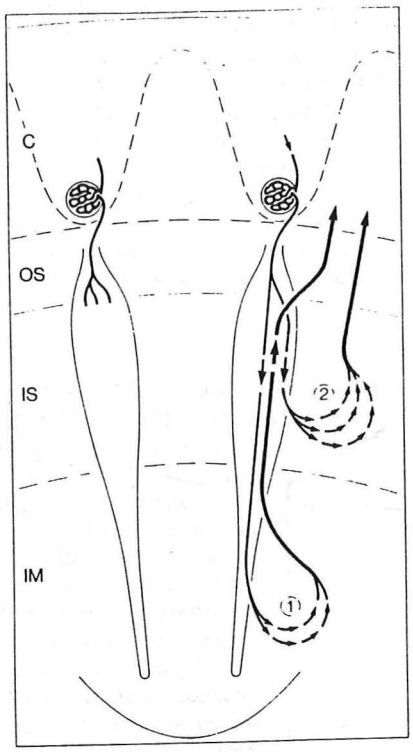
ISCHEMIC ACUTE RENAL FAILURE



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INTRODUCTION

Acute renal failure is commonly encountered in the hospital setting and its development in a patient has serious implications. Approximately 5% of patients admitted to the hospital will develop acute renal failure during their hospital stay (1). The development of acute renal failure is associated with a sixfold increase in risk of dying and increases the hospital stay by an average of 16-23 days (2). Despite major advances in the management of patients with acute renal failure, severe underlying illnesses and complications currently limit survival to 50%, a figure not substantially improved since 1950 (3-7). Thus, in order to manage or prevent this serious and costly disorder, it is important for the physician-scientist to understand the pathophysiologic principles involved in the development of acute renal failure.

Ischemic acute renal failure can be loosely defined as a syndrome triggered by underperfusion of the kidneys which results in the rapid detioration of renal function and accumulation of nitrogenous wastes. Renal underperfusion plays an important pathophysiologic role in the development of all non-nephrotoxic-mediated acute renal failure.

PATHOPHYSIOLOGY

Normally, renal blood flow to the kidney is high and the oxygen supply exceeds by far the requirement for oxygen utilization (8). However, when the kidney is underperfused, it appears to have a particular susceptibility to injury. Clinically, as shown in Figure 1, renal underperfusion is manifest by a syndrome which displays a decrease in glomerular filtration rate (GFR). This may occur in the absence of remarkable hypotension, which is documented in less than 50% of the cases of postsurgical hypotension (3). When the underperfusion is corrected, the GFR either returns to normal (this portion of the syndrome we call prerenal azotemia) or it remains markedly depressed for a prolonged period of time and we call this portion of the syndrome, ischemic acute renal failure, i.e., acute tubular necrosis. Thus, underperfusion of the kidney is manifest by a continuum of disorders ranging clinically from prerenal azotemia to acute tubular necrosis (acute renal failure).

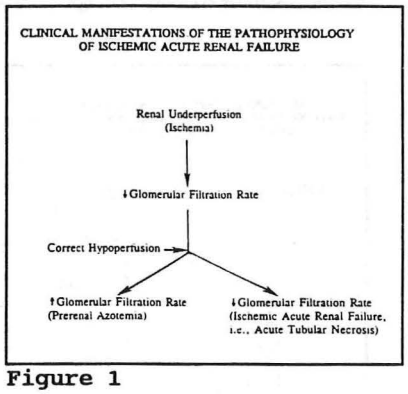


Figure 1

Alterations in Renal Blood Flow

In human studies, renal blood flow, measured by a variety of techniques, has been shown to be decreased for a prolonged period of time after the initial precipitating event (during the so-called maintainence phase, 9-18, see Table 1).

TABLE 1
RENAL BLOOD FLOW IS REDUCED IN ESTABLISHED HUMAN ACUTE RENAL FAILURE

Method of RBF Measurement	Time After Onset of ARF	Results
Inert gas washout	Established ARF	↓RBF (67%)
PAH clearance	4-12 days	↓RBF (45%)
Inert gas washout, angiography	2-28 days	↓RBF (67%)
Inert Gas washout	Established ARF	↓RBF
Inert gas washout, angiography	2-24 days	↓RBF (67%)
Inert gas washout, isotope accumulation	Established ARF	↓RBF (75%)
Dye dilution	Established ARF	↓RBF (50%)
Inert gas washout, angiography	2-9 days	↓RBF (75%)
PAH clearance	1-2 days	↓RBF (50%)

Adapted from Brenner and Lazarus: Acute Renal Failure, 1983.

However, when renal vasoconstriction, mediated by either circulating catecholamines or renal nerve activity is blocked by the α-adrenergic blocking agents, phenoxybenzamine or phentolamine, renal blood flow is unchanged (10,19). The lack of effect of these agents implies that vasoconstriction is not mediated by mechanisms involving either circulating catecholamines or renal nerve activity. Even when renal blood flow is increased by vasodilators, GFR remains markedly depressed (10,12). In addition in most experimental animal studies, GFR is disproportionately reduced in relation to renal blood flow (22), and renal blood flow returns to normal at a time when GFR remains markedly depressed (20,21). Thus, reduced renal blood flow seems an unlikely cause for the sustained reduction in GFR. In fact, superficial cortical blood flow rapidly returns to normal following an ischemic event. However, regional changes in perfusion may be of greater importance than changes in total renal blood flow.

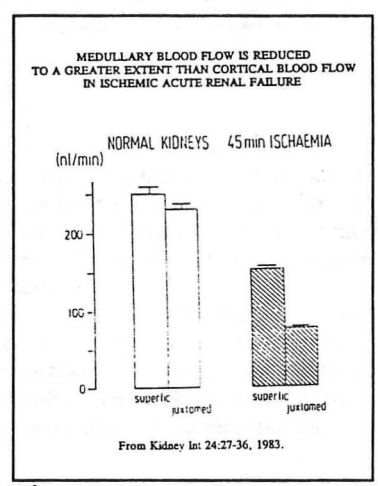


Figure 2

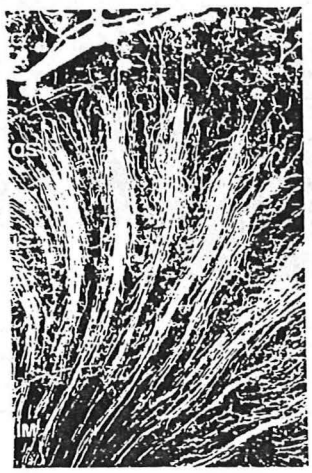
Medullary Blood Flow. Medullary blood flow is decreased to a greater extent than cortical blood flow and remains reduced for a more prolonged period of time. As shown in Figure 2, renal plasma flow is decreased 67% in the juxtamedullary nephrons at a time when it is reduced only 35% in the superficial

nephrons (23).

This disparate reduction in juxtamedullary plasma flow has been shown to be secondary to aggregated erthrocytes in the medullary inner stripe capillaries (24,25). Cell swelling in the corticomedullary proximal straight tubules (26,27) or polymorphonuclear leukocyte-mediated post-ischemic capillary leakage of fluid (28) have been proposed as possible mechanisms for this erythrocyte aggregation. In these studies, a direct relationship between medullary congestion and decreased renal function was found.

The renal medulla is supplied by blood from the efferent arterioles of the juxtamedullary nephrons (26). These vessels turn downward toward the medulla forming the descending vasa recta. At the junction between the inner and outer stripe, the descending vasa recta coalesce to form the vascular bundle as shown in Figure 3.

ARTERIAL BLOOD SUPPLY OF THE RENAL MEDULLA



Mouse kidney: silicone rubber (Microfil) filling of arterial vessels. Longitudinal section through the deep cortex (C), outer stripe (OS), inner stripe (IS) and inner medulla (IM). Bundles of descending vasa recta arise from efferent arterioles of juxtamedullary glomeruli; descending vasa recta give off most of their branches within the inner stripe. Capillary plexuses are incompletely filled. (Magnification X ~ 39. Produced in collaboration with Dr. L. Bankir.)

Figure 3

The sparse, elongated mesh of capillaries in the outer stripe of the outer medulla is supplied by branches off the efferent arterioles and relatively few branches off the descending vasa recta (see Figure 4). The inner stripe of the outer medulla is supplied only from branches of the descending vasa recta to form a dense capillary plexus providing blood to the tubules of the interbundle region, an area predominated by the thick ascending Limbs of Henle. Blood to the inner medulla is supplied by the descending vasa recta which have traversed the outer medulla in the vascular bundles. Thus, this anatomic arrangement allows blood to be delivered to the inner medulla that has not been previously exposed to tubules.

