Concise Review for Clinicians

A Practical Approach to the Management of Patients With Chronic Renal Failure

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The number of patients with significant chronic renal failure is expanding rapidly in the United States. All physicians and medical-care providers will have an increasingly important role in the detection and management of renal failure in patients who are not undergoing dialysis. Patients with diabetes or hypertension should be carefully monitored for the development of renal insufficiency by using screening tools such as blood pressure measurement, determination of serum creatinine, urinalysis, and determination of 24-hour urinary microalbuminuria. In order to slow the progression of renal disease, attenuate uremic complications, and prepare patients with renal failure for renal replacement therapy, all medical-care providers should "take care of the BEANS." *B*lood pressure should be maintained in a target range lower than 130/85 mm Hg, and in many patients, angiotensin-converting enzyme inhibitors may be beneficial. *E*rythropoietin should be used to maintain the hemoglobin level at 10 to 12 g/dL. *A*ccess for long-term dialysis should be created when the serum creatinine value increases above 4.0 mg/dL or the glomerular filtration rate declines below 20 mL/min. *N*utritional status must be closely monitored in order to avoid protein malnutrition and to initiate dialysis before the patient's nutritional status has deteriorated. Nutritional care also involves correction of acidosis, prevention and treatment of hyperphosphatemia, and administration of vitamin supplements to provide folic acid. *S*pecialty referral to nephrology should occur when the creatinine level increases above 3.0 mg/dL or when the involvement of a nephrologist would be beneficial for ongoing management of the patient.

Mayo Clin Proc 1999;74:269-273

ACE = angiotensin-converting enzyme; CRF = chronic renal failure; DPI = dietary protein intake; ESRD = end-stage renal disease; GFR = glomerular filtration rate; r-HuEPO = recombinant human erythropoietin

The number of patients with end-stage renal disease (ESRD) is increasing rapidly in the United States. In 1982, only 66,000 patients had ESRD; by 1998, the number had increased to 256,000, and by the year 2008, an estimated 600,000 patients will be receiving long-term dialysis. For every patient with ESRD, approximately five patients have advanced renal failure but do not yet require long-term dialysis. With use of this estimation, more than 3 million US patients will have significant chronic renal failure (CRF) by the year 2008. Because fewer nephrologists are being trained in the United States, general internists and family practitioners must have a general strategy for the detection and management of significant CRF.

DETECTION OF RENAL DISEASE

Diabetes and hypertension are the two most common causes of CRF in patients with ESRD, accounting for more than two-thirds of cases in these patients. Such patients, along with other high-risk patients (family history of renal disease, known chronic glomerulonephritis), should undergo regular screening for significant renal disease. The screening tools that are readily available to clinicians include blood pressure measurement, determination of serum creatinine, urinalysis, and determination of 24-hour urinary microalbuminuria. Blood pressure should be monitored at least quarterly in high-risk patients, whereas the three other laboratory determinations should be monitored annually. Detection of microalbuminuria (which should be evaluated annually) in patients with diabetes is an indicator of early diabetic nephropathy and may also be useful in determining early renal involvement in other nondiabetic renal diseases.[1] Determination of the serum creatinine is still one of the most widely applied tools for the detection of significant renal disease. Although this test is fast, inexpensive, and convenient, several associated shortcomings must be appreciated by clinicians. Patients with a low muscle mass and decreased protein intake may have lower than expected levels of serum creatinine. Patients with advanced renal failure have changes in the renal tubular secretion of creatinine and production of an enzyme, creatinase, in the bacterial flora of the intestinal tract, which tend to alter serum creatinine. The total effect of these factors is that the serum creatinine level is misleadingly low and the creati-

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nine clearance overestimates the true glomerular filtration rate (GFR) in the presence of advanced renal failure. The creatinine clearance can be estimated by using the Cockcroft-Gault formula[2]—estimated creatinine clearance = (140 – age [yr] x weight [kg]/72 x serum creatinine [mg/dL]) (15% less in female patients)—which considers factors of age, gender, and body weight. There is no substitute, however, for an accurate determination of the GFR by using an iothalamate clearance, an inulin clearance, or the average of the 24-hour urinary clearances of creatinine and urea—all of which usually provide a reliable estimation of GFR.

