

Chronic Renal Insufficiency

A Diagnostic and Therapeutic Approach

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Chronic renal insufficiency ultimately culminating in end-stage renal disease requiring dialysis or transplantation is a major health problem in the United States. The first task confronting the physician caring for a patient with renal disease is to decide whether the renal insufficiency is acute or chronic. The initial differential diagnostic approach to chronic renal insufficiency consists of determining whether the patient has glomerular disease or interstitial or vascular disease on the basis of a careful history taking, urinalysis, and measurement of 24-hour protein excretion. Further refinement of diagnostic considerations often requires serologic studies, renal biopsy, or imaging the urinary tract with ultrasonography or computed tomography. Management considerations begin with the identification and correction of any acute reversible causes of renal insufficiency in patients with chronic renal disease. Recent studies have shown that effective antihypertensive therapy, especially with angiotensin-converting enzyme inhibitors, restriction of dietary protein, and excellent glycemic control in patients with diabetes, can retard the progression of chronic renal disease. Once these therapeutic strategies are in place, it is important to anticipate and treat the multiple manifestations of chronic progressive renal insufficiency: fluid overload, hyperkalemia, metabolic acidosis, abnormalities of calcium, phosphorus, and vitamin D metabolism, and anemia. *Arch Intern Med.* 1998;158:1743-1752

Chronic renal failure (CRF) is a significant cause of morbidity and mortality in the United States. Currently more than 170 000 patients receive maintenance dialysis and approximately 60 000 patients have functioning kidney transplants.¹ The incidence of end-stage renal disease (ESRD) has increased steadily over the last decade; in 1993, the adjusted incidence rate of treated ESRD was 210 per million population per year, yielding a growth rate of 7.5% per year since 1984.¹ Treatment for ESRD costs approximately \$9.5 billion per year and represents a significant financial burden to the health care system.¹ Diabetes, hypertension, and chronic

glomerulonephritis are the most common causes of ESRD responsible for 37%, 30%, and 12%, respectively, of incident cases of ESRD. Cystic kidney diseases, interstitial nephritis, obstructive nephropathy, and other causes account for the remaining cases of ESRD.¹

Optimal management of patients with chronic renal insufficiency requires initial nephrologic consultation. However, prior to the development of ESRD, many patients with mild to moderate renal insufficiency receive the majority of their medical care from primary care physicians rather than nephrologists. Thus, a sound understanding of the pathophysiological features and clinical manifestations of CRF is essential to treat patients with declining renal function. This review summarizes key concepts in the di-

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Table 1. Diagnostic Approach to Chronic Renal Insufficiency

Glomerular Disease	Interstitial or Vascular Disease
Diagnostic features: red blood cell casts, >3.5 g of protein excretion, or systemic disease associated with a glomerulopathy	Diagnostic features: bland urinalysis, <2-3 g of protein excretion, no systemic disease associated with a glomerulopathy
Primary	Anatomical abnormalities
Focal glomerulosclerosis	Obstructive nephropathy
Membranous nephropathy	Polycystic kidney disease
Membranoproliferative glomerulonephritis	Hypertensive nephrosclerosis
Secondary	Analgesic abuse
Diabetic nephropathy	Nephrolithiasis
Lupus nephritis	Idiopathic
Amyloidosis	Ischemic nephropathy

agnosis and treatment of pre-end-stage chronic renal insufficiency and provides practical guidelines for management.

MEASUREMENT OF RENAL FUNCTION

Measurement of glomerular filtration rate (GFR) either by inulin or iodine I 125-iodothalamate clearance has been the criterion standard for estimation of renal function.² However, these techniques are cumbersome to perform on a routine basis and, hence, limited to research protocols. In clinical practice, determinations of serum creatinine, creatinine clearance, and the reciprocal of the serum creatinine are commonly used for diagnosis of renal dysfunction and monitoring progression of renal disease. Factors other than GFR, including generation, tubular secretion, and extrarenal elimination of creatinine, affect serum creatinine concentration. Therefore, these determinations may not always be accurate estimates of renal function, especially in patients with mild renal insufficiency.³ While the slope of the reciprocal of serum creatinine vs time has been advocated to monitor the rate of progression of chronic renal disease,⁴ the occurrence of spontaneous break points in the slope, with improvement, stabilization, or accelerated decline in renal function, limits the use of this technique.⁵ Furthermore, drugs such as trimethoprim and cimetidine inhibit tubular secretion of creatinine and can increase serum creatinine levels,^{6,7} especially in patients with moderate to severe renal dysfunction.⁸

Consequently, although measurement of serum creatinine and creatinine clearance are the only practical clinical methods to follow renal function, the potential limitations of these techniques should be recognized.