The capillaries from the inner stripe form the ascending vasa recta which do not rejoin the vascular bundle and instead drain towards the outer stripe inbetween the vascular bundles. In contrast, in the inner medulla the capillaries form ascending vasa recta that return to the vascular bundle before ascending through the outer medulla. Thus, blood returning from the inner medulla is in a countercurrent relationship with blood that is supplying the inner stripe region (see Figure 5,[30]).

This countercurrent relationship of the vasa recta prevents the dissipation of the cortico-medullary gradient of osmolality, however, it occurs at the cost of countercurrent diffusion of oxygen between the arterial and venous limbs of the vasa recta. Under hypoxic conditions, it has been shown that blood flow in pathway 2 of the diagram may be severely impaired, whereas

blood flow in pathway 1 remains relatively intact (31,32). A characteristic pattern of cell injury occurs in the isolated perfused kidney, a model useful for examining renal ischemia (33). The medullary thick ascending Limb of Henle in the outer and inner stripe of the outer medulla suffers severe ischemic damage (see Figure 6). In addition, the S_3 segment of the proximal tubule in the outer stripe suffers ischemic damage as well. The injury is most pronounced in those tubules supplied by pathway 2, that are located away from the vascular bundle (31-33). The capillary-like ascending vasa recta of pathway 2 are extremely susceptible to compression by ischemic tubular swelling (24,34).

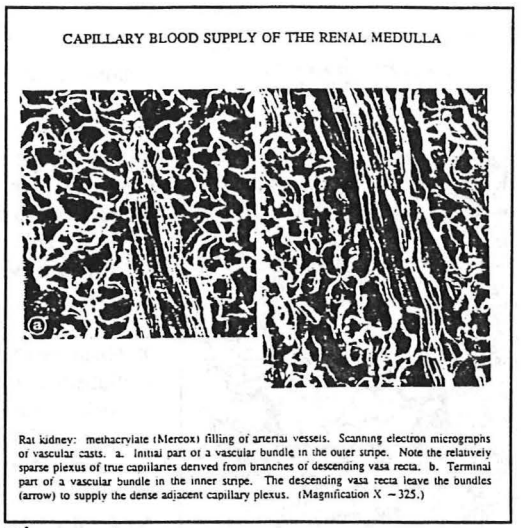


Figure 4

Under normal conditions, the partial pressure of oxygen has been found to be around 10 mm Hg in the medullary region (see Figure 7,[35,36]). The low oxygen pressures are secondary to the countercurrent diffusion of oxygen between the limbs of the vasa recta. Because of its reliance on both aerobic and anaerobic glycolysis, the medulla appears to function adequately (37), however, it operates on the verge of anoxia.

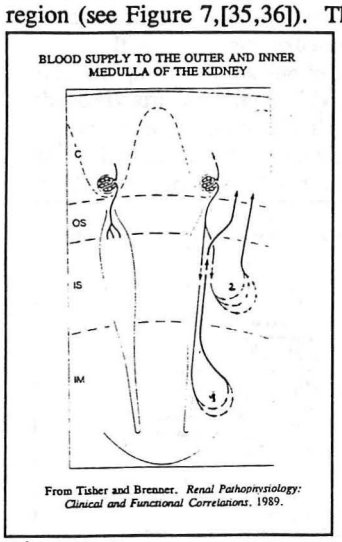


Figure 5

Optical spectroscopic measurements of the redox state of cytochrome a,a_3, the terminal electron carrier of the mitochondrial chain, which transports electrons directly to oxygen has been estimated to be at least 20% reduced even under normal conditions in the renal medulla (38), and is even further reduced (30-40%) when the kidney is excised and perfused in vitro (39). Inhibitors of transport in the thick ascending Limb of Henle (furosemide and bumetanide) produce a significant increase in the oxidized state of cytochrome a,a_3, suggesting that the medullary thick ascending Limb of Henle is an important site for this reduced cytochrome oxidase (39). Thus, the medullary thick ascending Limb of Henle with its high rate of metabolism (oxygen consumption) and low oxygen supply (imposed by the anatomic arrangement of the medullary vascular system) makes it extremely vulnerable to ischemic damage (32,35). In addition, the S_3 segment of the proximal tubule, which is also located in this area of the kidney and relies to a large extent on aerobic glycolysis (37), is also susceptible to ischemic

damage (see Figure 8,[41]).

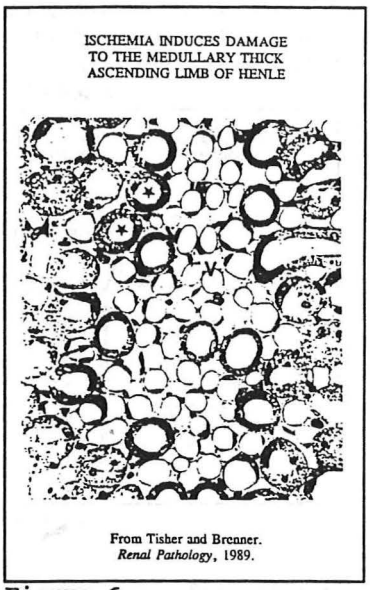


Figure 6

Tubular Injury. The term "acute tubular necrosis" is somewhat of a misnomer. Early biopsy series of acute renal failure described widespread tubular necrosis in specimens (42). In addition, ischemic models of acute renal failure have described a fairly extensive tubular necrosis (43-46). However, much of the necrosis described from early autopsy series was a direct result of autolysis (47). In deed, only patchy necrosis of individual cells on both biopsy and autopsy specimens is now found (48-51).

Only recently, has any attempt been made to quantify the difference between cortical and medullary lesions in human ischemic acute renal failure (49-51). Individual desquamated cells (presumably loci for previous necrotic cells) were found to be five-fold increased in the medullary thick ascending Limb of Henle over proximal tubular sites (51). Thus, the term "acute tubular necrosis" is misleading as only areas of focal necrosis of individual cells are found and these are predominantly localized in the distal nephron (mTALH).

If there is not extensive tubular necrosis, then why the profound decline in renal function? Although the cells are not irreversibly injured, they do exhibit striking changes in their morphology, especially in proximal tubule segments ($S_3 > S_1,S_2$). Several investigators have found that following an ischemic episode, there is a significant reduction in the proximal tubule brush-border membrane as shown in Figure 9 (48,50-52).

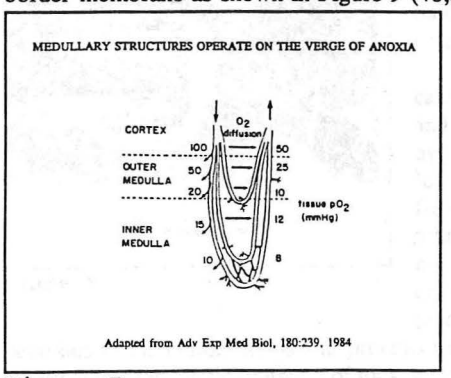


Figure 7

In addition, there is extensive changes in proximal, medullary thick ascending Limb of Henle, and distal tubular basolateral infoldings (50,51). These studies suggest that major changes in both the apical (urinary surface) and basolateral (blood surface) membranes occur in ischemic acute renal failure and that extensive tubular necrosis is not required for the development of acute renal failure.

Nature of the Cellular Dysfunction. Central to the issue of cellular dysfunction is the depletion of cellular ATP. It is well known that renal ischemia results in a rapid depletion of cellular ATP (53-55). ATP breakdown products are more permeant across the cell membrane and diffuse out of the cell. Upon correction of the

ischemia, a biphasic mode of correction has been noted, characterized by an intial rapid recovery of ATP, followed by a slower, more gradual return toward the preischemic level (53-55). The magnitude of the initial rapid rate of recovery of ATP is a good index of the residual adenine nucleotide pool in the kidney following ischemia. In addition, renal ATP content 2 hours after the ischemic insult is a good indicator of the GFR recovery at 24 hours (54).

Loss of cellular ATP leads to several events within the cell (see Figure 10) that ultimately results in cellular dysfunction. Some of these cell abnormalities only become apparent after the kidney has regained its perfusion pressure. This subject has been recently reviewed in greater detail (56). These processes are summarized in the following diagram.