The management of patients with CRF should include steps to slow the progression of renal disease, attenuate uremic complications, and prepare the patient for renal replacement therapy. To help clinicians remember these goals, I have coined the term "take care of the BEANS" (Table 1).

Table 1.—**Take Care of the BEANS***

Blood pressure control
Blood pressure <130/85 mm Hg
Strongly consider angiotensin-converting enzyme inhibitors
Erythropoietin
Maintain hemoglobin concentration at 10 to 12 g/dL
Avoid iron deficiency
Access for long-term dialysis
Create fistula when creatinine ≥4 mg/dL (glomerular filtration rate [GFR] <20 mL/min)
Nutritional care
Avoid protein malnutrition
Maintain normal serum albumin level
Monitor urinary creatinine, urea nitrogen, and protein excretion
Initiate dialysis in a timely manner
Treat acidosis and hyperphosphatemia
Administer appropriate vitamin supplements
Specialist referral
Refer to nephrologist when creatinine ≥3.0 mg/dL (GFR <30 mL/min)

*Management of chronic renal failure.

BEANS

B = Blood Pressure Control

The control of hypertension is a critical element in the strategy to slow the progression of renal disease. The currently recommended target blood pressure for patients with CRF is 130/85 mm Hg.[1,3] In patients with more than 3 g/day of proteinuria, the progression of renal disease can be slowed even further if the patient's blood pressure is less than 125/80 mm Hg.[3] Angiotensin-converting enzyme (ACE) inhibitors have been shown to slow the progression of diabetic nephropathy in comparison with other antihypertensive agents.[3,4] Currently, ACE inhibitors also seem advantageous for nondiabetic patients with significant proteinuria and, possibly, for those with most other renal diseases.[4,5] Nondihydropyridine calcium channel blockers may also have beneficial effects on the preservation of renal function.[5] The ACE inhibitors must be used carefully in patients in whom hyperkalemia could develop or in any patient with a serum creatinine level higher than 3.0 mg/dL (estimated GFR, less than 20 to 25 mL/min). In these high-risk patients, serum creatinine and serum potassium levels should be determined frequently to ensure that the ACE inhibitors do not exacerbate hyperkalemia or azotemia. The effects of angiotensin II receptor blockers on the progression of renal disease have not yet been clearly determined in patients with CRF, but the hope is that they have benefits similar to those associated with ACE inhibitors.

E = Erythropoietin

The availability of recombinant human erythropoietin (r-HuEPO) to treat the anemia of renal failure has dramatically reduced the morbidity and mortality of patients with advanced CRF. The correction of anemia in patients with CRF not only improves their overall well-being, aerobic capacity, and cognition but also attenuates their cardiac problems such as left ventricular hypertrophy, angina pectoris, and congestive heart failure. Despite the fact that anemia is a known risk factor for increased mortality in patients with advanced CRF, 52% of patients who initiated long-term hemodialysis in 1995 and 1996 still had a hematocrit value lower than 28%, but only 20% were receiving r-HuEPO. As clinicians, we must make a more concerted effort to correct anemia in these patients.

The anemia of renal failure is due to a decline in the production of erythropoietin from the failing kidneys, which begins to occur when the GFR is approximately 30 to 40 mL/min (serum creatinine level, greater than 2.5 mg/dL). The presence of anemia in a patient with chronic renal disease is almost always due to erythropoietin deficiency.[6] The evaluation of anemia in patients with CRF should include determination of the hemoglobin and hematocrit, erythrocyte mean corpuscular volume, serum iron factors including serum iron, transferrin saturation, and ferritin, and B_{12} and folate levels; in addition, patients should be assessed for the presence of occult fecal blood in order to exclude significant gastrointestinal bleeding. During this evaluation, the determination of erythropoietin levels is not recommended because of the difficulty in interpreting these levels in patients with renal disease.[6] When the hemoglobin level declines below 10.0 g/dL (hematocrit, less than 30%), active treatment of anemia is indicated, including the use of iron supplements to provide 200 mg/day of elemental iron and folic acid in a dosage of 1 mg/day. Parenteral iron dextran treatment may be necessary if

