents have been tested in clinical trials, these agents deserve further research.

Some of the therapeutic agents have multiple mechanisms of action and thus may not fit cleanly within a single paradigm. For example, IGF-1 also has important hemodynamic effects that increase GFR independent of effects

on cellular growth and differentiation [50]. IGF-1 also decreases the inflammatory response to renal injury [51]. RGD peptides also bind to the vasculature [52]. α-MSH also increases blood pressure and cardiac output during hemorrhagic and anoxic shock [53, 54].

Pathophysiology of human acute renal failure

Which of these paradigms describes human ARF? Human ARF is caused by heterogeneous factors (ischemia, nephrotoxins, etc.), and it is likely that the underlying pathophysiology differs in each case. However, human ARF is generally multi-factorial, so all three paradigms may be involved to some extent. A definitive answer may be impossible because of the relative lack of human biopsies early in ARF, and the near complete absence of the required functional measurements. I propose that the paradigms are best judged by their ability to lead to the development of clinically effective drugs. Ultimately, this issue will be answered by the results of clinical, not animal, trials. That many agents have multiple mechanisms of action may cloud the resolution of this issue; however, the ability to work at multiple levels may be quite helpful for successful treatment of human ARF.

NON-DIALYTIC TREATMENT OF ACUTE RENAL FAILURE

Acute renal failure can be treated by inhibiting injury or enhancing repair, or the injury process itself managed by treating the metabolic consequences of acute renal failure [reviewed in 2, 3, 55, 56]. These consequences include volume overload, solute overload (hyperkalemia acidosis, uremia, cytokines), endocrine deficiencies (erythropoietin), and the non-renal complications, including sepsis, gastrointestinal (GI) bleeding, delirium, and respiratory failure. The current treatment for ARF is empirical, that is, agents are used indiscriminately without regard to underlying etiology, with the hope that these agents will influence the course of acute renal failure. At the present time, more often than not this hope remains unfulfilled. Many agents are effective in animal models; however, most of these agents are effective only if started before injury. Since clinicians are generally not present at the time of injury, it is important that any pharmaceutical agents are effective when started after the injury has occurred (Table 1; for example, see [36, 37, 42, 57–59]).

Table 1. Interventions that prevent acute renal failure (ARF) in animal studies

Paradigm	Before injury	After injury
Hemodynamic	Diuretics	ACE inhibitor (30 min)
	Mannitol	Phosphodiesterase inhibitor (24 hrs)
	Dopamine	ANP (48 hrs)
	Calcium channel blocker	Endothelin antagonist (48 hrs)
	Endothelin antagonist	
Cell fate	IGF-1, EGF, HGF	IGF-1 (24 hrs)
Interactive cell biology	SOD-antagonist	PAF antagonist (30 min)
	anti-sense iNOS oligo	ICAM-1 antibody (2 hrs)
	P-selectin antagonist	α-MSH (6 hrs)
	CLTA-4lg	

Diuretics and mannitol (hemodynamic paradigm)

Furosemide is a loop diuretic and a vasodilator; it may decrease the metabolic work of the thick ascending limb and may flush obstructing casts from the nephron [60]. In addition, furosemide may decrease the concentration of toxins such as myoglobin or hemoglobin in the tubules. Based on the hemodynamic paradigm, furosemide should prevent ARF. In normal patients, furosemide does cause a large diuresis. In some patients with ARF, furosemide may convert oliguric ARF to non-oliguric ARF. However, there is no solid evidence that furosemide alters the natural history of human acute renal failure [56, 60–62]. The single randomized controlled trial did not show any change in azotemia or mortality [63]. Indeed, furosemide may worsen radiocontrast-induced acute renal failure [64]. Conversion of oliguric ARF to non-oliguric ARF simplifies the patient management because the patient can receive a more liberal fluid intake and it is easier to administer parenteral nutrition. However, the conversion does not alter the natural history of the disease, but instead supplies prognostic information that the patient had less severe ARF. Large doses of furosemide are ototoxic, and the large infusion volume can cause pulmonary edema [65]. Thus, it is reasonable to give a single trial of furosemide in escalating doses. If the patient does not respond to furosemide, the agent should not be readministered.

