

## REVIEW ARTICLE

## MEDICAL PROGRESS

## ACUTE RENAL FAILURE

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**A**CUTE renal failure is characterized by a deterioration of renal function over a period of hours to days, resulting in the failure of the kidney to excrete nitrogenous waste products and to maintain fluid and electrolyte homeostasis. In the past five decades, several important causes of acute renal failure and the pathophysiologic mechanisms that underlie renal dysfunction have come to be understood. In this article we highlight the epidemiology, general causes, and evaluation of acute renal failure in adults. We then expand on the pathophysiology of ischemic acute renal failure and discuss the rationale for both current and future therapies. Finally, replacement therapies are considered in the light of recent studies.

## BACKGROUND AND EPIDEMIOLOGY

When one attempts to review the subject of acute renal failure, one is immediately struck by the confusion in terminology and wide disparity in the definitions of terms. Notably, in a recent review of 26 studies on postoperative renal failure, no 2 studies used the same definition of acute renal failure.<sup>1</sup> Commonly used definitions of acute renal failure include an increase in serum creatinine of  $\geq 0.5$  mg per deciliter ( $44 \mu\text{mol}$  per liter) over the base-line value, an increase of more than 50 percent over the base-line value, a reduction in the calculated creatinine clearance of 50 percent, or a decrease in renal function that results in the need for dialysis.<sup>2-4</sup> There are also differences in the causes of acute renal failure in each study and lack of conformity in the use of the term "acute tubular necrosis." Acute tubular necrosis is a pathological diagnosis, and patients with ischemic or toxic insults to their kidneys might be expected to have tubular necrosis, but patients with acute renal failure due to other causes might not. In many studies, the analysis includes all causes of acute renal failure.<sup>5-7</sup> Finally, the frequency of acute re-

nal failure varies greatly depending on the clinical setting. For example, the frequency among patients is 1 percent at admission to the hospital,<sup>7</sup> 2 to 5 percent during hospitalization,<sup>6,8</sup> and as high as 4 to 15 percent after cardiopulmonary bypass.<sup>4</sup>

## CAUSES OF ACUTE RENAL FAILURE

Acute renal failure can result from decreased renal perfusion without cellular injury; an ischemic, toxic, or obstructive insult to the renal tubule; a tubulointerstitial process with inflammation and edema; or a primary reduction in the filtering capacity of the glomerulus (Fig. 1). If renal tubular and glomerular function is intact but clearance is limited by factors compromising renal perfusion, the failure is termed prerenal failure, or prerenal azotemia. If renal dysfunction is related to obstruction of the urinary outflow tract, it is termed postrenal failure, or postrenal azotemia. Acute renal failure due to a primary intrarenal cause can be called intrinsic renal failure, or renal azotemia. Prerenal failure and intrinsic renal failure due to ischemia and nephrotoxins are responsible for most episodes of acute renal failure. Prerenal azotemia accounts for approximately 70 percent of community-acquired cases of acute renal failure<sup>7</sup> and 40 percent of hospital-acquired cases.<sup>6</sup> Sustained prerenal azotemia is the most common factor that predisposes patients to ischemia-induced tubular necrosis.<sup>6,9-11</sup> Hospital-acquired acute renal failure is often due to more than one insult.<sup>12</sup> Frequently encountered combinations of acute insults include exposure to aminoglycosides in the setting of sepsis,<sup>2</sup> administration of radiocontrast agents in patients receiving angiotensin-converting-enzyme inhibitors,<sup>12</sup> or treatment with nonsteroidal antiinflammatory agents (NSAIDs) in the presence of congestive heart failure.<sup>13</sup>

## Prerenal Causes

Prerenal azotemia is rapidly reversible if the underlying cause is corrected. In the outpatient setting, vomiting, diarrhea, poor fluid intake, fever, use of diuretics, and heart failure are all common causes. Elderly patients are particularly susceptible to prerenal azotemia because of their predisposition to hypovolemia and high prevalence of renal-artery atherosclerotic disease.<sup>14</sup> The combination of angiotensin-converting-enzyme inhibitors and diuretics can cause prerenal azotemia in patients with large-vessel<sup>15</sup> or small-vessel<sup>16</sup> renal vascular disease. In patients with diminished renal perfusion, NSAIDs can precipitate prerenal azotemia.<sup>11,13,17</sup> Cyclosporine and tacrolimus also cause prerenal azotemia by inducing vasoconstriction of the small renal vessels.<sup>18,19</sup> Among hospitalized patients, prerenal azotemia is often due to cardiac failure, liver dysfunction, or septic shock.<sup>6,8</sup> In surgical patients, prerenal azotemia is a common cause of perioperative and postoperative renal dysfunction. Anesthesia decreases effective blood volume and, when accompanied by a reduction

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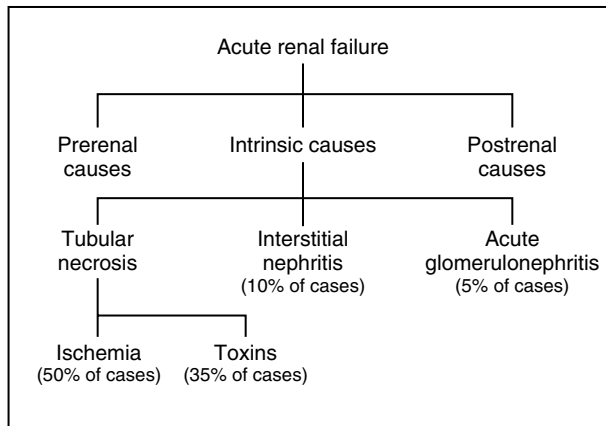


Figure 1. Main Categories of Acute Renal Failure.

The causes of acute renal failure can be categorized as prerenal, intrinsic, and postrenal. Once prerenal and postrenal causes have been excluded, one is left with intrinsic causes, which are associated with high rates of morbidity and mortality. The percentages listed reflect our experience; proportions may vary from institution to institution and from country to country.

in mean arterial pressure, can lead to a decrease in renal blood flow.