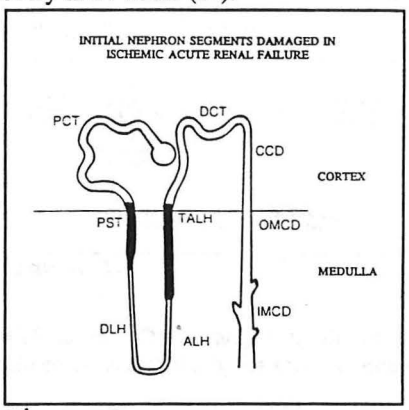


Figure 8

Depletion of cellular ATP leads to the disruption of microfilaments and loss of tight junction functional integrity. This results in a loss of surface membrane polarity. Loss of surface membrane polarity coupled with the activation of phospholipases, results in alterations of the surface membranes which are clinically manifest by a reduction in proximal tubule transepithelial transport. Ischemia also results in an increased production of nucleotide breakdown products. Some of these nucleotide breakdown products diffuse out of the cell, while some are further broken down into hypoxanthine leading to the cellular accumulation of hypoxanthine. Ischemia also leads to the conversion of xanthine dehydrogenase to xanthine oxidase which becomes important when oxygen levels are increased during reperfusion.

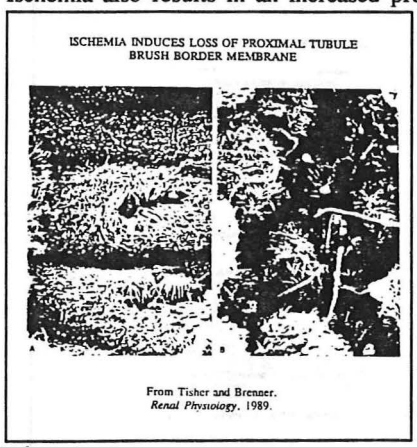


Figure 9

Following reperfusion, cellular energy stores cannot be regenerated owing to nucleotide depletion and mitochondrial dysfunction. Oxygen reacts with hypoxanthine in the presence of xanthine oxidase to form reactive oxygen species (free radicals). These free radicals in combination with increased mitochondrial calcium content leads to further mitochondrial dysfunction. In addition, increased cellular calcium and free radicals may lead to lipid peroxidation causing further membrane alterations. Alterations in membrane lipids and proteins result in cellular dysfunction and the cessation of the normal transepithelial transport of ions, water, and macromolecules between blood and urine.

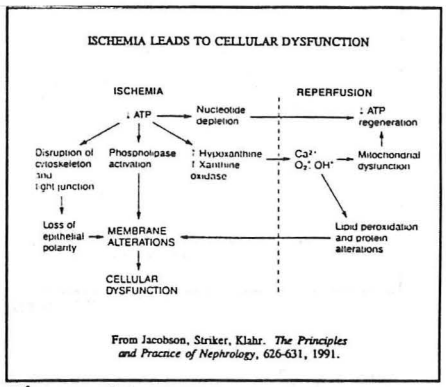


Figure 10

Loss of Cellular Polarity. Depletion of cell ATP has been found to result in a loss of polarity of the proximal tubule cell (57). The proximal tubule is a polar epithelia involved in the vectorial movement of ions, water, and macromolecules between the luminal (urinary) and blood compartments. To accomplish this task, the polar epithelial cell must have certain fundamental characteristics. These include: a) distinct apical and basolateral membrane surface domains (58,59); b) a functional junctional complex in the lateral membrane including tight junctions (maintains the lipid and protein differences of the two surface membranes), intermediate junctions, desmosomes, gap junctions, and cell adhesion proteins (60,61); c) a functional cytoskeleton (62,63) and, d) adequate ATP stores. This arrangement allows each surface membrane (apical and basolateral) to have defined tasks dictated by its specific proteins and lipids.

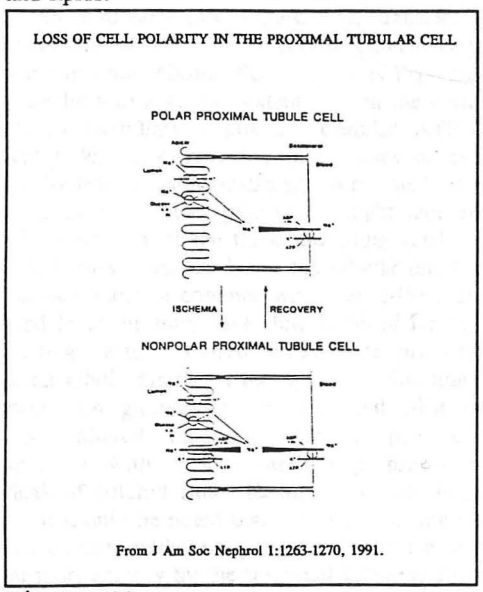


Figure 11

In the normal polar proximal tubule cell (see Figure 11), sodium is transported across the apical membrane into the cell via Na/H antiport in a secondary active manner. Sodium is transported across the basolateral membrane out of the cell via the Na-K-ATPase. Na-K-ATPase is tethered to the basolateral membrane by the actin cytoskeleton (64). Following ischemia, the combination of a "leaky" tight junction complex and a disrupted actin cytoskeleton allows the lateral migration of proteins (such as Na-K-ATPase) and lipids within the bilayer from one membrane domain to the other (65-69). Thus, duration-dependent ischemia in the proximal tubule leads to the disarrangement of surface transport proteins and the inefficient transepithelial transport of ions. This subject has recently been extensively reviewed (57,70).

Tubular Obstruction and Backleak. Portions of the proximal tubule brush border membrane are sloughed into the lumen following ischemia, as well as a few necrotic cells. These may coalesce in the distal portion of the proximal tubule or combine with Tamm-Horsfall

proteins in the distal nephron to form obstructing plugs (41,71-74). Tubular obstruction results in an increase in intraluminal proximal tubule pressure which dissipates the hydraulic pressure driving glomerular filtration (see Figure 12, [71,75,76]). In addition, depressed urine production and creatinine excretion can be partially attributed to the sequestration of tubular fluid within obstructed tubules (71,77). Finally, altered membrane permeability and increased tubular pressure can lead to the backleak of fluid from the tubular lumen to the blood which also decreases glomerular filtration. This has been confirmed in experimental models of ischemic acute renal failure by the inability to fully recover inulin from the final urine which has been injected into the tubular lumen (71,75,78). Using dextran molecules of varying size, Myers and colleagues have calculated that approximately 50% of inulin used for clearance studies is lost by transtubular backleak in human ischemic renal failure (77,79-81). Thus, tubular obstruction and backleak play important roles in the prolonged depression of GFR in ischemic acute renal failure.

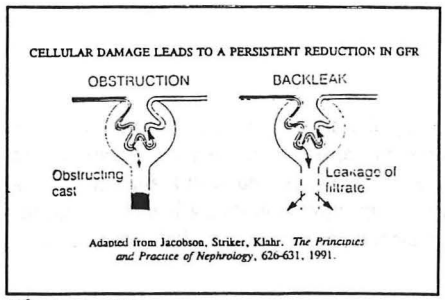


Figure 12

In summary (see Figure 13), transient ischemia results in afferent arteriolar vasoconstriction and a persistent decrease in renal plasma flow, which is depressed in the renal medulla to a greater extent than in the cortex. This results in medullary hypoxia. Cellular ATP becomes markedly depressed resulting in a series of events that eventually leads to cellular damage in the medullary section of the proximal tubule (proximal straight tubule) and the medullary portion of the thick ascending Limb of Henle. Cellular debris is released into the tubular lumen where it may coalesce and/or combine with Tamm-Horsfall proteins secreted from the thick ascending Limb of Henle, to form obstructing casts. Raised intratubular pressure in the proximal tubule dissipates the hydraulic filtration pressure necessary for glomerular filtration, and GFR falls. In addition, altered tubular membrane permeability, in combination with raised intratubular pressures allows backleak of filtered fluid, leading to further decreases in GFR. It should be noted that it is also possible that transient ischemia itself leads to hypoxic cellular damage without any requirement for a prolonged decrease in renal blood flow. Loss of transport activity by the proximal tubule and thick ascending Limb of Henle may flood the macula densa with solute activating tubuloglomerular feedback. Tubuloglomerular feedback-activated renal afferent arteriole vasoconstriction may then lead to the depression of renal blood flow that is sometimes found.

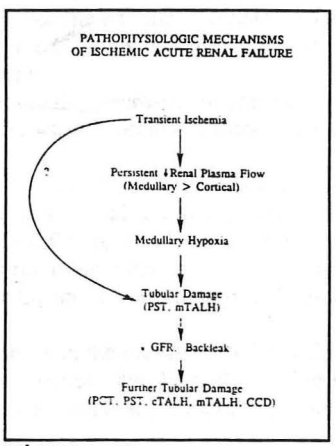


Figure 13

DIAGNOSIS

Approach to the Patient with Renal Disease

There is a long list of possible etiologies for a decline in renal function in patients. Thus, to facilitate a rapid clinical approach to the diagnosis and to expedite intervening measures, it has been convenient to classify these various causes of acute renal failure by their site of origin into prerenal, renal and postrenal etiologies. This distinction is important as rapid intervention in the case of prerenal and postrenal acute renal failure can prevent further renal damage.