Mannitol is a diuretic that also may scavenge extracellular free hydroxyl radicals, although the importance of this effect on ARF is unknown. Use of mannitol in ARF has been comprehensively reviewed recently [66]. Mannitol is beneficial when added to organ preservation solutions during renal transplantation [67]. Mannitol may also protect against ARF caused by crush injury involving myoglobinuria, but only if given extremely early [66]. Other than these limited uses, mannitol has not been shown to be useful in prevention or treatment of ARF. In contrast, mannitol aggravates radiocontrast induced ARF [64].

Renal low dose dopamine (hemodynamic paradigm)

Dopamine is a selective renal vasodilator that causes profound natriuresis and increases urine output. It is widely used despite little clinical data supporting its use. The renal selective dose of dopamine is about 1 μg/kg/min and not 3 to 5 μg/kg/min as routinely used [68]. The use of dopamine was examined in the placebo group of a recent randomized control trial of atrial natriuretic peptide. Dopamine did not improve survival or delay dialysis [69]. A recent review by Denton, Chertow and Brady concludes that "the routine

use of dopamine should be discouraged until it is shown to be effective" [68].

Atrial natriuretic peptide (hemodynamic paradigm)

Atrial natriuretic peptide (ANP) vasodilates the afferent arteriole and constricts the efferent arteriole, resulting in an increase in GFR. ANP also inhibits tubular sodium absorption. The net effect is dramatic increase in urine output. ANP is very effective in animal models even if first started two days after the ischemic or nephrotoxic insult [36, 37]. Because of these dramatic effects in animal studies, an open label trial of ANP was performed at the University of Colorado [70]. Fifty-three patients were selected based on a rise in creatinine of 0.7 mg% per day for three days. ANP had dramatic effects: it doubled the GFR and reduced the need for dialysis by almost 50%. Based on these positive results, a multicenter, randomized, double-blind, placebo-controlled trial in 504 critically ill patients with intrinsic acute renal failure was initiated [22]. Patients were included if they had an increase of creatinine greater than 1 mg over 48 hours. Many of the patients were critically ill; 85% of the patients were in the ICU; 50% of the patients were intubated. Patients were excluded if they were hypotensive despite pressors. The trial had an excellent balanced randomization, which was probably aided by the large size of the trial. However, ANP had no effect on 21-day dialysis-free survival, mortality, or change in plasma creatinine. A pre-specified subgroup analysis suggested that ANP improved dialysis-free survival in oliguric patients (baseline creatinine clearance 4 ml/min), but not in non-oliguric patients (baseline creatinine clearance 13 ml/min). It was hypothesized that ANP was ineffective in non-oliguric patients because the ANP induced hypotension and caused fresh ischemic injury. While the oliguric group was also hypotensive, their kidneys were already injured and evidently not subject to additional hypotensive ischemic injury. Of note, if ANP converted oliguric acute renal failure to non-oliguric acute renal failure, the outcome was improved. A follow-up randomized controlled clinical trial of ANP in oliguric patients with acute renal failure was initiated, but halted after an interim analysis showed that the trial was unlikely to find any therapeutic benefit.

Insulin-like growth factor-1 (cell fate paradigm)