#### Postrenal Causes

Acute renal failure occurs when both urinary outflow tracts are obstructed or when one tract is obstructed in a patient with a single functional kidney. Obstruction is most commonly due to prostatic hypertrophy, cancer of the prostate or cervix, or retroperitoneal disorders<sup>20</sup> and often presents in the outpatient setting.<sup>6,7,21</sup> A neurogenic bladder can result in functional obstruction. Other, less frequent, postrenal causes of acute failure can be intraluminal, such as bilateral renal calculi, papillary necrosis, coagulated blood, bladder carcinoma, and fungus, or extraluminal, such as retroperitoneal fibrosis, colorectal tumor, and other malignant conditions. Furthermore, within the kidney, intratubular obstruction can be caused by various crystals, including uric acid,<sup>22</sup> calcium oxalate,<sup>23</sup> acyclovir,<sup>24</sup> sulfonamide,<sup>25</sup> and methotrexate,<sup>26</sup> as well as myeloma light chains. Postrenal causes are important to rule out quickly, since the potential for recovery of renal function is often inversely related to the duration of obstruction.<sup>27</sup> In addition, even in patients with advanced stages of cancer, ureteral stenting or percutaneous nephrostomy can relieve the obstruction and may improve short-term outcome.<sup>28</sup>

#### Intrinsic Causes

Intrinsic renal diseases that result in acute renal failure are categorized according to the primary site of injury: tubules, interstitium, vessels, or glomerulus. Injury to the tubules is most often ischemic or toxic in origin. Prerenal azotemia and ischemic tubular necrosis represent a continuum, with the former leading to the latter when blood flow is sufficiently compromised to result in the death of tubular cells. As shown in Figure 2, many clinical conditions can lead to kidney ischemia

as a result of either extrarenal or intrarenal factors that compromise renal blood flow. Although most cases of ischemic acute renal failure are reversible if the underlying cause is corrected, irreversible cortical necrosis can occur if the ischemia is severe, especially if the disease process includes microvascular coagulation such as may occur with obstetrical complications, snake bites, or the hemolytic-uremic syndrome.<sup>29</sup>

After ischemia, toxins account for the largest number of cases of acute renal failure. Aminoglycoside antibiotics and radiocontrast agents are the most common toxins encountered, but heme pigments,<sup>30</sup> chemotherapeutic agents such as cisplatin,<sup>31</sup> myeloma light-chain proteins,<sup>32</sup> and other drugs may also be responsible. Drugs can cause acute renal failure by directly damaging tubular cells or by various other mechanisms (Table 1). Ischemia and toxins often combine to cause acute renal failure in severely ill patients with conditions such as sepsis, hematologic cancers, or the acquired immunodeficiency syndrome.<sup>33,34</sup>

Acute renal failure due to acute interstitial nephritis is most often caused by an allergic reaction to a drug.<sup>35</sup> Other less frequent causes include autoimmune diseases (e.g., lupus), infiltrative diseases (e.g., sarcoidosis), and infectious agents (e.g., legionnaire's disease and hantavirus infection).<sup>36</sup> Renal failure due to acute interstitial nephritis is often reversible after the withdrawal of the offending medication or treatment of the underlying disease. Corticosteroids may hasten the recovery of renal function during acute interstitial nephritis,<sup>37</sup> but their role remains controversial because controlled studies are lacking and corticosteroids may be contraindicated in patients with underlying infection.

Glomerulonephritis can present as subacute or acute renal failure. Serologic assays and immunopathological examination of the kidney can identify specific causes of rapidly progressive glomerulonephritis. It is important to diagnose glomerulonephritis quickly, since prompt use of immunosuppressive agents, plasma exchange, or both may be indicated to reduce the occurrence of life-threatening complications and decrease the risk of end-stage renal failure.<sup>38,39</sup>

#### RISK FACTORS, MORBIDITY, AND MORTALITY

In patients with prerenal azotemia renal injury is more likely to be caused by drugs that can alter intrarenal hemodynamics, such as NSAIDs,<sup>13,17</sup> or reach high concentrations in renal tissue, such as aminoglycosides.<sup>2</sup> Patients with preexisting renal insufficiency are predisposed to acute renal failure due to radiocontrast agents,<sup>40</sup> aminoglycosides,<sup>35</sup> atheroembolism,<sup>41</sup> and cardiovascular surgery.<sup>4,42</sup> Patients with both renal insufficiency and diabetes mellitus are at particularly high risk for toxic reactions to radiocontrast agents.<sup>40</sup> Patients with hyperbilirubinemia also appear to be predisposed to acute renal failure. Elderly patients are susceptible to many forms of acute renal failure because the aging kidney loses functional reserve and its ability to withstand acute insults is compromised.<sup>14</sup>

Acute renal failure can be oliguric (urinary output,

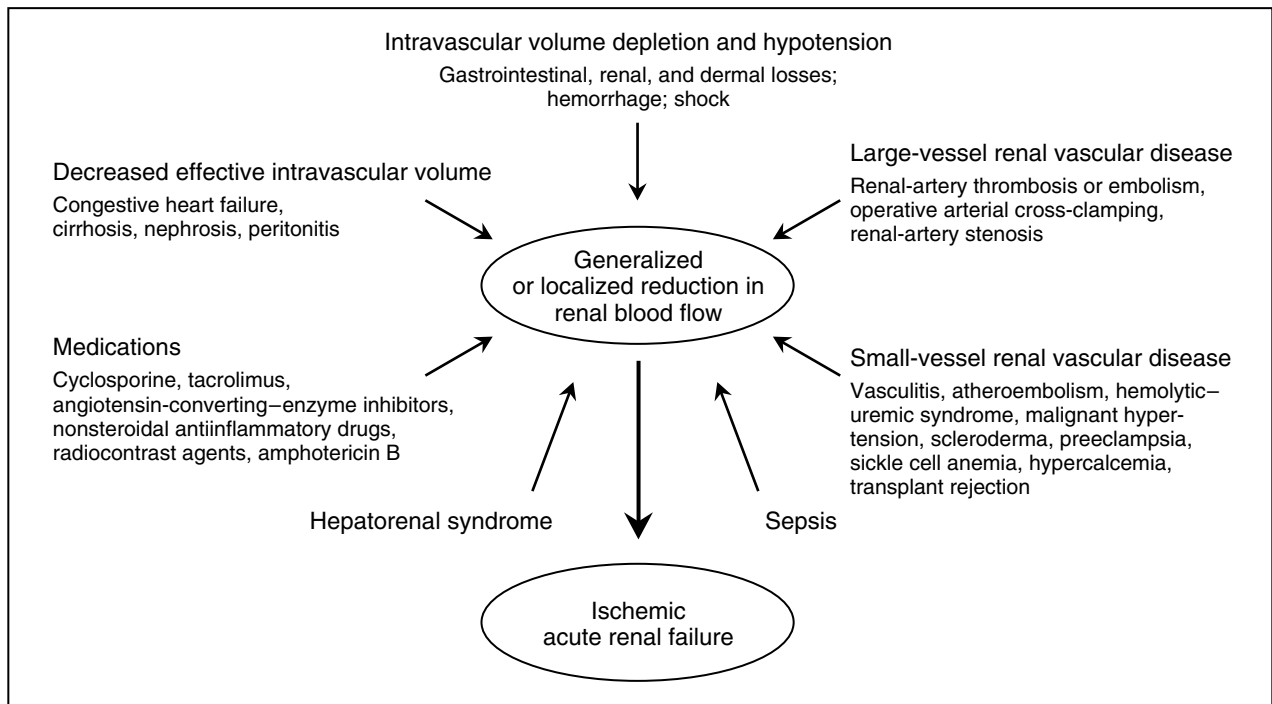


Figure 2. Conditions That Lead to Ischemic Acute Renal Failure.

