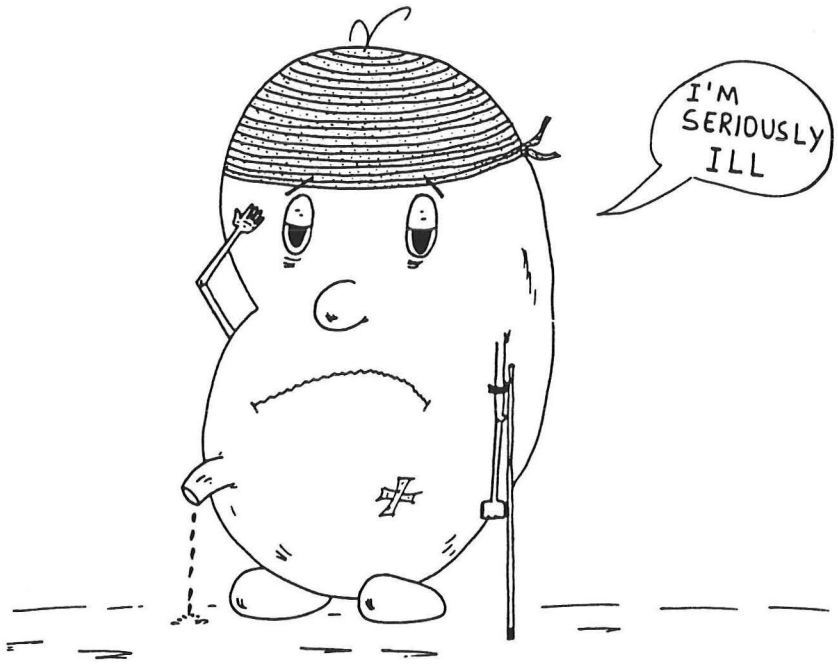
TREATMENT OF ACUTE RENAL FAILURE 1997



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INTRODUCTION

The mortality of acute renal failure has remained high over the last 50 years, despite advances in supportive care. Dialysis, the only FDA-approved treatment for acute renal failure, can also cause renal injury that prolongs renal failure. Several drugs developed by the academic community have now been tested in clinical trials. The purpose of this Grand Rounds is to review the tremendous advances in the epidemiology and treatment of acute renal failure. I will end with a vision of what it might be like to treat acute renal failure in the 21st Century.

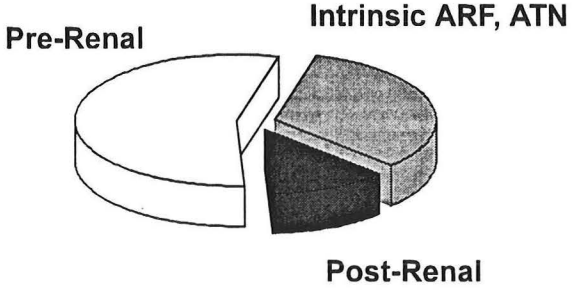
Let us begin with a typical case of acute renal failure. A twenty-one year old male is admitted to the Parkland Memorial Hospital Emergency Room with a gunshot wound to the abdomen which lacerated his spleen and colon. His surgical course is complicated by hypotension and intermittent sepsis. On the fourth hospital day, his urine output falls and BUN and creatinine begin to rise. Patient is modestly hypotensive off pressers with normal volume status. There is no evidence for urinary tract obstruction. Patient is receiving antibiotics, but none of them are nephrotoxic. A renal consultation is called. The ensuing argument about whether to continue the diuretics and dopamine will abate only once the patient starts dialysis. This Grand Rounds will review the other available avenues of treatment.

DEFINITION OF ACUTE RENAL INSUFFICIENCY AND ACUTE RENAL FAILURE

Acute renal insufficiency is defined as the decrease in the excretory capacity of the kidneys of sufficient magnitude to increase the concentration of nitrogenous wastes in the blood, i.e., BUN and plasma creatinine. A clinician often senses the development of acute renal insufficiency once the BUN rises above 40 or plasma creatinine above 2, or a change in creatinine of more than 0.5 mg% above baseline, or a rise of 25-50%. There is also a tendency to observe this rise over several days, in which case the creatinine concentration should rise by about 0.5-1 mg%/day. The second most common signal of acute renal insufficiency is a fall in urine output to less than 30 ml/hr.

It is traditional to divide acute renal insufficiency into three categories: (1) pre-renal azotemia, (2) post-renal azotemia, and (3) intrinsic acute renal failure, otherwise known as acute tubular necrosis. Pre-renal azotemia, present in about 55% of patients with azotemia, is caused by poor perfusion of the kidneys either due to hypotension or hypovolemia. Pre-renal azotemia is fully reversible by volume infusion; there is no structural damage to the kidneys. Post-renal azotemia is due to obstruction of the urinary tract, most commonly caused by benign prostatic hypertrophy, or less commonly by bilateral ureteral obstruction. It accounts for about 10-15% of azotemia. However, the largest fraction of patients, about 40%, with acute renal failure have intrinsic

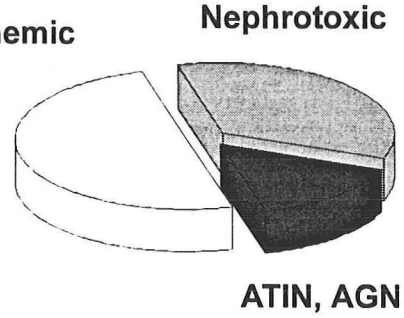
Categories of Acute Renal Insufficiency



acute renal failure which is caused by structural damage to the kidneys. This is also called acute tubular necrosis or ATN. The remainder of the talk will focus on intrinsic acute renal failure, which has been the subject of several excellent reviews (1-4).