Urine volume. It is important at this time to discuss the urine volumes that are seen with acute renal failure. Anuria can be defined as less than 100 ml/day of urine output via a Foley catheter. Oliguria is defined as less than 400 ml/day of urine output via a Foley catheter. Urine output of greater than 500 ml/day is classified as nonoliguria.

The prolonged absence of urine following bladder catheterization is unusual and implies either: a) absence of urine delivery to the bladder as seen with bilateral ureteral obstruction; b) absence of perfusion of the glomeruli as seen with bilateral renal artery or vein occlusion; or c) complete lack of cortical function as seen with bilateral cortical necrosis. Sometimes urine output is less than 100 ml/day in the absence of the above conditions, and is characterized by severe vasoconstrictive states (shock syndromes), or under conditions of extremely disrupted glomerular function (rapidly progressive glomerulonephritis).

Although oliguria is suggestive of oliguric acute tubular necrosis, an intrinsic renal disease process, it is also the hallmark of prerenal azotemia when it occurs in association with avid sodium and water absorption.

Nonoliguria is commonly seen with intrinsic renal disease and is usually associated with nephrotoxic-mediated acute renal failure (1). Nonoliguric acute renal failure can also be seen with incomplete urinary tract obstruction. In fact, acute renal failure secondary to urinary tract obstruction can present as anuria, oliguria, fluctuating oliguria, or nonoliguria (82). The amount of urine produced with urinary tract obstruction depends on the underlying etiology and duration and degree of obstruction.

With ischemic acute renal failure, there is no difference in the prevalence of nonoliguric versus oliguric acute renal failure (4). Although urine volumes have limited usefulness in distinguishing the site of origin of acute renal failure, they can provide some useful information.

Consider urinary tract obstruction. Acute renal failure secondary to obstruction accounts for less than 10% of all cases (1). However, as the potential exists for relief of the obstruction and possible return of renal function, it should always be considered in cases of acute renal failure. Evaluation of obstruction should always begin with a catheterization of the bladder after the patient has voided. This allows one to diagnose lower urinary tract obstruction and to test the post-void residual of urine which may be increased in partial lower urinary tract obstruction.

The sequence of tests used to diagnosis obstruction should begin with ultrasonography (82-84). Ultrasonography in experienced hands has a 98% sensitivity and 74% specificity for

detecting obstruction, when compared to intravenous pyelography and avoids the risk of contrast (82,84). Sonography also allows one to determine kidney size, and the finding of small bilaterally shrunken kidneys is suggestive of a more chronic irreversible process. There is approximately a 15% false positive rate for detecting obstruction with sonography (84,85). In addition, the sonogram may fail to detect obstruction if: a) the patient has been obstructed for less than 1-3 days; or b) encasement of the collecting system with tumor or fibrosis is present (86). CT is also useful for detecting obstruction, especially if inadequate visualization by sonography is achieved due to patient obesity or the presence of congenital collecting system abnormalities (84,85). Thus, ultrasound and CT should be useful for diagnosing obstruction in most patients.

When a high suspicion for obstruction is entertained, and ultrasound or CT detect no obstruction, but they find normal or enlarged kidney size, further urologic work-up may still be needed (84). High-grade obstructive nephropathy may present with minimal or no dilation of the collecting system, especially if an infiltrative process prevents dilation of the renal structures (85-87). This has been documented in as high as 11% of all patients with obstruction (86). Retrograde pyelography and antegrade pyelography can often be used for both diagnosis and treatment. Despite improvements in renal ultrasound, retrograde pyelography remains the gold standard (89).

Distinguishing Prerenal Azotemia from Oliguric Acute Tubular Necrosis.

Prerenal azotemia is probably the most common cause of acute renal failure (3,5,6,90) and is also potentially reversible. However, prolonged prerenal azotemia can lead to the development of ischemic acute tubular necrosis. Thus, recognition and prompt therapy of prerenal azotemia causes of acute renal failure is important. Prerenal azotemia and oliguric acute tubular necrosis both typically present with oliguria and acute renal failure. As the treatment and prognosis differ widely, it is important to distinguish between the two disorders. Evaluation of the effective arterial blood volume status is important in this regard.

Effective Arterial Blood Volume. Effective arterial blood volume refers to that part of the extracellular fluid that is in the vascular space and effectively perfusing the tissues. It is not a measurable entity, but rather refers to the rate of perfusion of the capillary circulation (91). Although effective arterial blood volume varies with the extracellular volume in normal people, it may be independent of the extracellular volume, the plasma volume, or even the cardiac output in a variety of disease states. Thus, effective arterial blood volume may even be decreased in a patient who has increased total body sodium i.e., in congestive heart failure, cirrhosis, and nephrosis. Multiple effectors are stimulated under conditions of a decrease in effective arterial blood volume and include the sympathetic nervous system, angiotensin II release, and an increase in tubular sodium and water absorption. The effective arterial blood volume can be assessed by the physical examination and blood and urine chemistries.

Physical Examination. While performing the physical examination, it is important to look for changes in skin color and temperature which might reflect inadequate tissue perfusion. In addition, a decrease in effective arterial blood volume will be manifest by orthostatic increases in pulse rate and orthostatic decreases in blood pressure (see Table 2).

TABLE 2
ASSESSMENT OF EFFECTIVE ARTERIAL BLOOD VOLUME

1. Physical Examination
   a. Skin color
   b. Temperature of extremities (sympathetic overactivity)
   c. Orthostatic pulse and blood pressure changes

2. BUN/Creatinine ratio
   a. > 20/1 Prerenal azotemia
   b. < 10/1 Intrinsic renal disease

BUN/Cr Ratio. In normal subjects and patients with intrinsic renal disease, the BUN/Cr ratio will be approximately 10:1. However, in conditions associated with hypovolemia, the BUN/Cr ratio is substantially increased as a result of increased proximal tubular absorption. The increase in proximal tubule sodium and water absorption increases the absorption of urea as it is passively linked to the absorption of these two entities. Thus, under conditions of prerenal azotemia, the BUN becomes elevated with little or no elevation in plasma creatinine concentration (as creatinine is not absorbed), resulting in a BUN/Cr ratio greater than 20:1 (92).

Urinary Chemical Indices. Chemical measurement of electrolytes and nitrogenous waste products has been used to help determine effective arterial blood volume and distinguish prerenal azotemia from oliguric acute tubular necrosis (see Table 3). Urinary Na and Cl are both highly specific (<90%) for prerenal azotemia, but the sensitivity in distinguishing between these two disorders is limited by the fairly high overlap of values which occur in the 20-40 mEq/L range (93-97). Generally, urine Cl varies with urine Na, except in cases when Na is excreted with another anion (98). This is most often seen in metabolic alkalosis, where the need to excrete excess HCO_3 may raise urine Na despite volume depletion. In this setting urine [Cl] may be low and is a better index of volume status (99). Thus, urine Cl should always be measured along with urine Na.

The urine osmolality is also highly specific for determining prerenal azotemia, but it also suffers from a relatively low sensitivity for distinguishing between the two disorders (95). Another index with a high specificity for detecting prerenal azotemia but a low sensitivity for distinguishing between the two disorders is the urine to plasma ratio of creatinine (95). Determining the urine to plasma osmolality ratio was found to increase the sensitivity for distinguishing between the two disorders but again overlap of values between the two disorders was quite common (100). Although this group (U_{osm}, U/P creatinine and osmolality ratio) has a fairly low sensitivity in being able to distinguish between prerenal azotemia and oliguric acute tubular necrosis, they provide a subtle indication of relative medullary ischemia.