ACUTE VS CHRONIC RENAL FAILURE

The initial diagnostic challenge in evaluating a patient with an elevated serum creatinine level is to determine whether the renal dysfunction is acute or chronic. In most cases, previous serum creatinine measurements will clarify the issue. Under some circumstances, however, these data are not available and the physician must depend on clinical evaluation, laboratory studies, and radiological features to make this important distinction.

Patients with acute renal insufficiency usually have a readily identifiable precipitating event such as volume depletion, urinary tract obstruction, or the administration of potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] or angiotensin-converting enzyme [ACE] inhibitors) temporally related to the increment in serum creatinine level. Moreover, individuals with acute renal insufficiency tend to be more symptomatic at any given level of renal dysfunction compared with patients with CRF. Moderate to severe anemia, hypocalcemia, and hyperphosphatemia are frequent accompaniments of CRF whereas these hematologic and biochemical abnormalities are less marked in acute

renal failure. Ultrasonographic determination of renal size is helpful in distinguishing acute from chronic renal insufficiency; while renal size can be normal in both acute and chronic renal disease, the presence of bilaterally small kidneys is diagnostic of chronic irreversible renal insufficiency.⁹ Hence, a combination of previous measurements of renal function, careful clinical evaluation, and selected laboratory and radiological studies generally permit the physician to establish the diagnosis of chronic renal disease with confidence.

ETIOLOGY OF CRF

From an etiologic perspective, chronic renal insufficiency can be broadly divided into glomerular disease and interstitial or vascular disease (**Table 1**). This distinction is usually made on the basis of several laboratory and clinical features. The presence of red blood cell casts on urinalysis, proteinuria of more than 3.5 g/24 h, or a systemic disease strongly associated with a glomerulopathy (eg, diabetes or lupus erythematosus) is highly suggestive of underlying glomerular disease.⁹ In contrast, patients who lack a systemic illness associated with a glomerulopathy have bland urinalysis findings and exhibit protein excretion of less than 2 to 3 g/24 h are likely to have interstitial disease⁹ or ischemic nephropathy.

Definitive diagnosis of nondiabetic glomerular disease usually requires a kidney biopsy. Although a variety of serologic studies (eg, complement levels or antinuclear antibody) can be obtained, they usually do not circumvent the need for a biopsy if a precise diagnosis is required. On the other hand, a reliable clinical diagnosis of diabetic nephropathy can be made in the presence of the proper duration of diabetes (7-8 years in type 2 diabetes mellitus or 12-15 years in type 1 diabetes mellitus), coexistent diabetic retinopathy, and nephrotic range proteinuria.¹⁰⁻¹² Chronic interstitial nephritis, however, can have similar histological findings regardless of cause.⁹ Therefore, establishing a specific diagnosis in patients with chronic interstitial nephritis requires knowl-

edge of the common diseases associated with chronic interstitial injury (Table 1), relevant historical data, and renal imaging studies. A careful history of analgesic ingestion should be obtained to exclude the possibility of analgesic nephropathy.¹³ Hypertensive nephrosclerosis is a common cause of chronic interstitial nephritis, particularly in African Americans. The diagnosis is likely in the presence of a long history of hypertension, especially if blood pressure has been poorly controlled, in association with nonnephrotic-range proteinuria.¹⁴⁻¹⁷ Obstructive nephropathy, polycystic kidney disease, and stone disease can be excluded by ultrasonography or computed tomography. Ischemic renal disease should be suspected in patients with a significant history of cigarette smoking who demonstrate clinical evidence of extrarenal vascular disease¹⁸ and have asymmetrical kidneys on renal ultrasonography.

MANAGEMENT OF CRF

The management of patients with chronic renal insufficiency has several components. First, the physician must identify and correct reversible causes of acute decrements in GFR superimposed on chronic renal disease. Second, in the absence of specific therapeutic maneuvers to stabilize or improve renal function, non-specific measures should be used to ameliorate the progression of renal disease. Third, the multiple clinical manifestations of progressive renal insufficiency should be recognized and treated. Finally, as renal failure progresses, patient education and planning regarding initiation of renal replacement therapy should be done well in advance to ensure a smooth transition to ESRD.

IDENTIFICATION AND TREATMENT OF REVERSIBLE DECREASES IN RENAL FUNCTION

Patients with chronic renal insufficiency of any cause are prone to develop further acute decrements in renal function under a variety of circumstances. Disturbed autoregulation of renal blood flow (RBF) and increased sensitivity to the nephro-

toxic effects of various pharmacological agents account for this enhanced susceptibility. Factors most frequently responsible for acute declines in renal function in patients with CRF are volume depletion; congestive heart failure; urinary tract obstruction; accelerated hypertension; nephrotoxic drugs (eg, aminoglycoside antibiotics or NSAIDs); radiocontrast media; and ischemic nephropathy.