A wide spectrum of clinical conditions can result in a generalized or localized reduction in renal blood flow, thus increasing the likelihood of ischemic acute renal failure. The most common condition leading to ischemic acute renal failure is severe and sustained prerenal azotemia. Kidney ischemia and acute renal failure are often the result of a combination of factors.

<400 ml per day) or nonoliguric ( $\geq 400$  ml per day). Patients with nonoliguric acute renal failure have a better prognosis than those with oliguric renal failure, probably due in large measure to the decreased severity of the insult and the fact that many have drug-associated nephrotoxicity or interstitial nephritis.<sup>10,12,43-45</sup> The percentage of patients with acute renal failure who require dialysis ranges from 20 to 60 percent.<sup>43,44</sup> Among the subgroup of patients who survive initial dialysis, less than 25 percent require long-term dialysis, demonstrating the potential reversibility of the syndrome.<sup>6,46</sup>

Mortality rates in acute renal failure range from approximately 7 percent among patients admitted to a hospital with prerenal azotemia<sup>7</sup> to more than 80 percent among patients with postoperative acute renal failure.<sup>1,4</sup> Despite major advances in dialysis and intensive care, the mortality rate among patients with severe acute renal failure (primarily ischemic in origin) requiring dialysis has not decreased appreciably over the past 50 years. This may be explained by two demographic changes: the age of patients continues to rise, and coexisting serious illnesses are increasingly common among these patients.<sup>10,47,48</sup> When acute renal failure occurs in the setting of multiorgan failure, especially in patients with severe hypotension or the acute respiratory distress syndrome, the mortality rate ranges from 50 to 80 percent.<sup>11,49-52</sup>

Before the development of dialytic therapies, the most common causes of death in patients with acute renal failure were progressive uremia, hyperkalemia, and

complications of volume overload. With the advent of dialysis, the most common causes of death are sepsis, cardiovascular and pulmonary dysfunction, and withdrawal of life-support measures.<sup>11,43,47,48</sup>

## DIAGNOSTIC EVALUATION

### History Taking and Physical Examination

Evaluation of the patient's history and physical examination often reveals the cause of renal dysfunction. For example, a history of exposure to nephrotoxic medication, a recent history of angiography, and physical findings of volume depletion all provide important diagnostic information and suggest specific interventions. Other diagnostic clues can be ischemia in an arm or leg, which suggests the presence of rhabdomyolysis, and anuria, which suggests postrenal acute renal failure. Allergic interstitial nephritis may be accompanied by a rash. Atheroembolic renal failure can be associated with livedo reticularis and signs of emboli to the legs. Bone pain in an elderly patient should suggest multiple myeloma as a possible cause of acute renal failure. Palpable purpura, pulmonary hemorrhage, and sinusitis should lead the physician to consider systemic vasculitis with glomerulonephritis as a cause.

### Urine Evaluation

Further diagnostic information should be obtained from the urinalysis and urine indexes, both of which are readily available, inexpensive, routine screening tests for patients with renal disease. Typical urine find-

Table 1. Drugs Associated with Acute Renal Failure.

MECHANISM	DRUG
Reduction in renal perfusion through alteration of intrarenal hemodynamics	NSAIDs, angiotensin-converting-enzyme inhibitors, cyclosporine, tacrolimus, radiocontrast agents, amphotericin B, interleukin-2*
Direct tubular toxicity	Aminoglycoside antibiotics, radiocontrast agents, cisplatin, cyclosporine, tacrolimus, amphotericin B, methotrexate, foscarnet, pentamidine, organic solvents, heavy metals, intravenous immune globulin†
Heme-pigment-induced tubular toxicity (rhabdomyolysis)	Cocaine, ethanol, lovastatin‡
Intratubular obstruction by precipitation of the agent or its metabolites or by-products	Acyclovir, sulfonamides, ethylene glycol,§ chemotherapeutic agents,¶ methotrexate
Allergic interstitial nephritis	Penicillins, cephalosporins, sulfonamides, rifampin, ciprofloxacin, NSAIDs, thiazide diuretics, furosemide, cimetidine, phenytoin, allopurinol
Hemolytic-uremic syndrome	Cyclosporine, tacrolimus, mitomycin, cocaine, quinine, conjugated estrogens

\*Interleukin-2 produces a capillary-leak syndrome with volume contraction.

†The mechanism of this agent is unclear but may be due to additives.

‡Acute renal failure is most likely to occur when lovastatin is given in combination with cyclosporine.

§Ethylene glycol-induced toxicity can cause calcium oxalate crystals.

¶Uric acid crystals form as a result of tumor lysis.

||Many other drugs in addition to the ones listed can cause renal failure by this mechanism.

ings in patients with acute renal failure are shown in Table 2. In the absence of erythrocytes, heme-positive urine suggests the presence of myoglobin or hemoglobin, supporting a clinical diagnosis of rhabdomyolysis or transfusion reaction. The characteristics of casts are helpful. Pigmented granular casts are typically found in ischemic or toxic acute renal failure, white-cell casts in interstitial nephritis, and red-cell casts in glomerulonephritis. The presence of eosinophils in urine may suggest allergic interstitial nephritis, although eosinophiluria is of limited value diagnostically since it is seen in other causes of acute renal failure, such as atheroembolism and pyelonephritis.<sup>41,53</sup> Oxalate crystals are seen in cases of ethylene glycol ingestion.

Urine indexes, which measure urine osmolality, urinary sodium concentration, and fractional excretion of sodium, help differentiate between prerenal azotemia, in which the reabsorptive capacity of tubular cells and the concentrating ability of the kidney are preserved, and tubular necrosis, in which both these functions are impaired. One of the earliest functional defects seen with tubular damage is loss of the ability to concentrate the urine. Patients with oliguria and acute renal failure due to prerenal causes tend to have a urine osmolality of more than 500

mOsm per kilogram, a urinary sodium concentration below 20 mmol per liter, and a fractional excretion of sodium below 1.0 percent. In contrast, in patients with tubular necrosis, urine osmolality is less than 350 mOsm per kilogram, the urinary sodium concentration exceeds 40 mmol per liter, and the fractional excretion of sodium exceeds 1.0 percent.<sup>54</sup> Although the urine indexes help differentiate prerenal azotemia from tubular necrosis, they do not completely segregate the two conditions.<sup>55</sup> As an example, early in the course of certain processes that lead to tubular damage, such as myoglobinuria, exposure to radiocontrast agents, sepsis, or obstruction, the urinary sodium concentration can be low.