TABLE 3
URINARY CHEMICAL INDICES

	Prerenal azotemia	Acute Tubular Necrosis
U_{Na} (mEq/L)	< 20	> 40
U_{Cl} (mEq/L)	< 20	> 40
U_{osm} (mosM/kg/H2O)	> 500	< 350
U/P osmolality ratio	> 1.3	< 1.1
U/P creatinine ratio (mg/dL)	> 40	< 20
RFI $\frac{U_{Na}}{U/P_{Cr}}$	< 1	> 1
FE_{Na} $\frac{(U/P)_{Na}}{(U/P)_{Cr}}$	< 1	> 1

The two best tests for distinguishing prerenal azotemia from oliguric acute tubular necrosis are the renal failure index (RFI) which combines the urine Na and the urine to plasma creatinine ratio, and the fractional excretion of Na (FE_{Na}). Handa found a RFI of < 1 in 85% of patients with prerenal azotemia and in no patients with acute renal failure (93). The FE_{Na} is 90% specific and sensitive in distinguishing prerenal azotemia from acute renal failure (95). Of interest in a later study, these same authors found that a urine Cl of < 20 was equal in sensitivity to the FE_{Na} of < 1 in determining patients with prerenal azotemia (101). Despite the usefulness of the FE_{Na} test, one should be aware of some conditions that do not fit the rule. Any early severe vasoconstrictive state such as the hepatorenal syndrome, nonsteroidal antiinflammatory agent-induced acute renal failure, myoglobinuria, radiocontrast dye exposure, acute glomerulonephritis, hypotensive septic shock, interstitial nephritis, nephrotic syndrome, cardiac failure, and early obstructive nephropathy may present with acute renal failure and a FE_{Na} < 1 (1,8,102-106). In addition, approximately 10-15% of patients with nonoliguric acute renal failure have a FE_{Na} of < 1 (95). Conversely, the FE_{Na} may be > 1 in some instances of prerenal azotemia (107).

Of interest, the FE_{Na} can also be used as a predictor of mortality in patients with acute renal failure. In 111 patients with clearly defined categories of acute renal failure, mortality in the presence of a FE_{Na} < 1 was 17.5%, while it was 38% when the FE_{Na} was > 1 (95,101). In addition, nonoliguric acute renal failure patients with a FE_{Na} < 1 had a mortality of 11% versus 48% when the FE_{Na} was > 1.

To summarize, the best urinary indices for distinguishing between prerenal azotemia and oliguric acute tubular necrosis are the RFI and the FE_{Na}. It should be remembered that we think of prerenal azotemia and oliguric acute tubular necrosis as having a clear-cut difference, when in reality, they represent a continuum of disorders characterized by renal underperfusion. Thus, no one test is perfect. Early signs of medullary ischemia may be manifest as a loss in

concentrating ability (U_{osm}, U/P osm and creatinine) even before a rise in serum creatinine. Further ischemia then results in a rise in serum creatinine and an increase in the FE_{Na}.

Distinguishing Different Types of Intrinsic Renal Disease

Once prerenal and postrenal causes of acute renal failure have been excluded, one attempts to distinguish between the various types of intrinsic renal disease (see Figure 14).

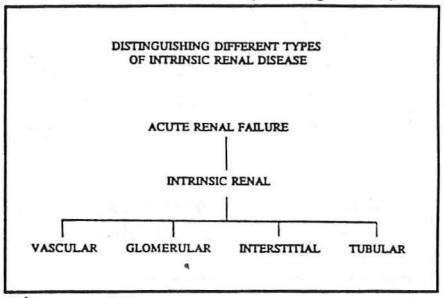


Figure 14

The vast majority of hospital-acquired acute renal failure is caused by various forms of acute tubular necrosis (108), whereas outside the hospital vascular, acute glomerular, and interstitial disease states assume a greater predominance, especially in the pediatric population where they account for > 50% of acute renal failure cases (109). The clinical history may be helpful if they have symptoms of multisystem disease (especially pulmonary-renal), rash, fever, exposure to potentially nephrotoxic drugs, new onset of edema, hypertension, and hematuria. However, examination of the urine and its sediment may be of greater use (see Table 4). Glomerulonephritis and vasculitis has a urine sediment with dysmorphic RBC's and/or RBC casts and is usually associated with proteinuria. Interstitial nephritis has a urine sediment characterized by eosinophils, WBC's and/or WBC casts. Acute tubular necrosis has a urine sediment characterized by renal tubular epithelial cells, renal tubular epithelial casts, and coarsely granular pigmented casts.

TABLE 4
DISTINGUISHING DIFFERENT TYPES
OF INTRINSIC RENAL DISEASE

Disease	Urinalysis Findings
Glomerulonephritis/Vasculitis	Dysmorphic RBCs, RBC casts, Proteinuria
Interstitial Nephritis	Eosinophils, WBCs, WBC casts
Acute Tubular Necrosis	Renal tubular epithelial cells, Renal tubular epithelial cell casts, Coarsely granular pigmented casts

The urinary chemical indices are not quite as helpful (see Figure 15). In fact, acute glomerulonephrites is characterized in one study as having a low urinary Na and low FE_{Na}, indices characteristic of prerenal azotemia (95).

In the elderly patient, consideration of ischemic acute renal failure secondary to atherosclerotic renal vascular disease should always be kept in mind, especially if the patient has a history of generalized atherosclerotic disease (110), recent onset of hypertension, history of flank pain and hematuria, or the presence of an abdominal or flank bruit.

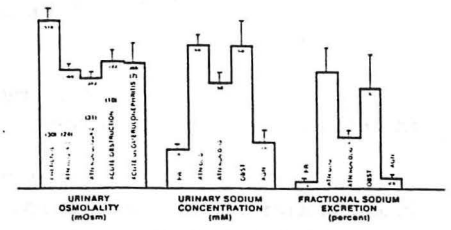


Figure 15

TREATMENT

Oliguric acute tubular necrosis carries a far worse prognosis than nonoliguric acute tubular necrosis (see Figure 16, [3-7]). In fact, oliguria is a major risk factor for death in numerous epidemiologic studies (6,7,111-114).

Can Oliguric Acute Tubular Necrosis be Converted to Nonoliguric Acute Tubular Necrosis?

The clinical advantages of nonoliguric acute tubular necrosis over oliguric acute tubular necrosis can be summarized in Table 5.

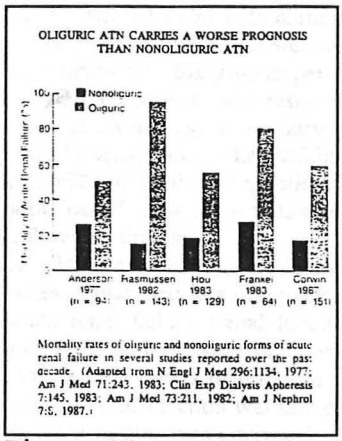


Figure 16

Diuretics. Diuretics have been used in three ways to alter the natural history of acute renal failure: a) prophylactically to prevent acute renal failure in clinical situations in which it is a frequent complication; b) in early renal failure to halt progression of the disease process; and, c) to accelerate the rate of recovery in established acute renal failure (115).

Although several studies suggest that prophylactic mannitol or furosemide in certain surgical settings prevents the occurrence of postoperative acute renal failure (116), the general consensus of several controlled studies suggests that prophylactic diuretics do not prevent the development of acute renal failure in open heart or vascular surgery (117-119) or surgical shock surgery (120,121). An exception to this may be the jaundiced patient undergoing surgery as two controlled studies indicate that postoperative GFR is improved with preoperative mannitol (122,123). In addition, prophylactic treatment with mannitol in patients receiving cis-platinum therapy (124) and mannitol or furosemide given to patients prior to radiocontrast studies has lessened the incidence of nephrotoxic acute renal failure in these patients (125-128). Recently, using a rat model of contrast-induced acute renal failure, prophylactic furosemide was found to reduce tubular damage and the incidence of acute renal failure (129). It should be noted that high doses of mannitol may be detrimental and even

TABLE 5
CLINICAL ADVANTAGES OF NONOLIGURIC ATN
VERSUS OLIGURIC ATN

1. Reduced mortality with nonoliguric ATN.
2. Easier management of electrolyte abnormalities, many of which require the use of Na^+.
3. Easier management of pulmonary edema.
4. Allows the use of enteral/parenteral alimentation with a reduced risk of volume overload.

result in the development of acute renal failure under certain conditions (130-132).

Furosemide and mannitol have been used in the early stages of acute renal failure (24-48 hours after onset). Levinsky and Bernard (115) have recently reviewed the literature and compiled the results. It should be noted that most of these studies are not controlled, thus, it is difficult to determine whether survival was more frequent in patients treated with diuretics. They attempted to determine whether patients whose urine flow increased with diuretics were more likely to survive than patients who remained oliguric after treatment. Sixty-seven percent of the patients responded with an increase in urine flow rate. Of 108 patients who responded to the diuretics, 82 survived (mortality 24%), whereas 31 out of 53 nonresponders survived (mortality 42%). The results were statistically different by the chi-square test. The usefulness of this analysis is limited by the compiling of data from a number of studies of questionable comparability. However, the results suggest that patients with "early" acute renal failure may be more likely to survive if their urine flow rate increases following diuretics.