Insulin-like growth factor-1 (IGF-1) is made in high concentrations by the developing kidney, where it induces cell proliferation and differentiation. It was hypothesized that IGF-1 might potentiate renal repair mechanisms after renal injury, since the cell fate paradigm states that repair recapitulates renal development [71]. In animal models of renal injury, IGF-1 enhanced repair following renal ischemia even when started 24 hours after injury [59, 72], and it may prevent renal injury following renal transplantation in dogs [73]. IGF-1 also has direct hemodynamic effects [50]. This agent was tested in two clinical trials. The first trial, performed at Washington University in St. Louis, was a randomized, double-blind, placebo-controlled trial of 58 patients undergoing vascular repair of the renal arteries or aorta [74]. The surgeries are associated with a relatively high rate of acute renal failure, often approaching 25%. IGF-1 was started post-operatively just as the patient entered the Intensive Care Unit. IGF-1 was well tolerated with no notable side effects. IGF-1 produced a modest ($\approx$ 8 ml/min) increase in creatinine clearance, whereas the placebo group had a slight fall in creatinine clearance. Thus, IGF-1 prevented the decline of GFR. There was no effect on morbidity, mortality, or length of stay. However, no patient needed dialysis in either group. Evidently the surgeons did not inflict very much renal injury during the operation. IGF-1 was also tested in a multicenter, randomized, double-blind, placebo-controlled trial [75]. The study enrolled 72 ICU patients with acute renal failure caused by surgery, trauma, hypertension, sepsis, or drugs of less than six days duration. Initial iothalamate GFR on randomization was 6.4 ml/min in the IGF-1 group and 8.6 ml/min in the placebo group. These patients had severe renal injury. Unfortunately, there was no difference in post-treatment GFR, need for dialysis, or morbidity. On the basis of this trial, testing of IGF-1 to treat or prevent acute renal failure was discontinued. IGF-1 is still being tested for use as an adjunct to nutritional supplementation in a variety of wasting disorders, including acute and chronic renal failure, and is being tested in kidney transplantation.

Nutritional support

Nitrogen balance is extremely negative in patients with ARF, and protein catabolic rate (PCR) is very high [reviewed in 76, 77]. Nutritional supplementation increases azotemia, which increases the need for renal replacement therapy, so that nutritional support is frequently delayed in these patients to obviate the need for dialysis. Initial studies showed the benefit of essential amino acid supplementation, but subsequent studies have been conflicting [reviewed in 55, 56, 76]. However, these studies were performed before the recent advances in parenteral nutrition and dialysis techniques [55, 56, 76]. Most nephrologists recommend that nutritional supplementation should not be withheld to minimize azotemia.

Nephrologic consultation

Only one non-dialytic intervention has been successful in improving the morbidity and mortality of acute renal failure. There is new evidence that early consultation with a nephrologist improves the outcome of patients with ARF [78]. Mehta et al showed that nephrologic consultation was delayed in 28% of ICU patients with ARF in the ICU [78]. Delay in consultation was associated with higher mortality, longer ICU length of stay, and increased number of organ systems failing at the time of consultation [78]. Delay in

nephrologic consultation was likely if the degree of ARF was underestimated because of low creatinine (4.5 mg%) or high urine output (400 ml/day). The lower creatinine was often a consequence of volume overload that diluted the plasma creatinine, or severe malnutrition that decreased creatinine generation. While delay in consultation may have occurred in sicker patients and thus may be a proxy for severity of illness, this study demonstrates that interventions early in the course of ARF may influence outcome.

DIALYSIS

The role of hemodialysis in ARF has been reviewed recently [79]. Dialysis is required in about 85% of patients with oliguric ARF, and 30% of patients with non-oliguric ARF. Retrospective studies have shown that dialysis is better than no dialysis [63, 80], but establishing a dose-response relationship has been very difficult. Dialysis is a risky procedure, with risks of bleeding and hemorrhage from the site of vascular access. Hypotension and arrhythmias are frequently produced as a consequence of rapid changes in compartment volumes. Finally, recent studies reviewed below have suggested that dialysis itself may delay the recovery of renal function with ARF. This may be caused by hypotension or activation of the inflammatory cascades by the blood-dialyzer interface. Hypotension occurs frequently during the dialysis of sick ARF patients and can cause recurrent ischemic renal injury. Animal studies have shown that kidneys with ARF have impaired renal autoregulation, and frequently have increased vasoconstriction because of injury to the vascular endothelium, that results in increased sensitivity to vasoconstrictors and a deceased release of vasodilators [81, 82]. Thus, hypotension in the setting of ARF causes additional ischemic injury because of impaired autoregulatory response to hypotension.