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. 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.

Etiology of Acute Renal Failure



Sources: Hou, *Am J Med* 74:243, 1983; Schusterman, *Am J Med* 83:65; Thadhani, *NEJM* 334:1448, 1996.

Major Risk Factors for ARF

- Hypotension
- CHF
- Septic Shock
- Volume depletion if diabetic
- Aminoglycoside
- Radiocontrast

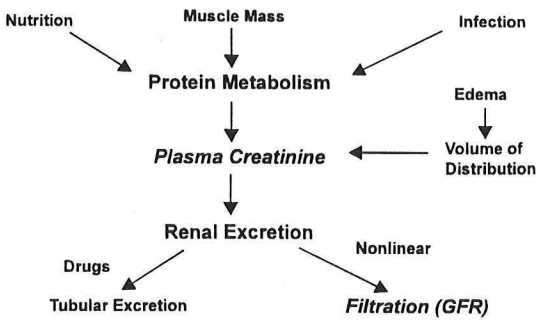
Studies from the 1980s found that the major risk factors for ARF are hypotension, congestive heart failure, septic shock, volume depletion in diabetic patients, aminoglycoside use, or radiocontrast procedures (5,6).

Acute renal failure also occurs in about 15-25% of patients after renal transplantation despite careful attempts to optimize fluid status and increase renal perfusion. There is 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 the donor is older than 60 years old. This form of acute renal failure has tremendous morbidity, since it prolongs the initial hospitalization by at least five days and increases the risk of acute and subsequent chronic rejection. 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. This would dramatically decrease the waiting time for renal transplantation, which currently averages about 3 years.

Acute renal insufficiency and acute renal failure are diagnosed by changes in serum creatinine (1,4). Unfortunately, creatinine is a poor indicator of renal dysfunction (7). The relationship between creatinine and GFR is not linear, but rectangular. At normal levels of creatinine, small 25% decrease in GRF increases creatinine from 1.0 to 1.25, which is barely detectable by a clinical laboratory. Thus, creatinine is an insensitive marker for changes in renal function near normal GFR. The concentration of creatinine is influenced by many non-renal events which regulate creatinine generation, volume of distribution, and creatinine excretion. Each of these can be dramatically

altered in acute renal failure. 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 50-100% once the true GFR is less than 15 ml/min (8). Clinical trials in chronic renal failure generally rely on more sensitive and direct measurements of GFR with inulin or iothalamate.

"Serendipitous" Relationship Between Plasma Creatinine and GFR in ARF



EPIDEMIOLOGY OF ACUTE RENAL FAILURE

"Who to treat may be as important as how to treat."

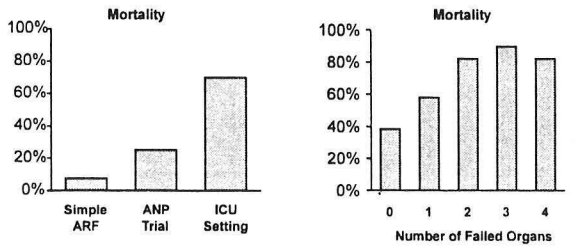
In the past 5 years there have been major advances in understanding the epidemiology of ARF. This is no small feat, since we still lack a centralized registry of patients with ARF.

Review of hospital discharge summaries indicates that the incidence of azotemia is increasing, according to the National Hospital Discharge Survey. When adjusted for the proportion of patients with azotemia who do not have intrinsic ARF, the incidence of intrinsic acute renal failure is about 110,000 cases/year. Thus, intrinsic acute renal failure should qualify as an orphan drug indication, which has important implications for future drug discovery.

Mortality

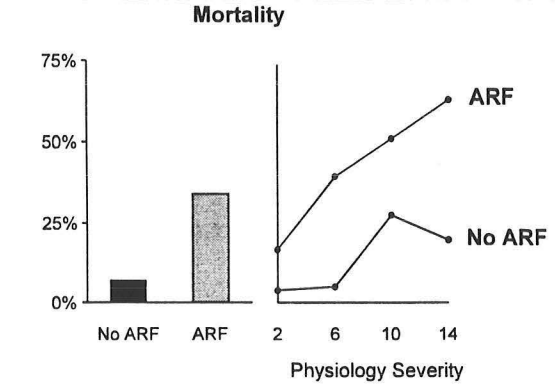
ARF is a devastating illness. Acute renal failure carries a high risk of mortality. Many studies have convincingly shown that the survival depends in part on underlying comorbid illnesses and hence, location in the hospital. For example, simple acute renal failure in the presence of no other underlying illnesses has about a 7% mortality, whereas the mortality of acute renal failure in an ICU setting is 50-80% (2,9-11). In a recent trial of ANP, the average mortality was probably more typical, 23% (12). Survival after acute renal failure is dramatically influenced by the severity of the underlying illnesses. For example, the mortality of ARF in patients on a ventilator is about 80%, and mortality dramatically increases with increasing numbers of failed non-respiratory organs (11).