### Blood Tests

Other blood tests in addition to the measurement of urea nitrogen and creatinine in serum help in the differential diagnosis of acute renal failure. The presence of hypercalcemia and hyperuricemia can point to a malignant condition as a cause, elevated creatine kinase levels may indicate rhabdomyolysis, abnormal serum immunoelectrophoresis results suggest myeloma, and the presence of eosinophilia is consistent with allergic interstitial nephritis. The presence of an osmolal gap (the difference between the measured and the calculated osmolality) suggests the presence of a low-molecular-weight nephrotoxin, such as ethylene glycol. Serologic tests for systemic immunologic diseases may confirm a clinical suspicion of glomerulonephritis.<sup>39</sup>

### Evaluation of Obstruction

In the early evaluation of acute renal failure it is important to rule out urinary tract obstruction, especially in patients who present with severe oliguria or anuria. Simple bladder catheterization can rule out urethral obstruction. Renal ultrasound examination is a useful

Table 2. Typical Urine Findings in Conditions That Cause Acute Renal Failure.

CONDITION	DIPSTICK TEST	SEDIMENT ANALYSIS	URINE	FRACTIONAL
			OSMOLALITY	EXCRETION OF SODIUM
			<i>mOsm/kg</i>	%
<b>Prerenal azotemia</b>	Trace or no proteinuria	A few hyaline casts possible	>500	<1
<b>Renal azotemia</b>				
Tubular injury				
Ischemia	Mild-to-moderate proteinuria	Pigmented granular casts	<350	>1
Nephrotoxins*	Mild-to-moderate proteinuria	Pigmented granular casts	<350	>1
Acute interstitial nephritis	Mild-to-moderate proteinuria; hemoglobin; leukocytes	White cells and white-cell casts; eosinophils and eosinophil casts; red cells	<350	>1
Acute glomerulonephritis†	Moderate-to-severe proteinuria; hemoglobin	Red cells and red-cell casts; red cells can be dysmorphic	>500	<1
<b>Postrenal azotemia‡</b>	Trace or no proteinuria; can have hemoglobin, leukocytes	Crystals, red cells, and white cells possible	<350	>1

\*In some conditions that lead to nonoliguric acute renal failure (e.g., exposure to radiocontrast agents and rhabdomyolysis), the initial fractional excretion of sodium can be <1 percent.

†When glomerulonephritis (e.g., post-streptococcal glomerulonephritis) is associated with tubulointerstitial abnormalities, the urine osmolality is <350 mOsm per kilogram and the fractional excretion of sodium is >1 percent.

‡Early in the course of obstruction, before tubular damage has occurred, the fractional excretion of sodium can be <1 percent.

means of diagnosing obstruction, but its sensitivity may be only 80 to 85 percent. A nondilated collecting system does not necessarily exclude the possibility of obstruction, especially when the condition is acute, in the setting of retroperitoneal fibrosis, or in patients with hypovolemia. Ultrasonography can also be used to identify stones and determine kidney size, which, if small, suggests chronic renal insufficiency. If there is a high index of clinical suspicion for obstruction, it may be necessary to proceed with antegrade or retrograde contrast studies of the urinary outflow tract to establish the site of obstruction and provide relief.<sup>56</sup>

#### **Role of Renal Biopsy in Acute Renal Failure**

In general, renal biopsy is not necessary in the evaluation and therapy of patients with acute renal failure. However, when the history, clinical features, and laboratory and radiologic investigations have excluded prerenal and postrenal causes and suggest a diagnosis of primary renal disease other than ischemic or toxin-related acute renal failure, a kidney biopsy may establish the diagnosis and guide therapy. There have been studies that assessed the value of renal biopsy in patients with atypical features of acute renal failure that suggested pathologic conditions other than tubular necrosis.<sup>57,58</sup> Histologic analysis revealed various conditions including glomerulonephritis, tubulointerstitial nephritis, vascular disease, and tubular necrosis. In a recent prospective study of patients with acute renal failure who underwent kidney biopsy, knowledge of histologic results altered management in nearly three fourths of cases.<sup>59</sup> In renal transplantation, a biopsy may be particularly important in the evaluation of early allograft dysfunction. Management decisions, especially those relating to the use of immunosuppressive agents, depend on accurate assessment of the histopathological findings. Advances in molecular genetics have led to sensitive techniques such as the polymerase chain reaction and *in situ* hybridization that supplement standard histologic and immunofluorescence examinations and may aid in the diagnostic evaluation.<sup>60</sup> The risks of renal biopsy are low. The overall incidence of serious complications (arteriovenous fistula, hematoma, infection, surgery, and death) is less than 1 percent.<sup>61</sup>

#### **PATHOPHYSIOLOGY OF ISCHEMIC ACUTE RENAL FAILURE AND RATIONALE FOR THERAPIES**

We will focus on the pathophysiology of ischemic acute renal failure because prerenal azotemia can be considered a preischemic state and prerenal azotemia and ischemia are common causes of acute renal failure. In addition, toxins that cause tubular necrosis share many pathophysiologic features with ischemic acute renal failure.<sup>62</sup> Structural and biochemical changes in the postischemic kidney that result in vasoconstriction, desquamation of tubular cells, intraluminal tubular obstruction, and transtubular back-leakage of the glomerular filtrate are pathophysiologic mechanisms that have been well characterized.<sup>63</sup> Better understanding of the vascular and cellular mechanisms responsible for the

loss of integrity of the nephrons has led to therapeutic approaches in animals and clinical studies in humans.

#### **Vascular Factors and Therapy with Vasodilators**

Intrarenal vasoconstriction caused by an imbalance between vasoconstrictive and vasodilative factors may result from systemic or local vasoactive agents that act on the small vessels of the kidney. The resulting ischemia can directly alter endothelial-cell function, decreasing the production of and response to vasodilative substances.<sup>64,65</sup> A number of therapeutic agents directed at the alleviation of renal vasoconstriction have been studied. These include dopamine, calcium-channel blockers, and natriuretic peptides; endothelin antagonists have been studied in animals.

##### *Dopamine*

Dopamine dilates renal arterioles and increases renal blood flow and the glomerular filtration rate.<sup>66,67</sup> Dopamine has been administered for both the prevention and treatment of acute renal failure in critically ill patients. Proponents of its use suggest that a trial of low-dose dopamine (0.5 to 2.5  $\mu\text{g}$  per kilogram per minute) can be useful for euvolemic patients with oliguric acute renal failure.<sup>68,69</sup> Clinical studies have not, however, demonstrated the efficacy of this approach,<sup>70,71</sup> and at this time we do not recommend the routine use of dopamine for either prophylaxis or treatment of established acute renal failure. Furthermore, dopamine can cause tachyarrhythmias, pulmonary shunting, and gut or digital necrosis.<sup>72</sup>

##### *Calcium-Channel Blockers*

Because increases in free calcium within vascular smooth-muscle cells enhance vascular tone and contribute to vasoconstriction, calcium-channel blockers have been used as renovascular vasodilators.<sup>63</sup> They may be useful for acute renal failure in selected clinical circumstances. In renal transplantation, calcium antagonists have been shown to reduce the incidence of tubular necrosis and delayed graft function.<sup>73</sup> Furthermore, calcium antagonists may reduce the vasoconstrictive action of cyclosporine.<sup>74</sup> Calcium-channel blockers may also prevent the vasoconstriction associated with radiocontrast agents.<sup>75</sup> Because calcium antagonists may cause hypotension and thereby decrease renal perfusion, however, their use is not justified in most forms of postischemic acute renal failure.