Volume Depletion

The normal kidney maintains a relatively constant RBF and GFR across a broad range of mean arterial pressure (80-180 mm Hg) by modulation of afferent arteriolar tone. However, in the presence of diabetes, hypertension, or reduced renal mass, autoregulation of RBF is impaired.¹⁹⁻²¹ Consequently, if systemic blood pressure decreases, the afferent arteriole cannot dilate appropriately, leading to an acute decline in GFR. In addition, patients with chronic renal disease have limited ability to abruptly curtail sodium excretion in the face of extrarenal volume depletion, thus potentially exacerbating the salt loss.²²

Volume deficits are often precipitated by gastrointestinal losses (eg, vomiting or diarrhea), excessive dietary sodium restriction, or overzealous diuretic administration. In severe cases, volume-depleted patients manifest weight loss, orthostatic changes in pulse and blood pressure, dry mucous membranes, and poor skin turgor. Under these circumstances, prompt identification of the source of volume depletion and correction of volume deficits generally stabilizes and improves renal function. Not infrequently, however, the diagnosis is more challenging and the clinical evidence of volume depletion is subtler. Under the latter circumstances, a cautious trial of volume repletion (eg, reducing the dose of diuretics or increasing dietary sodium) often establishes the diagnosis and restores renal function to baseline.

Congestive Heart Failure

The low cardiac output in patients with congestive heart failure reduces RBF and GFR.²³ In addition, activation of several neurohumoral

systems, including the renin angiotensin axis and the sympathetic nervous system,²⁴ causes intrarenal vasoconstriction further decreasing renal function. In the setting of an already limited ability to excrete salt and water, this additional constraint on sodium excretion can precipitate volume overload and pulmonary edema.

Since thiazide diuretics are usually ineffective at creatinine clearances less than 0.50 mL/s,²⁵ loop diuretics are the mainstay of management of patients with congestive heart failure and chronic renal insufficiency. Chronic administration of loop diuretics to patients with congestive heart failure decreases afterload and increases cardiac output.²⁶ Although ACE inhibitors reduce morbidity and mortality in patients with congestive heart failure and normal renal function, their routine application in patients with renal insufficiency and impaired systolic function should be considered carefully. As renal function declines, the beneficial hemodynamic and clinical effects of ACE inhibition are progressively attenuated.²⁷ Furthermore, ACE inhibitors can cause acute decreases in GFR in patients with chronic renal insufficiency.²⁸ Hence, if ACE inhibitors are used to treat systolic dysfunction in patients with underlying renal disease, the patients should be closely monitored for hypotension, worsening renal function, and hyperkalemia. Digitalis glycosides usually are not required; they are of marginal therapeutic benefit in this patient population and can impair extrarenal potassium homeostasis.^{29,30}

Urinary Tract Obstruction

The most common cause of obstructive nephropathy, particularly in elderly men, is prostatic hypertrophy. Other causes include renal papillary necrosis, stones, pelvic malignancy, retroperitoneal fibrosis, or neurogenic bladder.³¹ The effects of urinary tract obstruction on renal function are diverse and include marked reduction in RBF and GFR and significant defects in tubular reabsorption of water and solute.³² Ultrasonographic evaluation is the diagnostic modality of choice³³ and prompt uro-

logic consultation should be sought if obstruction is detected.

Accelerated Hypertension

Malignant hypertension generally presents with severe elevations in diastolic pressure (usually >140 mm Hg) associated with evidence of vascular damage as manifested by retinal hemorrhages, exudates, or papilledema. Renal parenchymal disease is the most common cause of malignant hypertension³⁴ and a further acute chronic decline in renal function can occur because of myointimal proliferation and fibrinoid necrosis of the renal vascular bed.³⁴ Although reduction of blood pressure in these circumstances often causes a further transient decline in renal function attributable to impaired autoregulation of RBF,^{19,21} continued good blood pressure control can improve renal function in the long-term.³⁵ In fact, some patients who require dialytic support have been able to discontinue dialysis with adequate blood pressure control.³⁶ The initial goal of therapy should be to decrease blood pressure to 160 to 170/100 mm Hg over 24 to 48 hours with a subsequent reduction to normotensive levels over days to weeks.