Hemodialysis with biocompatible membranes

Dialysis with a bio-incompatible membrane elicits an inflammatory response consisting of complement activation and subsequent neutrophil activation. The amount of the response can be easily measured by a transient neutropenia, as the activated neutrophils are removed from the circulation by the lungs. Animal studies have shown that activated neutrophils are also deposited in the kidneys, where they either infiltrate into the organs or block small blood vessels and cause renal injury [47]. Recent prospective randomized studies by Schiffl et al [83] and Hakim, Wingard and Parker [45, 84] have shown that dialysis with biocompatible membranes shortens the course of non-oliguric ARF, reduces hospitalization, and increases survival. Dialysis with biocompatible membranes resulted in less complement generation, better survival from sepsis, and fewer dialysis sessions [83, 85]. The results in the Hakim trials were more striking in the non-oliguric patients than the oliguric patients. Non-oliguric patients have higher renal blood flow and GFR [22], which may render the kidney more susceptible to ischemic injury. A similar selective deleterious effect of hypotension was also seen in the ANP trial [22]. The biocompatible membrane trials have been criticized because the criteria for dialysis was not defined, and the decision was left to the discretion of the nephrologist. However, subsequent analysis showed that the two groups had similar blood chemistries at the time of initiation and discontinuation of dialysis [84]. The hypothesis is also supported by data showing that biocompatible membranes preserve residual function in patients on chronic hemodialysis [46], and that bioincompatible membranes are associated with a higher rate of infections [86].

These positive results have not been reproduced in ARF after renal transplantation [87] nor in several studies published recently in abstract form [88–90]. A recent abstract by Mehta et al of a non-randomized study showed that the effect of dialyzer membrane on mortality and renal recovery was not significant when patients were stratified for APACHE III scores [91]; however, a more accurate scale such as the Liano or Cleveland Clinical Severity of Illness Score was not used. Finally, recent animal studies did not find any differences between dialysis membranes and recovery of renal function [92, 93]. Unlike the study by Schulman et al [47], the rats received hemodialysis rather than injection of complement activated plasma. On the other hand, the exposure to dialysis membranes was short, and only after the renal injury was established. Thus, the issue remains very controversial. Nevertheless, the published randomized trials do show impressive effects.

Does more dialysis enhance survival?

Retrospective trials have shown that dialysis used to keep BUN below 150 mg% improves survival, when compared to no dialysis [63, 80]. However, establishing whether more dialysis is beneficial has been extremely difficult. Conger performed a paired (not randomized) trial during the Vietnam war, and found that sufficient dialysis to keep the pre-dialysis BUN below 150 mg% caused an 80% mortality, while more dialysis to keep the pre-dialysis BUN below 70 was associated with a 36% mortality [94]. Unfortunately, because of the small size of the trial (8 to 10 patients per group), the difference was not statistically significant. In a prospective trial by Gillum et al that included a better randomized design [95], the more intensive dialysis (defined to keep BUN below 60 mg%) had less GI bleeding, but the mortality in the intensive dialysis group was higher (59%) than in the non-intensive group (47%) dialyzed to keep the predialysis BUN below 100 mg%.

Paganini et al recently showed a link between dialysis therapy and outcome in ICU patients with ARF; however, this link was only present when the underlying comorbidity was taken into account using the Cleveland Clinic Severity of Illness Score [19]. This severity of illness score incorporates male gender, intubation/mechanical ventilation,