##### *Natriuretic Peptides*

In animals the vasodilative atrial natriuretic peptides can attenuate the severity of renal failure and potentiate the recovery of renal function even when administered after an ischemic insult.<sup>76</sup> In a recent prospective study of ischemic or toxic acute renal failure, renal function continued to improve up to 24 hours after termination of the infusion of atrial natriuretic peptides.<sup>77</sup> Furthermore, the treated group had a reduced requirement for dialysis, as compared with the non-treated group. Prophylaxis with atrial natriuretic peptides, however, has not been demonstrated to have a

beneficial effect in other studies.<sup>78,79</sup> These agents were also found to impair renal function in diabetic patients receiving radiocontrast agents.<sup>80</sup> The role of atrial natriuretic peptides in acute renal failure is currently being evaluated; a preliminary analysis from a multicenter prospective study suggests that these agents may be useful in patients with oliguric acute renal failure.<sup>81</sup>

Other therapeutic approaches to counteract the vasoconstrictive component of acute renal failure will probably be tested in the near future. The renal vasculature is quite sensitive to endothelin, which reduces renal blood flow and the glomerular filtration rate.<sup>82</sup> In animals, the administration of anti-endothelin antibodies or endothelin-receptor antagonists protects the kidney against ischemic acute renal failure.<sup>83,84</sup>

### Medullary Hypoxia

Heterogeneity of intrarenal blood flow contributes to the pathophysiology of ischemic acute renal failure. An imbalance between the vasodilator nitric oxide and the vasoconstrictor endothelin may also impair medullary blood flow and contribute to tubular-cell damage.<sup>84-86</sup> In the outer medulla, where tubules have high oxygen requirements, ischemia causes swelling of tubular and endothelial cells<sup>87</sup> as well as adherence of neutrophils to capillaries and venules. These changes lead to vascular congestion and decreased blood flow,<sup>88</sup> tipping the tenuous balance between oxygenation and energy demand.<sup>62,89</sup> The important role of renal medullary hypoxia, the susceptibility of this particular segment to hypoxic injury, and the various mediators involved in this process have been recently reviewed in the *Journal*.<sup>62</sup>

### Tubular-Cell Injury

A hallmark of ischemic and toxic acute renal failure is injury and death of tubular cells. The pathophysiologic events leading to the death of necrotic tubular cells are complex and incompletely understood. We discuss the major structural and biochemical features believed to be important for necrotic tubular-cell injury and its consequences. Some of the cellular events associated with cell death and the restoration of tubule integrity are shown in Figure 3.

#### Structural Changes

Early morphologic changes observed with ischemia include the formation of blebs in the apical membranes of proximal tubule cells, with loss of the brush border.<sup>90,91</sup> Proximal tubule cells lose their polarity and the integrity of their tight junctions is disrupted,<sup>92</sup> perhaps as a consequence of alterations in the actin and microtubule cytoskeletal networks.<sup>93,94</sup> In addition, the  $\text{Na}^+/\text{K}^+$ -ATPase redistributes from the basolateral to the apical membrane,<sup>95</sup> contributing to a decrease in sodium and sodium-coupled vectorial transport. Integrins are redistributed to the apical surface,<sup>96</sup> and live and dead cells slough into the tubular lumen, contributing to cast formation.<sup>97</sup> The casts then cause increased intratubular pressure and a reduced glomerular filtra-

tion rate. Loss of the epithelial-cell barrier and of the tight junctions between viable cells can result in back-leakage of the glomerular filtrate, further reducing the effective glomerular filtration rate. Arg-Gly-Asp peptides, which are hypothesized to act by preventing adhesion between cells in the tubular lumen, prevent the increase in proximal tubular pressure<sup>96</sup> and mitigate ischemic acute renal failure in animals.<sup>98</sup>

#### Osmotic Agents and Diuretics

Mannitol has been administered to animals and patients with the rationale that preventing cell swelling and increasing intratubular flow might decrease intratubular obstruction and mitigate renal dysfunction. Furosemide and bumetanide have also been used to increase intratubular flow rates. Mannitol and other osmotic agents help preserve transplanted kidneys *ex vivo* and prevent delayed graft function, which is most often caused by ischemia.<sup>99</sup> Mannitol is recommended, along with vigorous volume replacement and sodium bicarbonate, for the prevention and treatment of early myoglobinuric acute renal failure.<sup>30</sup> This agent is also used together with adequate hydration in an attempt to prevent the nephrotoxic effects of cisplatin.

Although mannitol and furosemide have been shown in animals to help protect the kidney against ischemic injury,<sup>87,100,101</sup> most studies in humans have failed to demonstrate the effectiveness of these agents in the prevention or treatment of ischemic or toxic acute renal failure.<sup>71,79,102</sup> Both mannitol and loop diuretics, if administered early in the course of ischemic acute renal failure, can convert an oliguric to a nonoliguric state. Although nonoliguric acute renal failure is generally associated with a lower mortality rate,<sup>43,102,103</sup> there is little evidence that conversion from an oliguric to a nonoliguric state decreases the mortality rate. Patients with a response to diuretics may have less severe renal damage at base line than those with no response. Finally, diuretics can be detrimental in acute renal failure induced by radiocontrast agents.<sup>3,80,104</sup> At this time the use of loop diuretics can only be justified to increase urine output for fluid management, with no expectation that these agents will improve outcome.