Drugs

Patients with chronic renal insufficiency are at increased risk compared with subjects with normal renal function to develop drug-induced acute renal dysfunction. In this regard, aminoglycosides are an important cause of acute on chronic renal insufficiency. Aminoglycoside nephrotoxicity typically presents as nonoliguric acute renal failure 7 to 10 days after initiation of therapy. Risk factors for aminoglycoside nephrotoxicity include advanced age, prolonged duration of therapy, frequent dosing intervals, greater total aminoglycoside dose, liver disease, the presence of hypotension, hypovolemia, or shock, and chronic renal insufficiency.³⁷⁻³⁹ Although a once-daily regimen may be less nephrotoxic than multiple daily doses in patients with normal renal function,⁴⁰ similar data are not available in patients with chronic renal

insufficiency. Hence, aminoglycoside therapy should be administered cautiously to patients with chronic renal insufficiency, and renal function and serum drug levels should be monitored frequently.

Nonsteroidal anti-inflammatory drugs have been associated with multiple renal complications including acute reversible vasomotor renal failure, hyperkalemia, salt and water retention, acute interstitial nephritis and nephrotic syndrome, and interstitial nephritis with varying degrees of renal insufficiency.⁴¹ Acute vasomotor renal failure precipitated by NSAIDs usually occurs in the presence of chronic renal insufficiency, concomitant diuretic therapy, volume depletion, congestive heart failure, cirrhosis, nephrotic syndrome, or advanced age.^{41,42} Most of these pathophysiological circumstances are associated with increased production of vasoconstrictor compounds including angiotensin II, catecholamines, and vasopressin. These hormones not only decrease RBF and GFR but also simultaneously increase the synthesis of vasodilator prostaglandins in the kidney that attenuate the vasoconstrictor-induced reduction in RBF and GFR.⁴³ Administration of NSAIDs inhibits the synthesis of vasodilator prostaglandins and, hence, results in unopposed intrarenal vasoconstriction with a consequent decline in GFR. Some reports^{44,45} suggest that sulindac and piroxicam may be less nephrotoxic than other agents. Nevertheless, the use of NSAIDs should be avoided if possible, or minimized in patients with chronic renal insufficiency. If NSAIDs are required in patients with CRF, renal function should be carefully monitored.

Contrast Media

Radiopaque contrast agents are a frequent cause of nephrotoxic effects in patients with chronic renal insufficiency. Diabetes, preexisting renal insufficiency, and the volume of contrast administered are the major risk factors for development of contrast nephropathy.⁴⁶⁻⁴⁸ Contrast media-induced acute renal failure generally occurs within 24 to 48 hours of the dye administration.⁴⁹ The

clinical course is typical with peak serum creatinine concentration developing after 5 to 7 days and usually returning to baseline in 10 to 14 days.⁴⁹ However, a significant proportion of patients with a baseline serum creatinine concentration higher than 442 $\mu\text{mol/L}$ (5 mg/dL) may require temporary or permanent dialysis.^{48,50} Hydration with 0.45% normal saline solution before, during, and after the procedure, and use of non-ionic contrast media in patients with preexisting renal dysfunction, especially diabetic nephropathy,⁵¹ can minimize the risk of radiocontrast nephropathy.⁵²

Ischemic Renal Disease

Ischemic renal disease, defined as a clinically significant reduction in GFR in patients with hemodynamically significant obstruction to RBF,⁵³ is a more common cause of renal dysfunction than previously estimated.^{18,54} Clinical features indicative of ischemic renal disease include significant increments in serum creatinine associated with antihypertensive therapy, especially ACE inhibitors,⁵⁵ progressive azotemia in patients with refractory hypertension, and unexplained renal dysfunction in elderly patients with extrarenal vascular disease.⁵³ Recurrent pulmonary edema, poorly controlled hypertension, and renal insufficiency comprise a characteristic triad suggestive of ischemic renal disease.^{56,57} Ischemic nephropathy frequently progresses,⁵⁸⁻⁶⁰ often to total bilateral renal artery occlusion, and may account for 5% to 15% of all patients developing ESRD.^{18,54} Revascularization by angioplasty or surgery can improve renal function, control blood pressure, and eliminate recurrent episodes of pulmonary edema.^{56,57,61,62}

SLOWING THE PROGRESSION OF RENAL DISEASE

In most forms of chronic renal insufficiency, once GFR is reduced to 0.42 to 0.5 mL/s, renal function declines inexorably regardless of the primary insult.^{63,64} While multiple factors such as intraglomerular coagulation, abnormal calcium and

phosphorus metabolism, and hyperlipidemia have been implicated in the progression of experimental renal disease,⁶⁴ their clinical relevance remains to be established. On the other hand, systemic hypertension,^{65,66} dietary protein intake,⁶⁷ and glycemic control in patients with diabetes⁶⁸ play significant roles in the progression of human renal disease. A National Institutes of Health workshop group⁶⁹ has recently summarized recommendations for prevention of progression in chronic renal disease.