Mortality of Acute Renal Failure Partly Depends on Comorbidity



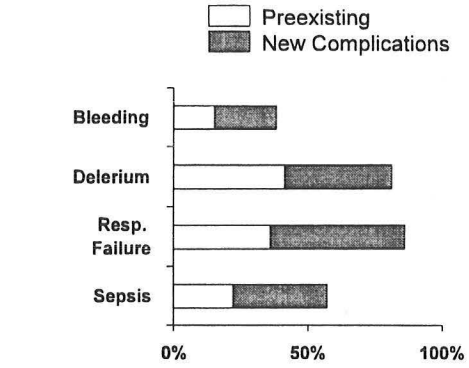
Sources: Thadhani, *NEJM* 334:1448, 1996; Allgren, *NEJM* 336:838, 1997; Douma, *JASN* 8:11, 1997; Chertow, *Arch Int Med* 155:1505, 1996.

Acute Renal Failure is an Independent Risk Factor for Death



Source: Levy, *JAMA* 275:1489, 1996.

Extra-Renal Morbidity of ARF



Source: Levy, *JAMA* 275:1489-1494, 1996.

Independent Risk

The previous data 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 (13). Levy and colleagues 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 (13). 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 (13,14).

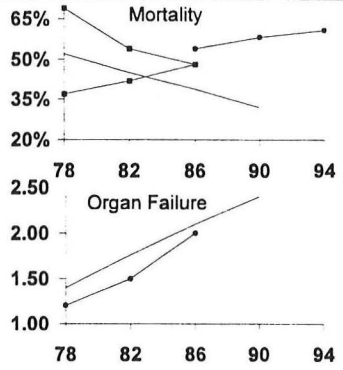
Morbidity of ARF

How does acute renal failure result in excess mortality? Patients who died after developing acute renal failure had complicated clinical courses characterized by sepsis, bleeding, delirium, and respiratory failure (13). 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 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.

Change in Mortality

The mortality rate of ARF was 91% during World War II, 68% in Korea, and 67% in Vietnam. The mortality rate of acute renal failure has stabilized over the last several decades (15-18), despite provision of better supportive care. Several explanations for this lack of improvement have been proposed: worsening comorbidity, dialysis-induced morbidity, more invasive surgery in sicker patients, and older patients. Are these explanations correct?

Has the Mortality of ARF Changed?

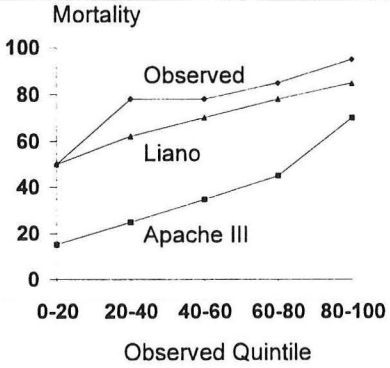


Source: Frost, *Scand J Urol Nephrol* 27:453, 1993.

Severity of Illness

But how does one adjust for comorbidity? Before discussing the treatment or treatibility of ARF, one must have an index of the severity of renal and comorbid illnesses that works 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 (19,20). 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 (19). Recently, ARF-specific severity of index scores have been developed for all patients with ARF (21,22), or ICU patients with acute renal failure (20,23-25). For example, Liaño in Madrid has developed an accurate index that has been validated retrospectively, prospectively, and in several different patient populations (19,22,26). This is important because previous indices worked quite well in the hospital in which they were developed but failed when

Indices of Risk of Mortality in ARF



Source: Douma, *JASN* 8:111, 1997.

Liano ARF Mortality "Severity Index"

Add		Subtract	
Constant	21	Pure Nephrotoxic	11
Age	3*decades	Alert	15
Female	9		
Oliguria	11		
Hypotension	12		
Jaundice	12	**Total = Expected**	
Coma	15	**% mortality**	
Asst. Ventilation	18		

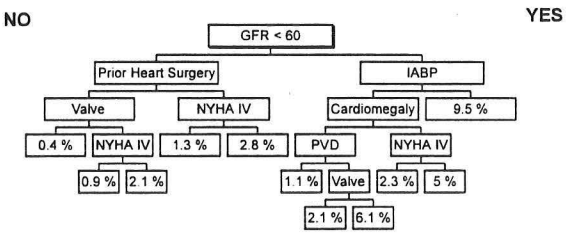
Source: Liano, *Nephron* 63:21, 1993.

transported to other settings (20). Renal dysfunction accounts for 21% of the index; the remainder is accounted for by comorbid illnesses (19). This index is quite interesting because it points to 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. Adjusting for the severity of illness, it is likely that outcome has improved (15,17,18).