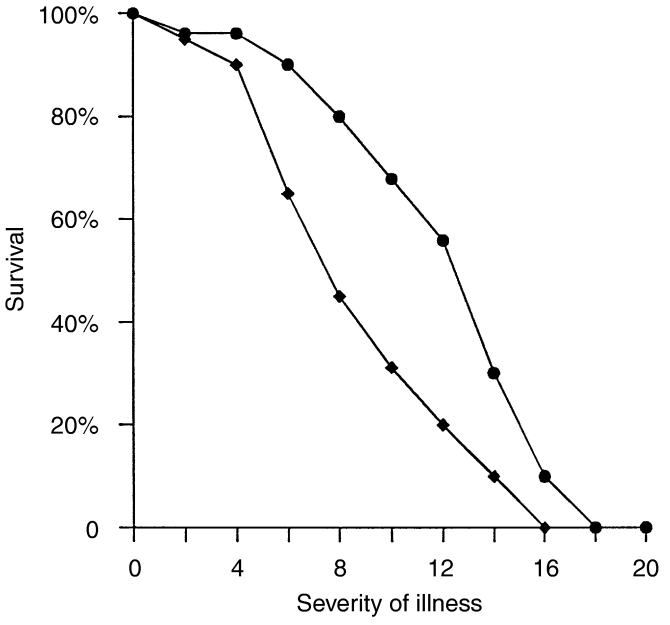

Fig. 8. More dialysis enhances survival. Data from [19]. Symbols are (●) more dialysis; (♦) less dialysis.

platelet and leukocyte count, bilirubin level, number of organ failures, change in BUN since admission, and serum creatinine. This index shares some similar variables (intubation, bilirubin) with the Liano index, although there are differences of which the gender is most notable. Without factoring for comorbidity, dialysis had no effect on survival. When comorbidity was taken into account, dialysis had no effect at the two ends of the spectrum: mortality of 0% in patients with very low (<4) severity of illness scores and nearly 100% at high (>15) scores (Fig. 8). However, the dose of dialysis did affect outcome in patients with an intermediate score. Higher delivery of dialysis (URR 58%, Kt/V 1, TAC urea 45 mg%) was associated with significant reduction in morbidity when compared to low dose delivery in the same severity of illness quartile. Whereas the underlying patient morbidity has a significant effect on survival in ARF, the dose of dialysis also plays a major role in patients with intermediate severity of illness.

Schiffl et al have recently reported the preliminary results of a trial in 72 critically ill patients with ARF who were randomized to either daily or alternative day dialysis using biocompatible high-flux dialyzers [96]. The two groups were well matched in age, severity of ARF, APACHE II scores, and prescribed dialysis techniques. Overall mortality was significantly improved in the daily dialysis group (21% vs. 47% for the alternative day group). When analyzed in terms of delivered dialysis dose (Kt/V), mortality was 16% in the group receiving a weekly Kt/V greater than 6, which was significantly less than the 57% mortality in patients receiving underdialysis (weekly Kt/V < 3). This is the first study to show that the amount of dialysis is an independent determinant of mortality in critically ill patients with acute renal failure. Why did this trial have a positive result that was not seen in previous trials? Unlike previous dosing trials, this trial used biocompatible synthetic membranes, which may have allowed an effect of dialysis dose to be seen for the reasons discussed above. The study also suggests that the alternative day dialysis typically prescribed for acute renal failure is 'grossly inadequate.' More studies are needed to define how to measure dialysis dose in patients with acute renal failure [97]. Recent studies in chronic renal failure have found that equilibrated or 'double pool' Kt/V is more accurate than the traditional single pool Kt/V [98, 99]. Whether reliance on equilibrated kinetics is also more accurate in acute renal failure is unknown.

Mode of renal replacement therapy

In the past, intermittent hemodialysis (IHD) has been the therapy of choice for ARF, since peritoneal dialysis does not remove sufficient solute or volume. However, IHD is associated with wide swings in body wt, blood pressure, ventricular filling pressures, and solute concentrations (BUN, potassium, and bicarbonate). Because of the concern that recurrent hypotension perpetuates renal injury and lengthens recovery from ARF, newer modes of dialysis therapy have been developed that minimize hypotension. Continuous renal replacement therapy (CRRT) removes fluid and solutes at a slow and controlled rate, thus minimizing hypotension [reviewed in 91, 100–102]. Because it is more complicated to perform, CRRT is usually reserved for hemodynamically unstable patients (including those with sepsis, burns, and multiple organ dysfunction syndrome) in the ICU who often cannot tolerate the hemodynamic effects of intermittent hemodialysis. The solute clearance of CRRT may be larger than IHD with four treatments a week. The CRRT dialysis membrane has large pores that may allow removal of inflammatory cytokines. CRRT also allows for easier drug dosing. Because of its theoretical advantages, it was hoped this would lead to improved patients survival or recovery from renal failure.