Control of Blood Pressure

Hypertension is an important manifestation of chronic renal disease and increases in prevalence as renal function declines.⁷⁰ Systemic hypertension can have a deleterious effect on renal function in 2 ways. First, it may be the primary factor initiating renal dysfunction in patients with hypertensive nephrosclerosis.¹⁴ Second, poorly controlled blood pressure accelerates progression of both diabetic and nondiabetic renal disease.^{70,71} The adverse effect of elevated blood pressure on renal function may be mediated by increased intraglomerular pressure^{63,72} or glomerular hypertrophy⁷³ or both, leading to progressive glomerular sclerosis and renal dysfunction.

The beneficial effects of blood pressure reduction to decrease cardiovascular morbidity and mortality are well established. In addition, numerous prospective trials⁷⁴⁻⁷⁶ have shown that excellent blood pressure control can ameliorate the progression of renal disease. The available data indicate that control of hypertension to 130/80 to 85 mm Hg should be a minimum goal in patients with chronic renal insufficiency.⁶⁹ Furthermore, a secondary analysis of the recently concluded Modification of Diet in Renal Disease Study⁷⁵ suggests that patients with proteinuria (>1 g/24 h) may benefit from reduction of blood pressure to a goal of less than 125/75 mm Hg. Several classes of drugs can be used to control blood pressure in patients with chronic renal insufficiency. Due to their ability to inhibit the proliferative and intra-

renal hemodynamic effects of angiotensin II, ACE inhibitors are generally considered to be more renoprotective than other antihypertensive agents.⁶⁹ However, the ongoing African American Study of Kidney Disease and Hypertension⁷⁷ should provide comparative data about several different classes of antihypertensive agents with regard to preservation of renal function in hypertensive renal disease.

Restriction of Dietary Protein

In experimental renal disease, dietary protein restriction decreases intraglomerular pressure and retards the decline of renal function.^{78,79} Clinical trials of protein restriction in humans, however, have yielded variable results. Some studies^{80,81} have shown no benefit with regard to the rate of loss of renal function, while others⁸²⁻⁸⁴ have found that progression of renal disease is ameliorated by a low-protein diet. The Modification of Diet in Renal Disease Study⁸⁵ was the largest prospective trial examining this issue, but after a mean follow-up of 2.2 years it was not able to show a statistically significant benefit of a low-protein diet (0.58 g/kg per day) or a very low-protein diet (0.28 g/kg per day), supplemented with keto acids, compared with a usual-protein diet (1.3 g/kg per day) in retarding the progression of renal disease. However, after an initial decline in GFR that may have been hemodynamically mediated, the low-protein group demonstrated a slower decline in renal function compared with the usual-protein group. No significant adverse effects of protein restriction were noted.

In patients with moderate loss of renal function (GFR, 25-55 mL/min per 1.73 m²), the National Institutes of Health workshop group⁶⁹ recommends a standard protein intake (>0.8 g/kg per day). If there is evidence of progression of renal insufficiency or development of uremic symptoms, an intake of 0.8 g of protein per kilogram per day may be appropriate. For patients with more severe renal dysfunction (GFR, 13-25 mL/min per 1.73 m²), a diet containing 0.6 g of protein per ki-

logram per day is recommended. Hence, dietary protein restriction can be an important therapeutic modality to slow the progression of renal disease, especially in normotensive patients with nondiabetic renal disease. However, because some patients with chronic progressive renal insufficiency spontaneously reduce dietary protein intake and develop other indexes of malnutrition,⁸⁶ implementation of such a diet should be done under the auspices of a renal dietician and with a dequate long-term nutritional counseling.

Control of Blood Glucose

Diabetic nephropathy develops in 30% to 40% of patients with type 1 diabetes mellitus and 10% to 20% of patients with type 2 diabetes mellitus.⁸⁷⁻⁸⁹ A genetic predisposition to hypertension,^{90,91} poor glycemic control,⁹⁰ and an increased GFR⁹² are risk factors for the development of diabetic nephropathy. Microalbuminuria (30-300 mg/d or 20-200 µg/min) is a good marker of early nephropathy and identifies patients at high risk for development of other microvascular and macrovascular complications.⁹³ Therefore, patients with type 1 diabetes mellitus for more than 5 to 10 years and/or a family history of renal disease or hypertension should be screened annually for microalbuminuria.⁶⁹ Recent studies^{68,94} have confirmed that excellent control of blood glucose in type 1 diabetes mellitus (preprandial glucose, 3.8-6.6 mmol/L [70-120 mg/dL]; hemoglobin A_{1c}, <0.07) prevents or delays development of long-term complications. Consequently, the goal should be to maintain the blood glucose within or close to normal range while minimizing hypoglycemic attacks.⁶⁹ Because ACE inhibitors have been shown to delay progression of renal disease in type 1 diabetes mellitus compared with conventional antihypertensive therapy (exclusive of calcium channel blockers),^{95,96} they are the preferred antihypertensive drugs in hypertensive patients with diabetes, especially those with persistent microalbuminuria or overt proteinuria.^{69,97} Despite the fact that most