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. After cardiac surgery, ARF requiring dialysis develops in 1-5% of patients and is strongly associated with perioperative mortality and morbidity. Can this event be predicted? Chertow and colleagues recently collected prospective data from 43,600 patients from 43 VA hospitals during 1987-1995 (9). 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 risk groups. This 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.

Preoperative Risk Stratification for ARF Requiring Dialysis after Cardiac Surgery



Source: Chertow, *Circ* 95:878, 1997.

PATHOPHYSIOLOGY

"Everything should be as simple as possible, not simpler." -Einstein

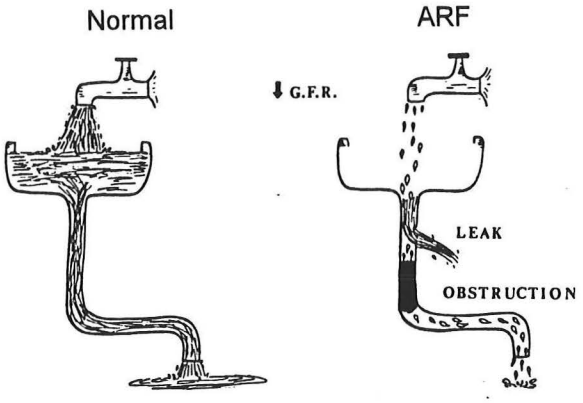
The pathophysiology of acute renal failure is quite complex and not well understood. The pathophysiology is generally viewed from several different viewpoints, or paradigms [reviewed in (2,27)]. These paradigms are best judged, as we will see later, by their ability to lead to the development of clinically effective drugs.

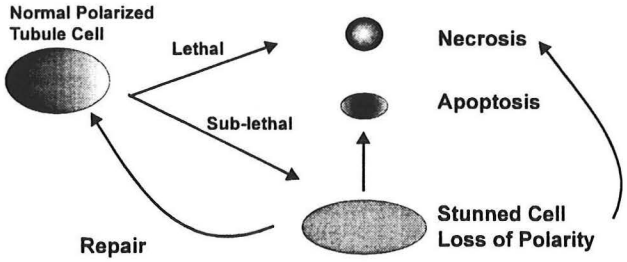
Hemodynamic Paradigm

The hemodynamic paradigm, developed in the 1970s and 1980s, views the nephron as a tube with blood coming in one end, being filtered, and then the glomerular filtrate being processed by the nephron (28). As such, acute renal failure, i.e. failure to produce good urine, could be produced either by an impairment of the filtration process, obstruction of the tubules, or backleak of urine into the interstitium. In the original formulation, plugging of the filter was broken down into several categories including afferent arteriole vasoconstriction and decreased glomerular surface area or

permeability (KF). This paradigm led to the testing of vasodilators (ANP, dopamine), diuretics (furosemide, mannitol), and anti-integrin drugs to prevent acute renal failure (29-31).

Hemodynamic Paradigm | **Cell Fate Paradigm**



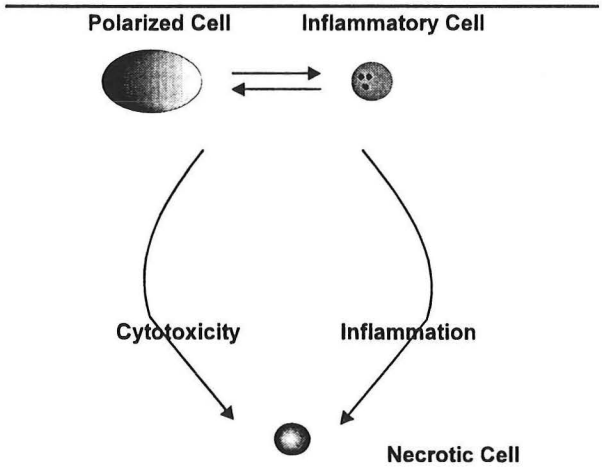


Cell Fate Paradigm

The cell fate paradigm, developed in the late 1980s and early 1990s, focuses on the fate of an individual polarized tubular cell after it is injured (27). After injury the cell becomes stunned and loses its polarity. This stunned cell can either undergo necrosis (death from the outside in) or apoptosis (death from the inside out), or the cell can initiate a repair program which would return the cell to its normal polarized state. One major assumption of this paradigm is that repair follows developmental pathways. Hence, researchers have focused on the use of growth and differentiation factors elaborated by the developing nephron (i.e. IGF-1, HGF, EGF, etc.).

Interactive Cell Biology

Interactive Cell Biology Paradigm



In the early 1990s, it became apparent that these paradigms ignored the anatomical complexities of the kidney. As reviewed by Dr. Biff Palmer, tubule cells act as immune cells and actively participate in 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 TNF α, IL-1, IL-8, and MCP-1 (32). The kidney also synthesizes cytotoxic agents that injure tubular cells, including superoxide and, more recently discovered, nitric oxide (33-35). There is good evidence for inflammation both in animal studies as well as human data. The animal studies show quite convincingly 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. Support for this comes from the ability of anti-neutrophil agents, such as neutrophil depletion and anti-ICAM-1 antibodies, to decrease injury following

ischemia reperfusion (32,36,37). This paradigm is supported by human data, which shows that dialysis membranes, which activate neutrophils, prolong the course of acute renal failure (38). Animal studies have shown that activated neutrophils deposit in the kidney, where they increase renal damage (39).