#### Biochemical Changes

**Calcium.** Depletion of cellular ATP, which accompanies ischemia, leads to an increase in the cytosolic calcium concentration in cells.<sup>105</sup> In addition to its vasoconstrictive effects, calcium can contribute to epithelial-cell toxicity through its ability to activate proteases and phospholipases, break down the cytoskeleton, and interfere with mitochondrial energy metabolism. Although increases in calcium occur soon after hypoxia in experimental systems,<sup>106</sup> there remains some controversy about the extent to which increased intracellular calcium causes the ischemic tubular-cell injury.<sup>63</sup>

**Reactive oxygen species.** Partially reduced species of oxygen can cause marked tissue injury. With the restoration of oxygen after a period of ischemia there is a rapid burst of oxidant formation. The sources of these oxidants in the kidney include cyclooxygenases, mito-

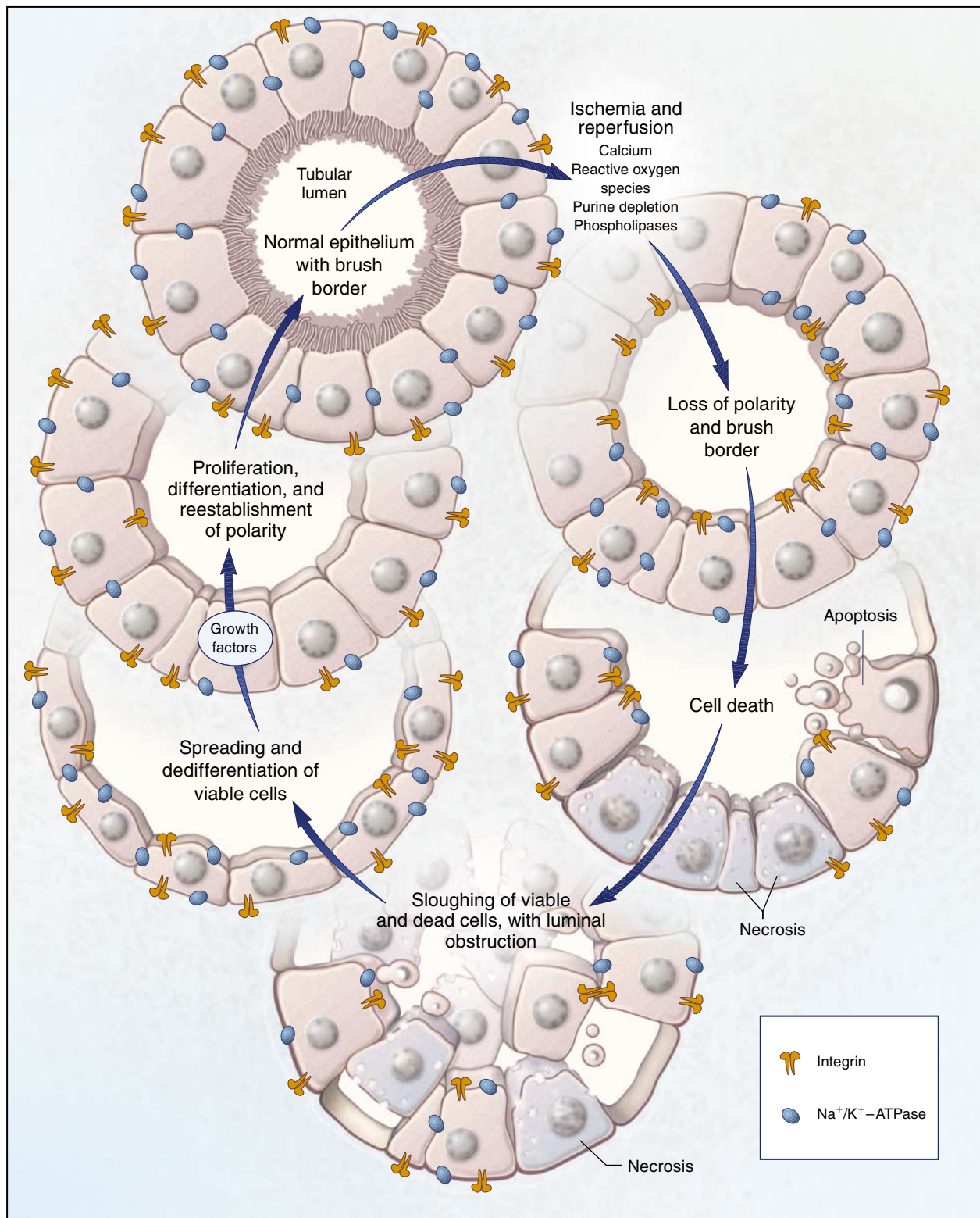


Figure 3. Tubular-Cell Injury and Repair in Ischemic Acute Renal Failure.

After ischemia and reperfusion, morphologic changes occur in the proximal tubules, including loss of the brush border, loss of polarity, and redistribution of integrins and Na<sup>+</sup>/K<sup>+</sup>-ATPase to the apical surface. Calcium, reactive oxygen species, purine depletion, and phospholipases probably have a role in these changes in morphology and polarity as well as in the subsequent cell death that occurs as a result of necrosis and apoptosis. There is a sloughing of viable and nonviable cells into the tubular lumen, resulting in the formation of casts and luminal obstruction and contributing to the reduction in the glomerular filtration rate. The severely damaged kidney can completely restore its structure and function. Spreading and dedifferentiation of viable cells occur during recovery from ischemic acute renal failure, which duplicates aspects of normal renal development. A variety of growth factors probably contribute to the restoration of a normal tubular epithelium.

chondrial electron transport, mixed-function oxidases of the endoplasmic reticulum, the xanthine oxidase system, and neutrophils. The role of reactive oxygen species in ischemic acute renal failure remains in question. Some studies in animals show that antioxidants or scavengers of reactive oxygen species protect against functional tissue damage, whereas other studies do not.<sup>63,107</sup> Currently, there is no compelling evidence to support the use of scavengers of reactive oxygen species in patients with acute renal failure.

**Purine depletion.** Ischemia leads to the breakdown of ATP and the formation of adenosine, inosine, and hypoxanthine, all of which can leak out of cells, constrict intrarenal arterioles, and contribute to the formation of reactive oxygen species.<sup>63</sup> Although in one study ATP and magnesium protected against ischemic injury in rats,<sup>108</sup> other experiments showed that ATP injured oxygenated proximal tubules<sup>109</sup> and was vasoconstrictive.<sup>110</sup>

**Phospholipases.** Phospholipase A<sub>2</sub>, a family of enzymes that hydrolyze phospholipids to free fatty acids and lysophospholipids, can contribute to ischemic cellular injury in various organs.<sup>63</sup> Activated phospholipase A<sub>2</sub> can alter the permeability of cell and mitochondrial membranes, disturbing the bioenergetic capacity of the cell. Peroxidation of membrane lipids due to ischemia and reperfusion enhances the susceptibility of membranes to phospholipase A<sub>2</sub>.<sup>111</sup> In addition, arachidonic acid, a product of phospholipase A<sub>2</sub>, is converted to eicosanoids that are vasoconstrictive and chemotactic for neutrophils.<sup>112</sup> No specific inhibitors of phospholipase A<sub>2</sub> are available for use in humans.