Table 2. Clinical Manifestations of Chronic Renal Insufficiency

Cardiovascular	Hematologic
Fluid overload	Anemia
Hypertension	Platelet dysfunction
Electrolyte and acid-base levels	Neurologic
Hyperkalemia	Peripheral neuropathy
Metabolic acidosis	Encephalopathy
Endocrine	Rheumatologic
Calcium, phosphorus, vitamin D abnormalities	Crystal-induced arthritis
Gonadal dysfunction	Amyloid deposition

of the data and recommendations in the literature relate to type 1 diabetes mellitus, it is reasonable for the clinician to plan a similar regimen of good glycemic and blood pressure control, along with ACE inhibition, in patients with type 2 diabetes mellitus provided no contraindications exist.⁶⁹

MANIFESTATIONS AND TREATMENT OF CRF

Chronic progressive renal insufficiency results in multiple clinical manifestations involving several organ systems. Some of the more prominent features are shown in **Table 2**. As renal function decreases, the clinical manifestations increase in severity and prevalence. Whereas fluid overload and hypertension can occur with mild renal dysfunction, hyperkalemia, abnormalities of calcium and phosphorus metabolism, acidosis, and anemia develop with moderate to severe renal failure. All of these consequences occur in patients with ESRD.

Fluid Overload

The ability of patients with CRF to excrete salt and water is limited not only because of a decrease in GFR but also because of the activation of various salt-retaining neurohumoral stimuli (eg, angiotensin II, aldosterone, and the sympathetic nervous system).⁷⁰ Hence, as renal insufficiency advances, dietary intake of sodium should be restricted to 80 to 90 mmol/d particularly if patients are hypertensive. Diuretic therapy eventually is necessary in most patients with progressive renal dysfunction to maintain salt and water balance. In patients with a GFR of less than 0.42 to 0.33 mL/s,

thiazide diuretics are generally ineffective^{25,98} and high doses of loop diuretics in a twice-daily regimen are required to achieve adequate natriuresis. However, administration of thiazides in addition to loop diuretics can result in a marked natriuresis even in patients with advanced renal failure.⁹⁹ In patients resistant to high doses of oral diuretics or in those requiring acute diuresis, parenteral administration is often necessary. In this regard, a continuous infusion of a loop-blocking diuretic is more effective than administration of repeated boluses.¹⁰⁰

Hypertension

Abnormal salt metabolism is a central factor in the development of hypertension in patients with CRF. In addition, other vasoconstrictor stimuli (eg, angiotensin II or sympathetic nervous system) that also limit sodium excretion play important roles in the development and maintenance of high blood pressure in these patients.¹⁰¹ Hence, salt restriction and diuretic therapy are essential for adequate control of blood pressure and form the cornerstone of treatment. Most patients, however, require additional antihypertensive drug therapy. Although multiple classes of antihypertensive agents are available, we prefer calcium channel blockers, ACE inhibitors, and centrally acting sympatholytics because they are effective and rational from a pathophysiological perspective. Calcium channel blockers and ACE inhibitors reduce blood pressure in patients with renal insufficiency and probably exert a beneficial renoprotective effect.^{74,102-105} In addition, calcium channel blockers are also effective at extremes of dietary salt

intake.¹⁰⁵ Finally, centrally acting agents such as clonidine inhibit the central sympathetic outflow that is increased in hypertensive patients with chronic renal disease¹⁰⁶ and are effective antihypertensive agents. Whichever antihypertensive regimen is selected, reduction of blood pressure to 130/80 to 85 mm Hg should be the goal.