Active Defense Paradigm

A fourth paradigm, developed within the last 5 years, considers the ability of the tubular cells to mount an active defense against injury. It is quite clear that many cells throughout the body protect themselves from injury by elaboration of heat shock proteins, sphingolipids, and new classes of novel mediators, such as anti-inflammatory cytokines like α-MSH (35,40-42). While little has been done in this area, I view it as a quite fruitful area and deserving of further research.

TREATMENT OF ACUTE RENAL FAILURE

"The difficult can be done immediately, the impossible takes a little longer." - Santayana

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 (2,3,43,44). These consequences include volume overload, solute overload (hyperkalemia acidosis, uremia, cytokines), endocrine deficiencies (erythropoietin), and the non-renal complications, including sepsis, GI bleeding, delirium, and respiratory failure. 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 once the injury has occurred [for example, see (29,30,35,45-47)].

Prevention of ARF

Acute renal failure can be prevented currently in three situations: (1) aminoglycosides; (2) radiocontrast; (3) pigment nephropathy.

Once-a-day gentamycin dosing reduces the incidence of acute renal failure (3,48). This topic was reviewed by Dr. James Luby in his May 18, 1997, Grand Rounds on Advances in Antimicrobial Therapy and will not be further discussed here. Radiocontrast-induced ARF is a common cause of hospital acquired ARF. Risk factors include renal insufficiency, diabetes mellitus with renal insufficiency, multiple myeloma, and large volume of contrast media (49). The use of low osmolar nonionic contrast media should be reserved for patients at high risk of contrast-induced ARF, i.e., patients with chronic renal insufficiency, especially if also diabetic (50). Recent studies by Solomon et al. have shown that radiocontrast-induced acute renal failure can be largely prevented by volume repletion (51). In the past, nephrologists have used combinations of volume, diuretics, mannitol, and bicarbonate. However, their studies show quite convincingly that diuretics and mannitol are detrimental, whereas volume repletion alone is quite beneficial.

Pigment nephropathy, caused by myoglobinuria or hemoglobinuria, can be minimized if one maintains a very high urine flow rate with volume and mannitol and the urine is alkalined with sodium bicarbonate. The key point is that these agents must be started before renal injury (2). This

necessitates that mannitol be given at the site of injury before the patient is transported to the hospital. Systemic alkalosis should be avoided.

Non-dialytic Treatment

The current treatment for ARF is to empirically and discriminately apply agents to patients without regard to underlying etiology, with hope that these agents will influence the course of acute renal failure. As we will see, more often than not this hope remains unfulfilled.

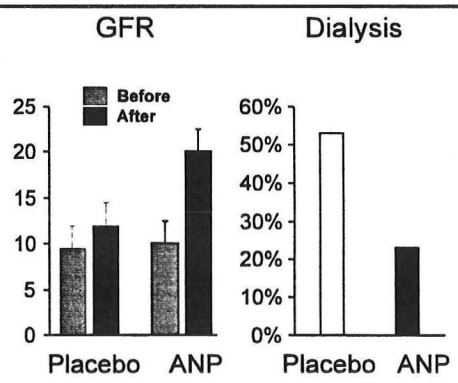
Furosemide and Loop Diuretics (Hemodynamic Paradigm)

Furosemide is a loop diuretic, but also is a vasodilator, decreases the metabolic work of the thick ascending limb, and flushes out obstructing casts from the nephron. In addition, furosemide may decrease the concentration of toxins such as myoglobin or hemoglobin in the tubules. Based on the plumbing 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 absolutely no solid evidence that furosemide alters the natural history of human acute renal failure (44,52,53). The single randomized controlled trial did not show any change in azotemia or mortality (54). Indeed, furosemide may worsen contrast-induced acute renal failure (51). 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 that patient had less severe ARF. Large doses of furosemide are ototoxic and the large infusion volume can cause pulmonary edema (55). Thus, it is reasonable to give a single trial of furosemide in escalating doses. If the patient responds, furosemide can be continued several times a day to keep the patient euvolemic. If the patient does not respond to furosemide, the agent should not be readministered.

Renal Low Dose Dopamine (Hemodynamic Paradigm)

Dopamine is a selective renal vasodilator which 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 microgram/kg/min and not 3 to 5 micrograms/kg/min as routinely used (56). The use of dopamine was examined in the placebo group of a recent randomized control trial of atrial natriuretic peptide. There was no benefit on survival or delaying dialysis by the use of dopamine (57). A recent review in *Kidney International* concludes that "the routine use of dopamine should be discouraged until it is shown to be effective" (56).

Open Label Trial of ANP



Source: Rahman, *Kid Int* 40:21-28, 1991.