Diuretics in established acute renal failure have also been extensively studied (4,115,117,118,133-146). The only agreement on these studies is that their is a disagreement as to whether diuretics influence the clinical course of acute renal failure (renal function, requirement for dialysis, and mortality). However in almost all patients, high doses of diuretics did increase urine flow rate. Levinsky and Bernard have compiled the results of these studies (see Table 6). Of 18 studies in which the effect of the diuretic on renal function was tested, 7 indicated a favorable action, 9 found no improvement, and in 2 the results were equivocal. Of 14 in which the need for hemodialysis was evaluated, 7 found a reduced need for dialysis, 5 found no effect, and 2 were equivocal. Of the 15 reports in which survival was examined, only one uncontrolled study found a lower mortality rate (4). Although equal weight was given to each study of widely varying quality, the evidence against a beneficial effect of diuretics on patient survival is impressive.

Diuretics and Dopamine. In some patients who do not respond to furosemide alone, the combination of dopamine and furosemide has been found to induce a diuresis (see Table 7, [147,148]). Dopamine was used at 1 to 3 μg/kg/min and furosemide was used at 200-400 mg IV every 4 to 6 hours. This combination markedly reduced the need for dialysis, but did not

TABLE 6
INFLUENCE OF DIURETICS
IN ESTABLISHED ACUTE RENAL FAILURE

Number of Studies	Improved	Not Improved	Equivocal
Effect of diuretic on renal function (n=18)	7	9	2
Hemodialysis requirement (n=14)	7	5	2
Survival (n=15)	1	14	

Adapted from Brenner and Lazarus, Acute Renal Failure, 1988.

effect the overall mortality rate.

To summarize, spontaneous nonoliguric acute tubular necrosis has a better prognosis than oliguric acute tubular necrosis, most likely reflecting a lesser degree of tubular injury in the patients with nonoliguric acute tubular necrosis. Use of diuretics in early acute renal failure may reduce the energy requirements (ATP utilization) of the injured medullary thick ascending Limb of Henle and prevent further damage. However, even though loop diuretics increase the flow rate of urine in established acute renal failure, they do not necessarily reproduce the syndrome of spontaneous nonoliguric acute tubular necrosis. Thus, loop diuretics appear to only be beneficial in early acute renal failure.

TABLE 7
INFLUENCE OF DOPAMINE AND FUROSEMIDE ON ACUTE RENAL FAILURE
(RESPONSE RATE 83%)

	Responders	Non-responders
Need for dialysis	24%	100%
Mortality	28%	20%

Adapted from Nephron 33:121-126, 1983;
37:39-42, 1984.

Recommendations for Treatment. The most important initial treatment of early acute renal failure is to correct any hypotension or fluid deficits that may exist (see Table 8). One can then try mannitol or preferably furosemide at fairly high doses to promote a diuresis. Addition of dopamine may be considered if no response to the above maneuvers is noted. It should be remembered that frequent or high doses of mannitol may result in acute renal failure itself (130-132). Continuous therapy with large doses of diuretics to maintain or establish small increases in urine output are not recommended.

TABLE 8
TREATMENT OF ACUTE RENAL FAILURE
IN THE FIRST 24 TO 48 HOURS

1. Correct hypotension or fluid deficits.
2. Furosemide (80-320 mg) initial dose, can be repeated two or three times (or Mannitol 12.5 to 25 g can be repeated one or two times).
3. Trial of dopamine 1 to 2 mcg/kg/min for 4 to 6 hours plus furosemide (80-320 mg).

Continuous therapy with large doses of diuretics to establish or maintain higher urine volumes is not recommended.

What are the Indications for Dialysis?

Despite conservative management, dialysis may be required in acute renal failure. This is paricularly true for oliguric acute tubular necrosis. However, despite good urine outputs, even patients with nonoliguric acute tubular necrosis may require dialysis. The indications for dialysis include: a) uremia; b) fluid and electrolyte abnormalities; and, c) to maintain the BUN < 100 mg/dL.

Uremia. Occasionally with prolonged acute renal failure, symptoms of uremia may develop. These include seizures, coma, pericarditis, bleeding from the gastrointestinal tract, and intractable vomiting. However, with the advent of early dialysis these are uncommonly manifest.

Fluid and Electrolyte Abnormalities. The most common causes of mortality in the early resuscitative phase of acute renal failure are pulmonary edema due to overhydration and hyperkalemia (149). Overhydration with the development of pulmonary edema is almost always secondary to vigorous hydration to restore urine output and renal function.

Hyponatremia occurs much more commonly than hypernatremia in acute renal failure (see Table 9, [150,151]) and is almost always secondary to an iatrogenic increase in free water intake. Hyperkalemia is one of the more common and serious complications of acute renal failure (152). Hyperkalemia > 6.0 mEq/L without EKG changes can initially be managed with the cation-exchange resin Kayexalate. It should be mentioned that Kayexalate mixed with

TABLE 9
FLUID AND ELECTROLYTE ABNORMALITIES INDICATING THE NEED FOR ACUTE HEMODIALYSIS

Abnormality	Non-dialytic Treatment
Hyponatremia (< 120 mEq/L)	Restriction of water
Hyperkalemia (> 6.0 mEq/L)	25-50 g Kayexalate plus 20 ml 70% sorbitol
Acidemia (HCO_3^- < 10 mEq/L)	$NaHCO_3$
Pulmonary edema	Furosemide

sorbitol administered as a rectal enema can induce intestinal necrosis which appears to be secondary to the sorbitol (153). Therefore, Kayexalate by this mode of therapy may need to be administered dissolved in another solvent. Acidemia with a persistent pH < 7.20 despite therapy is a relative indication for dialysis. Thus, the management of the electrolyte disorders in acute renal failure by non-dialytic therapies requires in most cases the use of Na containing salts and runs the risk of inducing volume overload in the oliguric patient.

Maintaining the BUN < 100 mg/dL. Conger investigated the effect of dialytic therapy to maintain the BUN < 100 mg/dL in the treatment of acute renal failure in Vietnam war casualities (see Table 10, [154]). He found that maintaining the BUN < 100 mg/dL decreased the mortality rate from 80% to 37% and reduced the complications of septicemia and hemorrhage. These results have been confirmed in another study (155).

TABLE 10
HEMODIALYSIS IN ACUTE RENAL FAILURE

	Group A	Group B
Number of patients	8	10
BUN (mg/dl)	50±10	120±19
Septicemia (gram-negative)	50%	80%
Hemorrhage	36%	60%
Mortality	37%	80%

Adapted from J Trauma 15:1056-1063, 1975.

TABLE 11
INTENSIVE HEMODIALYSIS IN ACUTE RENAL FAILURE

	Group A (Intensive)	Group B (Non-intensive)
Number of patients	17	17
BUN (mg/dl)	60±23	101±18
Septicemia	47%	65%
Hemorrhage	24%	59%
Mortality	59%	41%

Adapted from Clinical Nephrology 25:249-255, 1986.

In a later study, Conger et al investigated the role of even more intensive dialysis (see Table 11, [156]). Patients were dialyzed 5-6 hours daily to maintain the BUN even lower than 100 mg/dL. The other group of patients were dialyzed every other day to keep the BUN < 100 mg/dL. The more intensively dialyzed patients experienced less episodes of septicemia and hemorrhage, but the therapy did not increase the survival rate. Thus, dialysis to keep the BUN < 100 mg/dL appears beneficial in reducing the mortality in patients with acute renal failure, but more intensive dialysis does not appear to result in any additive benefit.

TABLE 12
FACTORS FAVORING DIALYSIS OR HEMOFILTRATION MODE OF TREATMENT

PERITONEAL DIALYSIS	HEMODIALYSIS	ARTERIOVENOUS HEMOFILTRATION
Minimal increase in catabolic rate	High catabolic rate	Moderately high catabolic rate
Slow fluid-electrolyte correction required	Rapid fluid-electrolyte correction required	Rapid fluid correction required
Intact peritoneum without infection or adhesions	Hemodynamically stable patient	Moderately fast electrolyte correction required
Hemodynamically unstable patient	Trained staff, equipment	Hemodynamically unstable patient
Untrained or minimally trained staff		Intermediate level of staff training and equipment relative to peritoneal dialysis and hemodialysis

From Jacobson, Striker, Klahr, *The Principals and Practice of Nephrology*, 1991

Mode of Dialysis Treatment

Once it has been determined that conservative management is inadequate and dialytic therapy is required, the type of dialysis to be used must be decided upon. We have the choice of hemodialysis, peritoneal dialysis, or continous arteriovenous hemofiltration or hemodiafiltration. Each technique has advantages and disadvantages with different complication rates (see Tables 12,13).