Accumulating data indicate that both ACE inhibitors and calcium channel antagonists slow the rate of progression of renal disease to a greater extent compared with other classes of antihypertensive agents.^{74,95,102-105,107-117} In patients with diabetic nephropathy, multiple studies have demonstrated that ACE inhibition reduces proteinuria^{96,117,118} and retards the progression of renal disease^{95,97,107,119,120} compared with noncalcium channel blocker-based conventional antihypertensive therapy. While no large-scale trials comparing the renoprotective effects of ACE inhibition with calcium channel blockade in diabetic nephropathy have been published, 2 recent small studies have shown similar effects of both classes of drugs with regard to urinary albumin excretion and GFR after 1¹¹² and 3¹¹³ years of treatment. In nondiabetic kidney disease, similar data are emerging. A recent meta-analysis of randomized trials¹⁰⁷ found that 5 of 8 studies comparing ACE inhibition with noncalcium channel blocker antihypertensive therapy demonstrated slower progression of renal disease in the group that received ACE inhibitors. A recent Italian multicenter trial¹¹⁶ confirmed these findings. However, the 2 long-term prospective studies^{74,107} comparing ACE inhibition with calcium channel blockade found that both retarded the decline in renal function to a similar extent. Taken together, these observations indicate that both classes of drugs are similarly effective in ameliorating the progression of renal disease and that therapy with either is superior to alternative antihypertensive regimens in slowing the decline in renal function. Whether this beneficial effect is the result of greater antihypertensive efficacy^{74,107,111} or intrinsic renoprotective properties^{109,110} remains to be determined.

Hyperkalemia

Although most patients with chronic renal insufficiency can maintain potassium homeostasis until creatinine clearance is 0.25 to 0.33 mL/s,¹²¹ several factors (**Table 3**) predispose to the development of hyperkalemia with lesser degrees of renal dysfunction. Multiple drugs such as ACE inhibitors, NSAIDs, potassium-sparing diuretics, nonselective β -blockers, and digitalis can precipitate hyperkalemia in patients with underlying renal insufficiency.¹²² Patients with diabetic nephropathy are especially prone to develop hyperkalemia because of type IV renal tubular acidosis and because of impaired cellular potassium uptake consequent to insulin deficiency.¹²³ Dietary intake of potassium should be limited to 60 mmol/d to minimize the development of hyperkalemia, and salt substitutes should be avoided. Occasionally, treatment with sodium-potassium exchange resins such as sodium polystyrene sulfonate is required to control hyperkalemia as patients approach ESRD.

Calcium, Phosphorus, and Vitamin D Abnormalities

Renal osteodystrophy is frequently seen in CRF and is characterized by varying amounts of osteitis fibrosa cystica, osteomalacia, and adynamic bone disease.¹²⁴ Hyperphosphatemia due to the decrease in GFR and reduced renal synthesis of 1,25-dihydroxy D₃ results in low serum calcium levels and secondary hyperparathyroidism.¹²⁵ Elevated parathyroid hormone concentrations cause mobilization of calcium from bone eventually leading to osteitis fibrosa cystica. Complex interactions of hyperparathyroidism, 1,25-dihydroxy D₃ deficiency, aluminum intoxication, local cytokines, β_2 -microglobulin, and associated gonadal dysfunction ultimately determine the development of 1 of the above 3 lesions.¹²⁴ Although a bone biopsy is required to make a definitive histological diagnosis, most clinicians rely on serum concentrations of calcium, phosphorus, parathyroid hormone, aluminum, and alkaline phosphatase to guide therapy.

The goals of management of renal osteodystrophy should be to

maintain calcium and phosphorus levels within normal limits and parathyroid hormone at 2 to 3 times the upper limit of normal. In addition to a low-phosphate diet, a calcium-based phosphate binder (calcium acetate or carbonate) is usually required. The starting dose of calcium carbonate of 0.5 g with each meal can be increased until the serum phosphorus concentration is normalized; patients generally require between 5 and 10 g/d.¹²⁶ Aluminum-containing phosphate binders should be avoided to limit the risk of aluminum toxicity (osteomalacia, anemia, or encephalopathy), but may be necessary on a temporary basis if the calcium phosphorus product is more than 65 to 70 (when calcium and phosphorus are expressed in milligrams per deciliter, or approximately 6 when measured in SI units) to minimize the potential for extracellular calcification. Oral calcitriol (0.125-0.25 μ g/d) is effective in increasing serum calcium concentration, reducing parathyroid hormone levels, and improving renal osteodystrophy.^{127,128} However, serum calcium levels should be monitored periodically in patients receiving calcitriol to prevent the development of hypercalcemia.

Metabolic Acidosis

Chronic renal insufficiency is associated with a progressive inability to excrete normal endogenously produced nonvolatile acid and usually results in systemic acidosis when the GFR is reduced to 0.42 mL/s or less.¹²⁹ Impaired renal ammonia production and reduced bicarbonate reabsorption are the major factors responsible for the development of the metabolic acidosis.^{130,131} Since bone buffering of the chronic acidosis may contribute to the development of renal osteodystrophy,¹²⁶ treatment with supplemental alkali (either as sodium bicarbonate or Shohl solution) at a dosage of 20 mmol of bicarbonate twice daily should be initiated and titrated upward to achieve a serum bicarbonate concentration of 22 to 24 mmol/L.¹²⁶