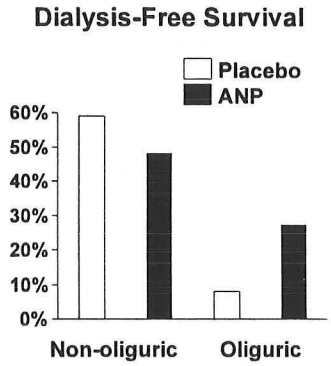
Atrial Natriuretic Peptide (Hemodynamic Paradigm)

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 2 days after the ischemic or nephrotoxic insult (29,30). Because of

these dramatic effects in animal studies, an open label trial of ANP was performed at the University of Colorado (58). Fifty-three patients were selected based on a rise in creatinine of 0.7 mg% per day for 3 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 (12). 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 retrospective, but planned, subgroup analysis demonstrated that there was a difference in the response to ANP between oliguric and non-oliguric patients. Although the serum creatinines at baseline were similar, there was a large difference in the creatinine clearance; non-oliguric patients had a creatinine clearance of 13, oliguric patients about 4 ml/min. ANP increased output in the oliguric patients, but also lowered blood pressure more in oliguric patients. ANP improved the dialysis-free survival in the oliguric patients. Presumably, 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.

ANP Trial: Subgroup Analysis



Source: Allgren, *NEJM* 336:828-834, 1997.

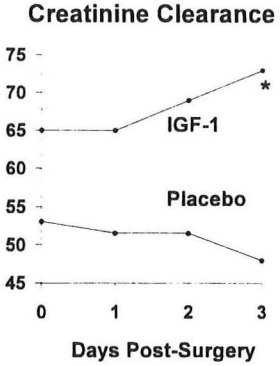
A follow-up randomized controlled clinical trial of ANP in oliguric patients with acute renal failure was initiated, with plans to randomize 250 patients. The study was cancelled after 200 patients, because no matter what happened to the final 50 patients, the study would not show any therapeutic benefit.

Insulin-like Growth Factor-1 (Cell Fate Paradigm)

Insulin-like growth factor-1, or IGF-1, is made in high concentrations by a 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. In animal models of renal injury, IGF-1 enhanced repair following renal ischemia even when started 24 hours after injury (47,59). 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 (60). 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 about 8 ml/min increase in creatinine clearance, whereas the placebo group had a slight fall in creatinine clearance. 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. Because this trial was viewed as positive, IGF-1 was then tested

in a multicenter, randomized, double-blind, placebo-controlled trial (61). The study enrolled 72 ICU patients with acute renal failure caused by surgery, trauma, hypertension, sepsis, or drugs of less than 6 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 is 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.

IGF-1 After Vascular Surgery



Source: Miller, *Am J Physiol* 41:F257-F259, 1997.

Problems with Drug Trials

Why did all these drug trials fail? Were the drugs ineffective, or were there problems in the design of the clinical trails?

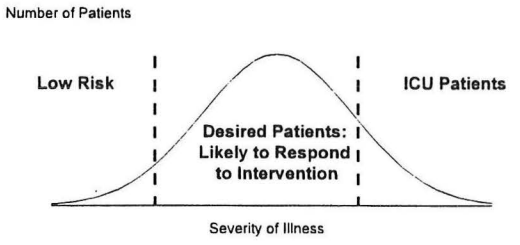
1) The diagnosis of ARF was based upon changes in plasma creatinine. Creatinine is a poor marker of renal function in ARF as discussed above. Large changes in GFR may cause nearly imperceptible changes in creatinine. Plasma creatinine is also influenced by nutritional changes, muscle breakdown, and volume expansion that are unrelated to changes in renal function. Thus, reliance on creatinine delays the diagnosis of ARF, which worsens the clinical outcome.

2) The animal data suggest that the interventions must be started early in the course of ARF. In the treatment trials of ANP and IGF-1, the intervention may have been started too late. In the ANP trial, the average creatinine at the time of randomization was 4.5 mg%. If creatinine rises at 0.5-1 mg%/day, this would indicate a delay of 3-7 days from the time of injury. The IGF-1 trial enrolled patients within 6 days of injury.

3) 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 (51,56).

4) The trials enrolled patients who did not need treatment or were untreatable. For example, the IGF-1 prevention trial enrolled patients with GFR of about 50% of normal, and none of the patients needed dialysis. These patients had very mild ARF, which would make it difficult to detect a small protective effect of the intervention. In contrast, the IGF-1 treatment trial was performed on patients in the ICU with ARF, a population which has a very high mortality in large part, because of underlying comorbid diseases. Even the ANP trial include patients with severe ARF; the average creatinine was 4.5 at the time of randomization, and the oliguric group had a creatinine clearance of 4 ml/min while the non-oliguric group had creatinine clearance of 11. Since

Who to Enroll in Clinical Trials?



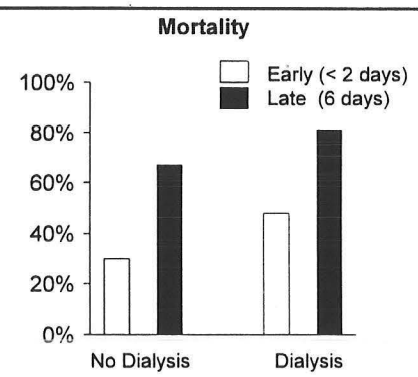
creatinine overestimates GFR by about 25-50% in this population, this was severe renal injury.