**Apoptosis.** To this point we have focused on processes that contribute to tubular-cell necrosis. Certain types of cell death, however, are finely controlled by active processes. For example, during metamorphosis and embryonic development, apoptosis, or programmed cell death, permits the proper formation of the organism. Pathological evidence of apoptosis has been found in postischemic kidneys in animals<sup>113,114</sup> and in clinical acute renal failure in humans.<sup>63</sup> Apoptosis seems to be particularly prevalent in post-transplantation acute renal failure, where it coexists with necrosis.<sup>115</sup>

### Neutrophils and Reperfusion Injury

The adherence of neutrophils to the vascular endothelium is an essential step in the extravasation of these cells into ischemic tissue.<sup>116,117</sup> Chemotaxis of neutrophils is partly due to the activation of the complement cascade, with local formation of C5a.<sup>118</sup> After adherence and chemotaxis, neutrophils release reactive oxygen species, proteases, elastases, myeloperoxidase, and other enzymes that damage the tissue. These substances, together with leukotriene B<sub>4</sub> and platelet-activating factor, can both increase vascular permeability and up-regulate the expression of adhesion molecules that promote further inflammation.<sup>112,119</sup> In models of renal, myocardial, and intestinal ischemia, the depletion of neutrophils, blockade of neutrophil adhesion to the endothelium, and inhibition of the complement system all reduce tissue injury.<sup>118,120-122</sup>

Intercellular adhesion molecule 1 (ICAM-1) on endo-

thelial cells interacts with CD11a/CD18 and CD11b/CD18 on neutrophils, promoting the adhesion of neutrophils to endothelial cells.<sup>116</sup> The administration of a monoclonal antibody directed against ICAM-1 protects animals from ischemic acute renal failure, even when given two hours after the ischemic event.<sup>123</sup> In addition, mice with a deficiency of ICAM-1 are protected against acute renal failure.<sup>120</sup> Antibodies against ICAM-1 have been administered safely to allograft recipients in a phase I trial.<sup>124</sup>

### Acute Renal Failure in Transplant Recipients

Ischemic injury to an allograft from a cadaveric donor can lead to delayed graft function, which has been associated with acute rejection and decreased graft survival.<sup>125,126</sup> Extensive local release of cytokines, complement activation, and increased expression of MHC class I and II molecules occur as a result of kidney ischemia.<sup>127,128</sup> Furthermore, at the site of ischemia, local production of tumor necrosis factor and complement fragments induces the expression of selectins and ICAM-1 on endothelial cells.<sup>129,130</sup> Preliminary studies with antagonists of platelet-activating factor and antibodies against ICAM-1 suggest that platelet activation and leukocyte-endothelial-cell interactions may be important in early post-transplantation renal failure and rejection in humans.<sup>119,124</sup> In the future, other approaches to decrease ischemic injury and rejection in the allograft may include the use of complement inhibitors,<sup>131</sup> anticytokine agents,<sup>132</sup> or endothelin antagonists.<sup>133</sup>

### Role of Growth Factors in Recovery from Ischemic Acute Renal Failure

In contrast to the heart and brain, where ischemia results in permanent cell loss, the kidney, when severely damaged by ischemia or toxins, can completely restore its structure and function. Increased mitotic activity and epithelial-cell regeneration are characteristic of ischemic acute renal failure in humans. Postischemic recovery duplicates certain aspects of renal development.<sup>134</sup> Proteins normally expressed only in the early phase of nephron development are expressed in the epithelium of the recovering kidney. An understanding of the mechanisms responsible for this pattern of expression may lead to therapies designed to potentiate the regenerative response and reverse functional renal failure rapidly. Epidermal growth factor, hepatocyte growth factor, and insulin-like growth factor I, when administered to animals subjected to renal ischemia, reduce the extent of renal dysfunction and accelerate the recovery of the kidney.<sup>135,136</sup> Administration of thyroid hormone may also be beneficial, inducing the synthesis of epidermal growth factor in the kidney.<sup>137</sup> Clinical trials evaluating the effectiveness of insulin-like growth factor I in ischemic acute renal failure are under way.<sup>138</sup>

## MANAGEMENT OF ACUTE RENAL FAILURE

### General Principles

The initial care of patients with acute renal failure is focused on reversing the underlying cause and correcting fluid and electrolyte imbalances. Fluid manage-



ment is based on careful physical examination and invasive monitoring if appropriate. The decision to administer or remove fluids, however, is often difficult for the clinician, since both strategies can have detrimental consequences if pursued inappropriately. Although restoration of renal blood flow with intravenous volume resuscitation is ineffective in restoring renal function once tubular necrosis is established, volume replacement remains our most effective prophylactic strategy.<sup>71</sup>

Every effort should be made to prevent further kid-

ney injury and provide supportive measures until recovery has occurred. Nephrotoxins should be discontinued or avoided. Hyperkalemia can be treated with binding resins, glucose and insulin, correction of acidosis, and when refractory to treatment or life-threatening, dialysis. If metabolic acidosis is due to renal dysfunction, the administration of sodium bicarbonate may be appropriate. The doses of medications that are eliminated by the kidney or by dialysis should be adjusted. Anemia often results from phlebotomy, decreased production of erythropoietin, and a uremia-induced decrease in red-