TABLE 13
RISKS AND COMPLICATIONS OF DIALYSIS AND HEMOFILTRATION

PERITONEAL DIALYSIS	HEMODIALYSIS	ARTERIOVENOUS HEMOFILTRATION
Slow fluid and solute removal	Hemodynamic instability	Volume depletion
Drainage failure	Hypoxemia	Hemorrhage
Unpredictable fluid removal	Hemorrhage	Electrolyte disturbances
Peritonitis	Osmolar disequilibrium	
Puncture of abdominal viscus	Dialyzer clotting	Filter clotting
Respiratory compromise	Access thrombosis	Vascular thrombosis
Hyperglycemia	Infection	Infection
	Arrhythmias	Arrhythmias

From Jacobson, Striker, Klahr, *The Principles and Practice of Nephrology*, 1991.

Peritoneal Dialysis. Peritoneal dialysis has little effect on systemic blood pressure and is ideal for the hemodynamically unstable patient who is not extremely catabolic (157). This technique can be managed by personnel with little background training. Fluid removal and electrolyte correction is relatively slow by this technique. It does cause abdominal distension and thus, respiratory compromise, and may not be as suitable for the patient with pulmonary complications. In addition, an inability to drain the fluid adequately may sometimes be a problem.

Hemodialysis. Hemodialysis has the advantage of being able to rapidly correct fluid and electrolyte abnormalities as well as remove catabolic wastes in a patient with a high catabolic rate. It requires a skilled staff to perform and may be difficult in the hemodynamically unstable patient.

Continuous Arteriovenous Hemofiltration. Continuous arteriovenous hemofiltration is presently reserved for the hemodynamically unstable patient with blood pressures < 90 mm Hg (157). Plasma water, electrolytes, and small molecles are filtered in bulk solution through a high flux membrane and up to 30-40 mL/minute of fluid can be removed by this technique. Close observation of fluid and electrolyte replacement are generally required, as well as the need for a skilled staff.

Prognosis

In addition to the increased mortality seen with oliguria, several other factors have been found to significantly increase mortality (2,7,111-114,158-162). When the kidney is the only organ to fail, mortality is only 8% (see Table 14, [158]). Unfortunately, these account for less than 10% of all cases of acute renal failure. However, when acute renal failure is associated with either, uncontrolled sepsis, pulmonary, liver, or heart failure, the mortality rate dramatically increases.

TABLE 14
MORTALITY OF ACUTE RENAL FAILURE ALONE AND IN ASSOCIATION WITH ORGAN FAILURE

	% Mortality
Acute renal failure alone, no other serious problems	8
+Uncontrolled sepsis	65
+Pulmonary failure	71
+Liver failure	65
+Circulatory failure	76

Data from the EDTA-European Renal Association Registry, presented at the meeting of the Association in Brussels, June 1985.

As the number of organs that have failed increases (see Table 15), the mortality rate increases even further. When 4 or more organs fail the prognosis is quite bad (158,163). Other factors that may adversely effect outcome are age (113,159), severity and duration of renal failure (3) and hypercatabolic state (160).

TABLE 15
PROGNOSIS OF ACUTE RENAL FAILURE WITH MULTI-ORGAN FAILURE

Organs Failed*	Survival
0	62%
1	44%
2	30%
3	19%
4	0%

*Organ failure: circulatory failure (BP $\leq$ 100), respiratory failure (mechanical ventilation), congestive heart failure, sepsis, gastrointestinal dysfunction (bleeding, ileus, or obstruction).

The mortality of patients dialyzed in the intensive-care unit (ICU) is extremely high ranging from 62-88% (164,165) and recovery of renal function has been reported to be only 23% (165). In contrast, mortality from acute renal failure dialyzed in the acute dialysis unit was only 37% (164). There was no difference in mortality rates in the medical ICU (83%) versus the surgical ICU (90%), while a 100% mortality was experienced in the burn ICU (165). In one study, a 100% mortality rate was found for patients requiring ventilatory support (27/31 had at least 2 associated comorbid factors, 165). This study and others have raised the ethical question of whether certain patients with multiple organ failure should be dialyzed at all (165,166).

Recovery of Renal Function. Following the development of oliguric acute renal failure requiring dialysis (see Figure 17), recovery of renal function is characterized by a period of time lasting several days where little or no improvement in renal function occurs that is dependent upon the severity of the insult. When renal function begins to return there is an initial relatively rapid return in renal function that lasts approximately 1-2 weeks, followed by a period of slower improvement. At a time six weeks from the last dialysis, little further improvement in renal function occurs. Ultimately, approximately one-third of patients with be left with residual renal insufficiency (159,167,168) and at least 5% will require long-term hemodialysis treatment (159). However, in a more recent review of patients with acute renal failure requiring dialysis, only 27% were able to come off dialysis long term (168a).

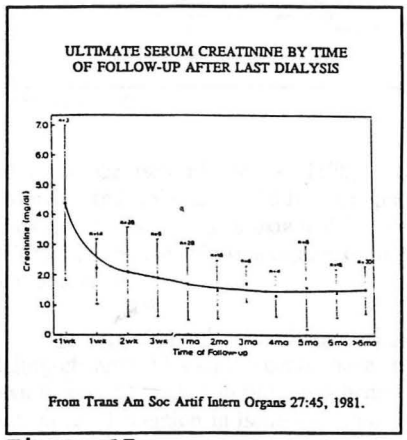


Figure 17

In the past, recovery of renal function from oliguric acute renal failure was said to have a diuretic phase to it with large urine volumes. We do not see this develop anymore in most of our patients as we tend to dialyze them early and keep excess extracellular fluid volume to a minimum. The diuretic phase described in the past was most likely secondary to excretion of excess extracellular fluid volume that these patients recieved while they were oliguric. True salt wasting during recovery from acute renal failure has to be quite rare.

Possible Future Modes of Therapy

Numerous studies have been performed examining the effects of a variety of agents on the development of ischemic acute renal failure using animal models.

Atrial natriuretic peptide and mannitol. High doses of atrial natriuretic peptide (ANP) have been found to be beneficial in preventing ischemic acute renal failure (169-174). However, the dose required for any benefit has been found to be associated with significant hypotension (170,172). Lieberthal et al (see Figure 18) found that a dose tenfold lower, in combination with mannitol, could produce similar results without the development of hypotension in the isolated

perfused rat kidney model (175). This dose of ANP alone had no beneficial effect. The authors proposed that the unique effect of ANP to increase intraglomerular pressure and mannitol to reduce cast formation and thus, tubule obstruction, resulted in the beneficial effect of these agents on renal function following ischemia.

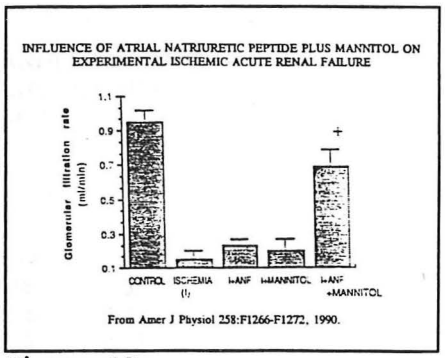


Figure 18

$MgCl_2$-ATP. Following ischemia, cellular ATP levels rapidly fall (53-55). Several investigators have tried to reduce this nucleotide loss by infusing nucleotides or nucleosides before or after ischemia (176-180). $MgCl_2$-ATP infusions given up to 48 hours after the ischemic event in a rat model significantly improved renal clearance (see Figure 19, [178]). The mechanism for this protection was examined by Mandel and colleagues (180). Exogenous adenine nucleotides were found to stabilize the plasma membrane during anoxia and following reoxygenation provide the precursors for rapid ATP formation by the diffusion of adenosine into the cells, where it is resynthesized into cellular AMP and ATP.

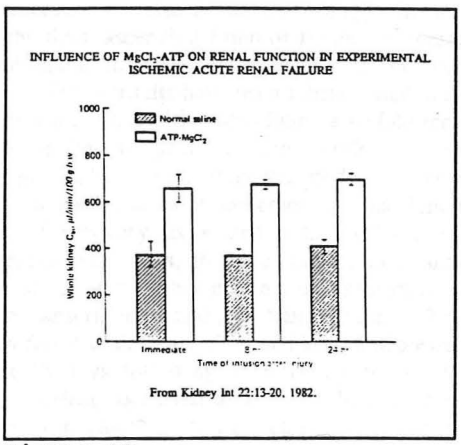


Figure 19

Calcium-channel blocking agents. Calcium-channel blocking agents have been shown in several studies to provide a beneficial effect on renal function in ischemic acute renal failure (181-189). A recent study using a rat ischemic acute renal failure model found that the dihydropyridine derivatives appear to have a greater effect than non-dihydropyridines (see Table 16, [189]).