How can these problems be solved? One approach is to diagnose ARF early using a rapid GFR test (see below) that directly measures the extent of renal injury. A second approach is to use an ARF severity of illness index to estimate the severity of comorbidity. Patients with moderate renal damage, and mild to moderate comorbidity.

NEPHROLOGIC CONSULTATION

Several interventions have 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 (62). Nephrology consultation was delayed in 28% of ICU patients with ARF in the ICU (62). 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 (62). 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 which diluted the plasma creatinine, or severe malnutrition which decreased creatinine generation. While delay in consultation may have occurred in sicker patients and thus be a proxy for severity of illness, this study demonstrates that interventions early in the course of ARF may influence outcome.

Nephrologic Consultation



Source: Mehta, *JASN* 7:471, 1996.

NUTRITIONAL SUPPORT

Nitrogen balance is extremely negative in patients with ARF, and protein catabolic rate (PCR) is very high. The factors for this negative balance are reviewed by Kopple (63). 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 (43,44,63)]. However, these studies were performed before the recent advances in

Nutritional Recommendations

- Energy: 30-45 kcal/kg/day with 30% from fat.
- High Biological Value Protein

	g/kg/day
° Nondialyzed:	0.6-1.0
° IHD	1.1-1.5
° CRRT	1.5-2.5

Source: Kopple, *J Parent Ent Nut* 20:3-12, 1996.

parenteral nutrition and dialysis techniques (43,44,63). Most nephrologists recommend that nutritional supplementation should not be withheld to minimize azotemia.

DIALYSIS

Hemodialysis with Biocompatible Membranes

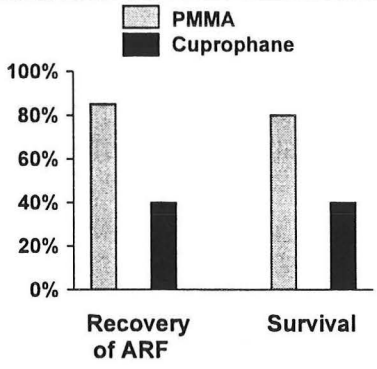
Indications to Start Dialysis

- Volume overload
- Solute overload
  - Hyperkalemia
  - Acidosis
  - Uremia

Dialysis is required for treatment of volume and solute overload (hyperkalemia, severe acidosis, and uremia). Dialysis is required in about 85% of patients with non-oliguric ARF, and 30% of patients with non-oliguric ARF. Retrospective studies have shown that dialysis is better than no dialysis (54,64), 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, it was recently discovered that dialysis itself may delay the recovery of renal function with ARF. This can be caused by two factors: hypotension, and 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. Animals 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 (65,66). Thus, the setting of ARF, the impaired autoregulatory response to a decrease in systemic blood pressure results in fresh renal ischemia.

Effect of Hemodialysis Membrane



Source: Hakim, *NEJM* 331:1338, 1994.

Dialysis with a bio-incompatible membrane can also active complement cascades, which then active circulating neutrophils. The result is neutropenia, as the activated neutrophils are removed from the circulation by the lungs. This effect is easily seen in humans. Animal studies have shown that activated neutrophils are also deposited in the kidneys, were they either infiltrate into the organs, or block small blood vessels. The net result is fresh renal injury.

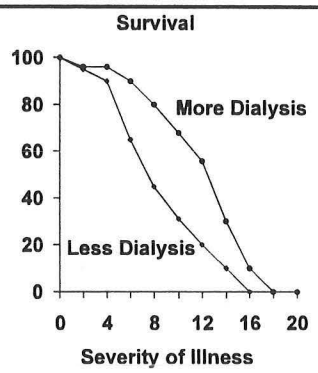
Recent studies by Schiffl (67) and Hakim (68) have documented that dialysis with bio-compatible membranes shortens the course of non-oliguric ARF and increases survival. Dialysis with bio-compatible membranes resulted in less complement generation, better survival from sepsis, and fewer dialysis sessions (67-69). The results in the Hakim trial were more striking in the non-oliguric patients than the oliguric patients. Non-oliguric patients have higher renal blood flow and GFR (12) which may render the

kidney more susceptible to ischemic injury. A similar selective effect of hypotension was also seen in the ANP trial (12).

Does More Dialysis Enhance Survival?

Retrospective trials have shown that dialysis to keep BUN below 150 mg% improves survival, when compared to no dialysis (54,64). 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 (70). Unfortunately, because of the small size of the trial (8-10 patients per group), the difference was not statistically significant. In a prospective trial by Gillum which included a better randomized design (71), the more intensive dialysis (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%.

More Dialysis Enhances Survival



Source: Paganini, *AJKD* 28:S81, 1996.

These studies did not stratify or randomize patients according to comorbid conditions, physiologic state, or previous renal injuries. Paganini has a recently established a link between dialysis therapy and outcome in ICU patients with ARF; this link was only present when the underlying comorbidity was taken into account (10). This severity of illness score incorporates male gender, intubation/mechanical ventilation, 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 Lianos 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 (less than 4) severity of illness scores and nearly 100% at high (greater than 15) scores. 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. In summary, moderate ARF is treatable. However, more research is needed on severity of illness scores, formulas to calculate the amount of dialysis delivered to ARF patients, and amount of dialysis to deliver (3).