Anemia

Most patients with chronic renal insufficiency develop a normocytic, normochromic, hypoproliferative

Table 3. Renal and Extrarenal Factors That Predispose to Hyperkalemia

Increased intake
Diet
Salt substitutes
Redistribution from intracellular to extracellular fluid or reduced cell uptake
Insulin deficiency
Acidosis
Nonselective β -blockade
Digitalis
Decreased renal potassium excretion
Potassium-sparing diuretics
Trimethoprim
Hypoaldosteronism
Idiopathic
Type IV renal tubular acidosis
Drug induced
Angiotensin-converting enzyme inhibitors
Nonsteroidal anti-inflammatory drugs
Heparin

anemia.¹³² Decreased erythropoietin production is the principal factor responsible for the anemia of CRF¹³³; however, shortened red blood cell survival,¹³⁴ associated iron and folate deficiencies, and "uremic" inhibition of erythropoiesis also contribute to the decrease in red blood cell mass.¹³² The reduction in red blood cell mass results in multiple clinical manifestations, including fatigue, dyspnea, anorexia, nausea, and depression. Recombinant human erythropoietin has been a landmark in the treatment of the anemia of chronic renal disease. Weekly subcutaneous administration of erythropoietin at a mean dose of 150 U/kg increases the hematocrit to more than 0.3 in predialysis patients with CRF¹³⁵⁻¹³⁷ and an average weekly dose of 75 U/kg is an effective maintenance dose once goal hematocrit has been reached. Amelioration of the anemia of CRF with erythropoietin not only improves symptoms but also exerts beneficial effects on the hyperdynamic circulatory state associated with the anemia¹³⁸ and improves quality-of-life measures.¹³⁹ However, erythropoietin can cause an increase in blood pressure, and patients should be closely monitored for the need of additional antihypertensive therapy.¹⁴⁰

DRUG THERAPY

The physiological changes associated with renal insufficiency exert

important effects on the pharmacology of many frequently used drugs. Decreased renal function can affect absorption, distribution, metabolism, and elimination of many pharmacological agents. Several excellent resources, including the *Physicians' Desk Reference*, can be consulted to guide drug dosing in the presence of renal insufficiency.^{141,142}

DIET

Dietary modification in chronic renal insufficiency is complex and best accomplished in coordination with a registered dietitian. Since a low serum albumin concentration is a strong independent predictor of mortality in patients undergoing dialysis,¹⁴³ every effort should be made to maintain adequate nutritional balance in patients with CRF. Restriction of sodium intake to approximately 100 mmol/d is indicated in patients with hypertension and fluid overload. Modification of protein intake in chronic renal disease was discussed in detail earlier. Limiting daily phosphate intake to 600 to 800 mg/d is important in the management of renal osteodystrophy,¹⁴⁴ and daily potassium intake should be less than 60 mmol/d. This diet should provide 147 to 168 kJ/kg per day in energy intake, chiefly from carbohydrate and polyunsaturated fats.¹⁴⁵

TREATMENT MODALITIES IN ESRD

Hemodialysis, peritoneal dialysis, and kidney transplantation are the 3 major treatment modalities in patients with ESRD.¹ In patients without diabetes, access for dialysis is usually constructed when the creatinine clearance reaches 0.16 mL/s, whereas in patients with diabetes, access is generally established at a creatinine clearance of 0.16 to 0.25 mL/s. Urgent indications for initiation of dialysis include uremic pericarditis, encephalopathy, and pulmonary edema due to fluid overload. Uremic symptoms (nausea, vomiting, or fatigue), acidosis, and hyperkalemia not responsive to medical therapy also prompt initiation of dialysis. Patients with diabetes are usually more symptomatic at any level of renal dysfunction compared with patients without diabetes and, hence, gen-

erally begin dialysis earlier than patients without diabetes.

The choice among the treatment modalities for ESRD depends on several factors. Transplantation is frequently the treatment of choice in infants and children with ESRD.¹⁴⁶ In contrast, patients older than 70 years have more complications with transplantation and are generally managed with hemodialysis or peritoneal dialysis. In other patients, absolute contraindications to either hemodialysis or peritoneal dialysis are few and the choice is usually based on coexistent vascular disease, patient preference, or other socioeconomic factors. With steadily improving 1- and 5-year survival rates, living related or unrelated donor transplantation is an attractive option for eligible patients.¹⁴⁷ It is important to emphasize that referral and evaluation for renal transplantation should be accomplished well in advance of the need for dialysis. With careful planning among the primary care physician, the nephrologist, and the transplant surgeon, transplantation can sometimes be performed before dialysis is required.

Accepted for publication March 23, 1998.

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