It is believed that these agents may lessen the increase in intracellular calcium accumulation which is found with ischemic acute renal failure. A recent study has found that pretreatment with nitrendipine improves proximal tubule phosphate transport in the rat ischemic acute renal failure model (189), although further elucidation of the mechanism was not examined. It is important to note that any beneficial impact of calcium-channel blockers requires there presence before the ischemic event. Given after the ischemic event, they generally do not have any beneficial effect.

Epidermal growth factor. As acute tubular necrosis involves some cellular death and regeneration, Humes et al (190) investigated the effect of exogenous epidermal growth factor (EGF), one of the most potent mitogens in renal epithelial cells (191), on renal function and

TABLE 16
INFLUENCE OF CALCIUM-CHANNEL BLOCKERS
ON RENAL FUNCTION IN EXPERIMENTAL
ISCHEMIC ACUTE RENAL FAILURE

	C_{Cr}
RI control, n = 10	1.52 ± 0.40
S-312-d, n = 10	3.74 ± 0.44**
Flunarizine, n = 10	3.06 ± 0.33
Nimodipine, n = 9	2.66 ± 0.35
Nicardipine, n = 9	2.37 ± 0.25
Verapamil, n = 10	1.28 ± 0.30
Diltiazem, n = 9	1.42 ± 0.28

**P<0.01

recovery in ischemic acute renal failure (see Figure 20). They found that EGF given 60-90 minutes after ischemia in the rat model, increased renal cell regeneration predominantly in the renal cortex, but also substantially in the inner stripe of the outer medulla, an area predominated by the thick ascending Limb of Henle. Associated with this increase in cell regeneration was a substantial improvement in renal function when compared to controls.

These results have been substantiated in a further study which in addition also found a sixfold increase in EGF binding following ischemia (192). Again, EGF was given after the ischemia was produced. Once again, the authors found an improvement in renal function and rate of recovery associated with an incease in cell regeneration. Thus, in these studies, EGF altered the rate of recovery rather than act in a protective manner. Both transcriptional and post-transcriptional effects have been found to decrease EGF and keep it depressed for at least 15 days following an ischemia event (193,194). These effects occurred at a time when early response genes (c-fos and Egr-1) were elevated. Associated with this decrease in EGF was an increase in EGF receptor density in both the renal cortex and medulla (192). The authors suggested that decreased EGF production may occur secondary to selective effects of renal ischemia on the thick ascending Limb of Henle as the thick ascending Limb of Henle and the distal tubule are the only sites of preproEGF mRNA production in the kidney. Thus, exogenous EGF appears to be a promising agent that hastens renal recovery from ischemic acute renal failure and may be beneficial as intrinsic EGF production appears to be inhibited and EGF receptor density is increased under these conditions.

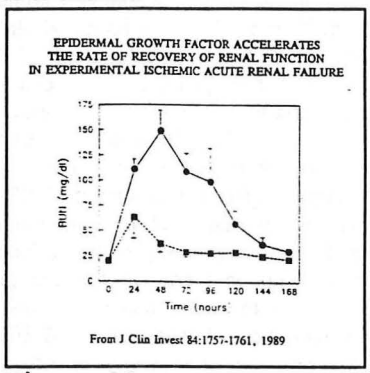


Figure 20

Glycine. Exogenous glycine when present at the time of renal ischemia, reduces the extent of renal damage which occurs (195-200). Glycine substantially lessened the extent of medullary thick ascending Limb of Henle injury in the isolated perfused kidney model (200). The mechanism has been extensively investigated, but at present, it is still unclear and appears to be unrelated to: a) changes in intracellular glutathione metabolism; b) changes in cell thiols or reactive oxygen species; c) ATP stores; d) a reduction in oxygen utilization; e) suppresion of short- and medium-chain acylglycine formation; or, f) glycolytic metabolism. It is possible that glycine protects the kidney by its unique ability to stabilize tertiary protein and membrane structure (198). Thus, if present at the time of ischemia, elevated levels of extracellular glycine may be protective against renal damage.

To summarize, multiple experimental agents are protective against renal failure induced by ischemia. However, to be effective they usually have to be present at the time of the ischemic event. This may not be practical in all instances of renal underperfusion, but may be extremely useful in certain surgical settings and for the harvesting of kidneys in preparation for renal transplantation. Of the agents discussed, EGF appears to have the most potential for benefitting patients with hospital-acquired ischemic acute renal failure. One of the new areas of interest involves the genetic response to ischemia. Following ischemia, several genes are induced and proteins are synthesized anew or in greater quantities (193,194,201,202).

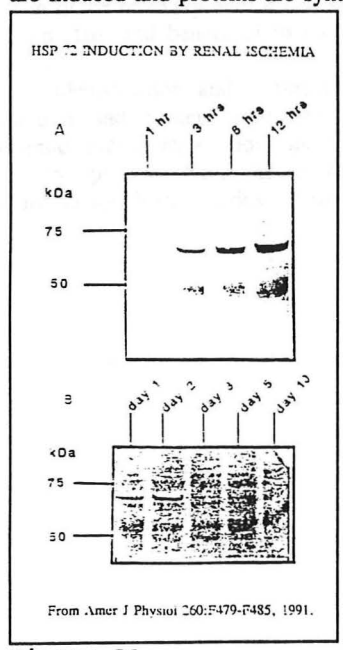


Figure 21

HSP 72. One of the group of proteins that is synthesized anew or in greater quantities is the heat shock protein family. Using a specific monoclonal anti-HSP 72 antibody, HSP 72 accumulation was detected by immunoblot analysis in the kidney (see Figure 21, [201]). The pattern of HSP 72 accumulation was independent of the duration of the ischemia and could be found with as little as 15 minutes of ischemia. HSP 72 accumulation was first detected 3 hours after recovery and persisted for up to 5 days (201).

Whether the prolonged accumulation of HSP 72 after ischemia is the result of slow degradation, persistent synthesis, or both was not distinguished in this study. In addition, whether HSP 72 functions primarily to ameliorate injury and/or accelerate the cellular repair process is not known. The heat shock family of proteins appears designed to protect, preserve, and recover the function of various protein complexes within the cell which may be injured following a stress (203,204). This may be accomplished by HSP 72 acting as a cytosolic chaperone to transport proteins in a partially unfolded state and target them to specific organelle sites within the cell (203,204). It is possible that following ischemia, the heat shock family of proteins serves a cytoprotective effect within the cell by salvaging denatured proteins through solubilization and facilitating their refolding and/or chaperoning them to a degradative system (204). Investigation of HSP 72 synthesis and accumulation in relation to the cellular repair process is

an area with potential importance to understanding renal ischemia.

Early response genes. As epithelial growth and regeneration may be an integral part to the recovery from renal ischemia, several laboratories have investigated the induction of immediate early response genes (c-fos, c-jun, Egr-1) following renal ischemia (193,194,202). Egr-1 mRNA detected by Northern blot analysis was found to be abundant one hour after 30 minutes of ischemia and persisted for greater than 24 hours (see Figure 22, [202]). The pattern of elevation was independent of the duration of ischemia.

In contrast, c-fos mRNA levels accumulated in proportion to the duration of ischemia, rising quickly (at one hour) and returning to control levels at 24 hours. Thus, induction of early response genes occurs following ischemia and investigation into their role in tissue recovery and/or cell regeneration may be important and beneficial to understanding renal ischemia.

Identification and characterization of gene induction and protein synthesis that follow an ischemic event, may allow us to potentiate the recovery process from acute renal failure, a syndrome which still carries a fairly dismal prognosis.

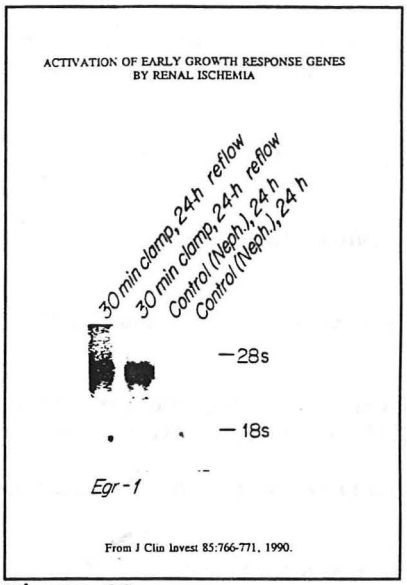


Figure 22

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