Mode of Renal Replacement Therapy

Modes of Dialysis

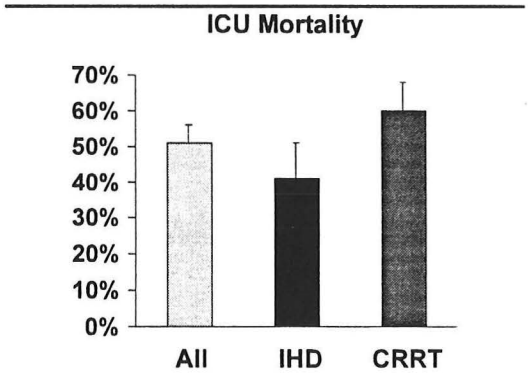
Mode	Intermittent	Continuous
Schedule	3 times a week	24 hrs a day
Risk of hypotension	Yes	No
Volume removal	Fast	Slower
Solute removal	40 L/treatment	350 L/wk
Remove inflammatory mediators	No	Yes
Drug Pharmacokinetics	Complicated	Simple

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 weight, 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 (72-75)]. 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 can not tolerate the hemodynamic effects of intermittent hemodialysis. The solute clearance of CRRT may be larger than IHD with 4 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 is hoped would lead to improved patients survival or recovery from renal failure.

IHD and CRRT have been compared in many non-randomized or retrospective studies [reviewed in (43,44,75)]. My meta-analysis of 25 published papers on CRRT and IHD shows that patients treated with CRRT had a similar survival rate (32%) to those treated with IHD (38%). Prospective randomized trials are difficult to perform because the hemodynamically unstable patients can not 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 (76). Mehta recently completed a multi-center prospective randomized trial of CRRT vs IHD in IHD patients with ARF (74). 166 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%), leading to the conclusion that the two modes of dialysis therapy are similar. Patients who crossed over from IHD to CRRT had a higher mortality than those who crossed over from CRRT to IHD. Despite the higher mortality in the CRRT group, patients initially treated with CRRT had higher rates of recovery of renal function. 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 still led to the same conclusion. Mehta has not reported his results using either the Lianos or Paganini Severity of Illness scales, which are more appropriate for renal patients. At the present time, it appears that intermittent hemodialysis and chronic renal replacement therapy are roughly equivalent methods for treatment of ARF.

CRRT vs IHD in ARF



Source: Mehta, *JASN* 7:1457, 1996.

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. Recent improvements in dialysis using a biocompatible membrane have increased survival and promoted renal recovery. However, dialysis only manages the electrolyte and fluid disturbances initiated by acute renal failure, whereas pharmaceutical agents could either prevent ARF from occurring or treat ARF by promoting recovery. My analysis today has pointed to several factors that have plagued all of the drug trials to date: ARF must be

recognized early and treated early. Unfortunately, reliance on rising creatinine and falling urine output delays recognition of renal injury, and does not provide an accurate assessment of the degree of renal damage. Therefore, my wish list for the 21th century includes the development of methods for rapidly measuring renal function, so that the administration of effective drugs is not delayed. One possibility is to use cimetidine to block the tubular secretion of creatinine, which allows creatinine clearance to more accurately measure GFR (77). A second wish is for development of scores that include specific risk factors that lead to ARF, measure the severity of renal and non-renal diseases, predict the need for dialysis, and perhaps identify patients who do not have a promising outcome. These indices could be used in clinical trials so that only patients with moderate ARF are included, and to ensure balanced randomization in a disease that is notorious for its heterogenous clinical course. A third factor on my wish list is the development of effective drugs that can 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. Agents to watch are new natriuretic peptides [urodilation (78)], anti-inflammatory agents [anti-ICAM-1 antibodies (36,37)], α-MSH (35), PAF antagonists (46), and anti-integrin RGD peptides to prevent tubular cell obstruction (79). Randomized trials are needed to determine the role of nutritional therapy, the mode of dialysis therapy, when to initiate dialysis, and how much dialysis to provide. My final wish is to be able to replace the reabsorptive, homeostatic, metabolic, and endocrinologic functions of the renal tubule. A bioarticificial kidney that uses progenitor epithelial cells is currently being tested in animal studies (80,81). We wish to actively prevent or treat acute renal failure. No more sitting on our hands.

CURRENT RECOMMENDATIONS

- Recognize early that renal function may deteriorate:
  - Risk assessment tool
  - High comorbidity
  - Increase in creatinine or fall in urine output.
- Measure GFR
- Treat Pre-renal ARF: NS challenge
- Treat Post-renal ARF: ultrasound, urinary drainage
- Nephrologic consultation
- Evaluate etiology
- Prevent further damage:
  - Monitor and optimize hemodynamics
  - Avoid hypotension, nephrotoxic drugs
- Drug therapy:
  - Try diuretics once; do not use 'renal' dopamine
- Nutritional support
- Start dialysis when indicated

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