IHD and CRRT have been compared in many nonrandomized or retrospective studies [reviewed in 55, 56, 102]. Prospective randomized trials are difficult to perform because the hemodynamically unstable patients cannot tolerate hemodialysis, while it may be ethically problematic to confine a hemodynamically stable patient to bed while receiving CRRT. A recent prospective trial from Barcelona failed to find any difference in survival [103]. Mehta et al recently completed a multi-center prospective randomized trial of CRRT versus IHD in IHD patients with ARF [91]. One hundred and sixty-six patients were randomized to receive either IHD or CRRT (which was performed as CAVH or CAVHD). The total mortality was only 50%, which was less than that expected from historical studies. An intention to treat analysis found that the mortality was

higher in the patients randomized to CRRT (65.5%) than IHD (47.6%). Unfortunately, the randomization did not balance the groups very well; for example, the APACHE III scores were significantly different (85 for IHD vs. 102 for CRRT). Attempts to control for the unbalanced randomization using the APACHE scores still led to the same conclusion. Mehta et al have not reported their results using either the Liaño or Paganini severity of illness scales, which are more appropriate for renal patients. Subgroup analyses suggest a beneficial effect of CRRT, since patients who crossed over from IHD to CRRT had a higher mortality than those who crossed over from CRRT to IHD. Also, despite the higher mortality in the CRRT group, patients initially treated with CRRT had higher rates of recovery of renal function. At the present time, it appears that intermittent hemodialysis and chronic renal replacement therapy are roughly equivalent methods for treatment of ARF.

PROBLEMS WITH CLINICAL TRIALS

Why did so many of the clinical trials fail? Did the interventions lack efficacy, or were there problems in the design of the clinical trails? If the former is true, then the hemodynamic and cell fate paradigms may not be very useful in guiding drug development. More research may be needed to gain a better understanding of the underlying pathophysiologic mechanisms responsible for human acute renal failure. Perhaps we need better animal models that more closely mimic human multi-factorial ARF. Since human ARF is likely to have a diverse pathophysiological basis, future trials may need to study the effects of several agents at once or in a sequential order, as is used in cancer chemotherapy. While these issues are difficult to resolve at this time, I think that there is much to learn from the design of the recent trials.

Delayed diagnosis and randomization

In all of the trials, ARF was diagnosed based upon changes in plasma creatinine, which, as discussed above, delays recognition of renal injury and does not allow accurate assessment of the degree of renal damage. As a result, the interventions may have been started too late to be effective. For example, in the ANP trial the average creatinine at the time of randomization was 4.5 mg%. If creatinine rises at 1 to 2 mg%/day, this would indicate a delay of two to four days from the time of injury. In the IGF-1 trial, patients were enrolled within six days of injury. The animal data suggests that the interventions must be started early in the course of ARF (Table 1); effective treatment of human ARF will likely also require prompt treatment. We need a blood or urine test that measures release of a renal-specific protein akin to cardiac tropoponin used in the diagnosis of myocardial infarction. Alternatively, ARF could be diagnosed with a rapid functional test that directly measures the extent of renal injury. For example, GFR can be accurately measured by creatinine clearance using a single dose of oral cimetidine to block tubular secretion of creatinine [104]. We are evaluating a new test that can measure GFR in 45 minutes. These tests would allow rapid determination of renal dysfunction, and therefore speed diagnosis and randomization, and perhaps increase the efficacy of therapeutic drugs.