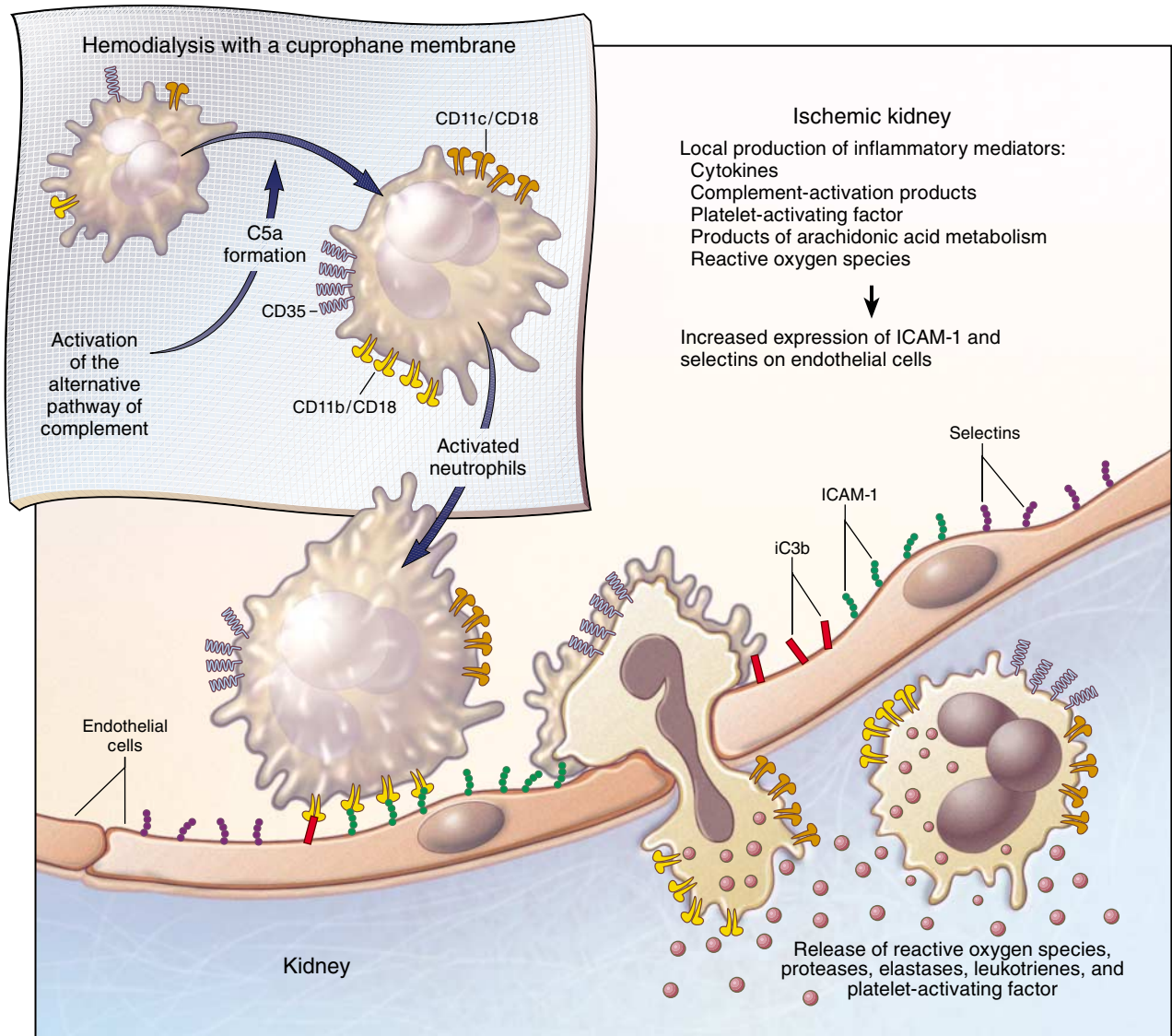


Figure 4. Possible Role of Neutrophil Activation by Dialysis Membranes in Ischemic Acute Renal Failure.

In the ischemic kidney, local production of inflammatory mediators is associated with increased expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and P- and E-selectins, on endothelial cells and increased production of counterreceptors on leukocytes. Interactions between leukocytes and endothelial cells may lead to the obstruction of small vessels, and extravasation of neutrophils may aggravate tissue damage in the postischemic kidney. Furthermore, when blood comes in contact with a foreign material (such as cuprophane membranes during hemodialysis), the complement system is activated by the alternative pathway, which leads to the release of biologically active fragments (e.g., the anaphylatoxins C3a and C5a). In particular, C5a-induced stimulation of neutrophils results in increased expression of various receptors, such as CD11b/CD18, which bind to ICAM-1 and to the inactivated complement fragment iC3b on endothelial cells. Similar interactions between leukocytes and endothelial cells potentiating kidney ischemia may occur in sepsis.

cell survival. Uremia also causes platelet dysfunction, which predisposes patients to bleeding. Bleeding disorders can be treated with packed red cells, vasopressin analogues, estrogens, and dialysis; however, the effectiveness of these interventions varies. Because the most common cause of death in acute renal failure is sepsis, considerable effort should be directed toward preventing and treating infectious complications.

### Replacement Therapy

For the past four decades intermittent hemodialysis has remained the standard replacement therapy for severe acute renal failure. Common indications for acute dialysis include volume overload, hyperkalemia, metabolic acidosis, and symptoms and signs of severe uremia. In recent years continuously administered (venovenous and arteriovenous) therapies have emerged as yet another type of replacement therapy in critically ill patients with renal failure.<sup>139</sup> The advantages of continuous over intermittent dialysis include more precise fluid and metabolic control, decreased hemodynamic instability, and (in patients with sepsis or multiorgan failure) an enhanced possibility of removing injurious cytokines.<sup>140,141</sup> Another possible advantage of continuous-replacement therapies is the associated ability to administer unlimited nutritional support.<sup>140,142</sup> The benefits and complications of parenteral nutrition in patients with acute renal failure have recently been reviewed.<sup>142</sup> The drawbacks of continuous therapies include the need for both prolonged anticoagulation and nearly constant and sophisticated surveillance. Peritoneal dialysis is also effective in acute renal failure for patients with hemodynamic instability or when technical support is scarce.<sup>143</sup> The cost effectiveness of the various replacement therapies in critically ill patients remains to be determined. Randomized studies are ongoing to determine whether continuous-replacement therapies improve the recovery of renal function and offer a survival advantage over intermittent therapies.<sup>140</sup> At present, the choice of one therapy over the other is often based on individual preferences, the availability of local resources, and the hemodynamic stability of the patient.

Whether the choice of the dialysis membrane has an effect on morbidity and mortality in acute renal failure remains a matter of debate among nephrologists. Although cuprophane (cellulose-based) membranes have been used since the 1960s, their interaction with blood leads to an intense activation of the alternative pathway of complement.<sup>144</sup> Activation of complement is associated with an up-regulation of certain leukocyte-adhesion molecules, which are responsible for pulmonary sequestration of leukocytes, hypoxemia, and transient neutropenia.<sup>145,146</sup> Studies in animals suggest that neutrophils activated by cuprophane may preferentially localize in the ischemic kidney and aggravate tissue damage (Fig. 4). Furthermore, in animals exposed to cuprophane, resolution of ischemic acute renal failure is slower than in controls or animals exposed to polyacrylonitrile membranes.<sup>147</sup> Synthetic membranes (such as those made of polymethylmethacrylate, polyacrylonitrile,

polysulfone, and other materials) activate complement to a lesser extent than cuprophane membranes; however, they may also activate other humoral pathways and cellular elements.<sup>148-150</sup> In three recent prospective, randomized clinical trials of patients with renal failure, intermittent hemodialysis with biocompatible membranes (either polyacrylonitrile or polymethylmethacrylate) as compared with cuprophane membranes improved the recovery of renal function and reduced the mortality rate.<sup>50,52,151</sup> These studies suggest that in patients with acute renal failure who require dialysis, biocompatible membranes should be used.

There is no consensus among nephrologists as to when to begin dialysis or how frequently to perform dialysis. Although studies that evaluated early and intensive dialysis suggested that such an approach improved survival and led to a more rapid recovery, most of these studies included patients with mild acute renal failure and retrospectively selected control groups.<sup>71</sup> In one prospective, controlled study, intensive dialysis did not improve recovery or survival.<sup>152</sup> It remains to be determined whether early and frequent dialysis with certain biocompatible membranes will increase the survival of patients with acute renal failure, particularly those with sepsis.<sup>153</sup>

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