Wrong target population

Some of the trials enrolled patients who did not need treatment or had severe renal injury that was unlikely to respond to any interventions. For example, the IGF-1 prevention trial enrolled patients with a GFR 50% of normal, and none of the patients needed dialysis [105]. These patients had very mild ARF, which would make it difficult to detect a small protective effect of the intervention. The unpublished ANP trial included patients with severe oliguric ARF, which probably corresponds to a creatinine clearance of 4 ml/min based upon the published ARF study [22]. Since creatinine overestimates GFR by about 25 to 50% in ARF, these patients had severe renal injury.

Choosing the target population is of critical importance to the design of a clinical trial [106]. A general rule is to select patients who are most likely to benefit from the study drug based upon the known mode of action of the drug and the postulated effect size. The IGF-1 trials and Paganini's dialysis study suggest that treatment should be aimed at patients with 'moderate' ARF (Fig. 9), either based upon moderate renal injury or moderate predicted mortality. Whereas the traditional daily creatinine cannot identify patients with moderately severe renal dysfunction, these patients may be identified by cimetidine-creatinine clearance or other rapid GFR tests described above. A second approach would be to enroll patients who are predicted to have moderate mortality (perhaps 20 to 55%) at the time of randomization. While general mortality estimates underestimate mortality in ARF (Fig. 5), the Liano and Cleveland Clinic ARF Severity of Illness Scores are accurate in hospitalized and ICU patients, respectively. Future versions of these scores are needed to predict the severity of renal and non-renal diseases and the need for dialysis, and to more accurately predict the mortality. Recent ANP and IGF-1 trials had overall mortalities in this range [22, 75], because they excluded patients with hypotension and severe non-renal illnesses such that improvement in renal function would not be expected to improve the clinical outcome. However, the addition of more formal inclusion/exclusion criteria may target the study to a more homogenous patient population.

Studies aimed at preventing ARF must also consider the incidence of ARF. Since ARF is rare in hospitalized patients, the target population must be enriched in patients who will develop ARF, to maintain a realistic study size.

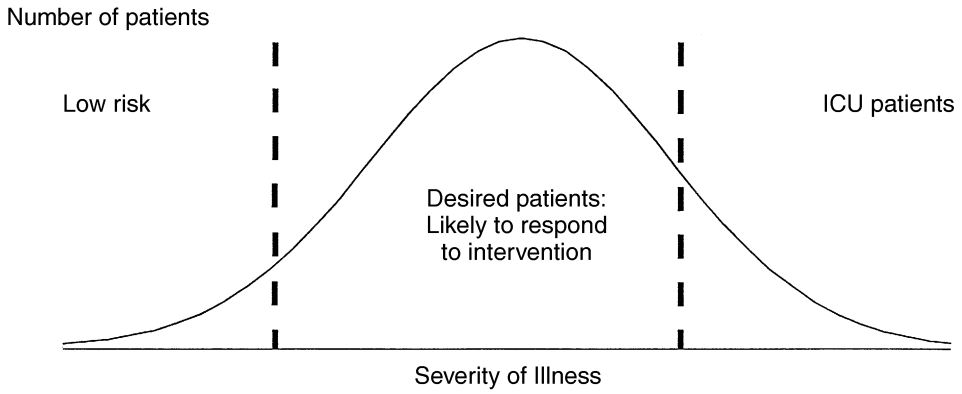

Fig. 9. Who to enroll in clinical trials with acute renal failure.

Unbalanced randomization

Human acute renal failure is a heterologous disease with multiple etiologies, a wide range of severity, and a heterogenous clinical outcome as discussed above. The heterogenous nature of ARF may promote unbalanced randomization, particularly in small trials. Whereas the placebo and ANP groups were well matched in the large scale Phase III trial of ANP involving 504 patients [22], there were significant differences in gender, severity of illness (APACHE II, APACHE III, and organ failure score), and presence of liver disease between the two groups in Mehta's CVVH versus intermittent hemodialysis trial of 166 patients [107]. While trial results can be adjusted for these factors using logistic regression, this post-hoc adjustment makes the trial results harder to interpret. One potential solution is to stratify patients before randomization using a severity of illness score. This may ensure balanced randomization in a disease that is notorious for its heterogenous clinical course.

Poorly defined endpoints

Dialysis was a so-called 'hard' endpoint in many of the trials. However, the decision to dialyze, a key endpoint, is usually left to the attending nephrologist. None of the trials controlled for the application of dialysis by setting up uniform criteria for initiating dialysis. Future trials using dialysis as an endpoint should set uniform criteria for starting and dosing dialysis treatments. This level of conformity may be difficult to achieve in a large multi-center trial, or even in a single large group practice. However, despite the lack of pre-specified criteria, a recent trial of dialysis membranes in ARF did have similar blood chemistries in the two groups at the time of dialysis initiation and at dialysis discontinuation [84].

Confounding effects

None of the trials controlled for the confounding effects of non-study drugs, especially diuretics and dopamine. These drugs do not benefit patients with ARF, and may do considerable harm [64, 68]. Future trials of new agents should exclude these drugs after randomization has occurred.

REQUIREMENTS FOR EFFECTIVE TREATMENT OF ACUTE RENAL FAILURE IN THE 21ST CENTURY

Management of acute renal failure is still a medical challenge to clinicians, since the current treatment of ARF is supportive. A more pro-active approach to acute renal failure is outlined in Table 2. Use of this approach would require the development of new tests to rapidly diagnose and determine the severity of ARF, and new drugs to prevent or treat ARF. Recent animal studies have identified new pharmaceutical agents that might lead to effective drugs able to modify the course of ARF, most importantly by primary prevention or, failing that, by treatment of established ARF to lessen additional injury and promote recovery [108]. Emerging therapies to watch include new natriuretic peptides (urodilation [109]), anti-inflammatory agents (α-MSH [42], anti-ICAM-1 antibodies [43, 44], and p-selectin antagonists [110]), PAF antagonists [58], anti-T-cell ligands (CTLA4-Ig [111]), and anti-integrin peptides to prevent tubular cell obstruction [38]. Several of these agents may need to be given simultaneously or sequentially, similar to cancer chemotherapy. The recent negative clinical trials have taught us the importance of early detection of ARF, enrolling mid-range patients, and stratifying enrolled patients by severity of illness. A consensus statement from a NIH-sponsored conference titled "Acute Renal Failure in the 21st Century" in May 1996 has advocated the development of a multicenter clinical trial network to develop appropriate outcome measures and severity of illness scores [3]. This group could also perform randomized trials to test the impact of hemodynamic monitoring, new pharmacologic agents and nutritional therapy, and to determine the optimal mode and amount of dialysis to deliver. Since dialysis does not replace the reabsorptive, homeostatic, metabolic, and endocrinologic functions of the renal tubule, a bioartificial kidney that uses progenitor

Table 2. Recognition and treatment of ARF in the 21st century

1. Recognize early that renal function may deteriorate or that renal injury is present
   Risk assessment tool
   High comorbidity
   Small increase in creatinine or fall in urine output
   Prospective screening of high risk patients
2. Measure renal glomerular and tubular function
3. Treat reversible causes
   Pre-renal ARF: NS challenge
   Post-renal ARF: ultrasound, urinary drainage
4. Nephrologic consultation
   Evaluate etiology
   Coordinate further care (nutrition, dialysis, etc.)
5. Prevent further damage
   Monitor and optimize hemodynamics
   Avoid hypotension and nephrotoxic drugs
6. Drug therapy
   Try diuretics once to identify less severe ARF
   Do not use 'renal' dopamine
   Start specific agent(s) based upon etiology of ARF
7. Start dialysis when indicated
   Choose therapy (mode, dialyzer, etc.) based upon co-morbid illnesses
   Measure delivered dialysis dose

epithelial cells may also be helpful in specific situations [112]. We wish to actively prevent or treat acute renal failure. No more sitting on our hands.

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Reprint requests to Dr. Robert A. Star, M.D., Department of Internal Medicine, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas 75235-8856, USA.
E-mail: Robert.Star@email.swmed.edu

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