the transferrin saturation is less than 20% or if the serum ferritin level is less than 100 μg/L. If these conservative measures fail to attain a target hemoglobin concentration of 10.0 g/dL, erythropoietin therapy is necessary. A reasonable dosage of r-HuEPO is 40 to 60 U/kg administered subcutaneously once or twice weekly. The patient's blood pressure, weight, and hemoglobin, hematocrit, and potassium values are monitored weekly. If the target hemoglobin level of 10.0 to 12.0 g/dL cannot be attained within 4 weeks, the erythropoietin dosage should be increased 25%. If the hemoglobin level increases to more than 12.0 g/dL, the r-HuEPO treatment is temporarily discontinued. The dosage of r-HuEPO is decreased by 25%, and its administration is resumed when the hemoglobin concentration declines below 12.0 g/dL. Laboratory values relating to renal function (creatinine and blood urea nitrogen) are monitored monthly; iron values (serum iron, transferrin saturation, and serum ferritin) are monitored quarterly. If the iron values decline substantially (see aforementioned discussion), parenteral iron therapy is initiated. Serious complications (hypertension and hyperkalemia) that were initially reported with the administration of erythropoietin seem to relate to the rate of increase in the hematocrit (hemoglobin concentration increase greater than 1 g/dL per week) or the absolute hematocrit level (hematocrit greater than 36%). Overall, few complications have been noted with erythropoietin therapy when it is administered in a carefully monitored manner.

A = Access for Long-Term Dialysis

The timely provision of access for long-term dialysis has numerous benefits for patients with CRF, including an improved survival, a greater likelihood of creation of a native arteriovenous fistula, a higher probability for choosing a self-dialysis modality such as peritoneal dialysis or home hemodialysis, and a lower likelihood of hospitalization at the time of initiation of long-term dialysis therapy.[7]

Patients who must urgently initiate long-term dialysis without a permanent dialysis access have a 1-year mortality rate of 20 to 30%, which is greater than the usual 1-year mortality rate of 15 to 20%. This increase in mortality may be due to the delayed initiation of long-term dialysis therapy but may also be related to the risks associated with insertion of a temporary venous dialysis catheter. Patients in whom insertion of a temporary venous dialysis catheter is necessary have a greater risk of hospitalization and development of complications such as pneumothorax, bleeding, or death. Placement of these catheters in the subclavian vein should be avoided because it will almost certainly cause stenosis of this vein, an outcome that will hamper all future efforts to create long-term vascular access in the ipsilateral arm.[7]

The National Kidney Foundation currently recommends that a long-term hemodialysis access should be created when the serum creatinine level reaches 4.0 mg/dL (GFR less than 20 mL/min).[7] In my opinion, access should be created when the need for long-term dialysis is anticipated to occur within 6 months. For a native arteriovenous fistula, often 3 to 6 months are needed for maturation. An arteriovenous synthetic graft can be used 2 to 4 weeks after its insertion. Peritoneal dialysis catheters are usually allowed to heal for 4 to 6 weeks before regular use. Because of the waiting periods, planning for timely provision of suitable access is important in the care of patients with progressive renal disease.

N = Nutritional Care

Malnutrition, as determined by the presence of hypoalbuminemia, at initiation of dialysis is associated with an increased mortality in patients with ESRD. Patients with CRF who have an albumin level lower than 3.0 g/dL have a 2-year mortality rate of at least 30 to 40% in comparison with the expected mortality rate of 20 to 30%. Thus, for patients with renal disease, the clinician must emphasize the importance of maintaining an optimal nutritional status. Many patients with CRF have spontaneous protein restriction of approximately 0.8 g/kg per day once the GFR declines below 20 mL/min, and their anorexia may be exacerbated by an enforced protein-restricted diet. With an increasing awareness of the importance of adequate nutrition, my colleagues and I have become more reluctant to introduce severe protein restriction as part of the therapeutic regimen for patients with renal disease. In our experience, protein restriction of less than 0.6 g/kg per day (40 g/day) is expensive, impractical, and unlikely to be rigorously followed by a patient. With the initiation of long-term dialysis therapy, protein intake is liberalized to at least 1.0 to 1.2 g/kg per day (Table 2).

The nutritional status of a patient with CRF must be closely monitored. The development of anorexia that leads to a sustained weight loss of 5 to 10% below ideal body weight, a caloric intake of less than 30 kcal/kg per day, or spontaneous dietary protein intake (DPI) of less than 0.8 g/kg per day is evidence of impending nutritional compromise,[8] as is the development of muscle wasting. Laboratory values such as serum albumin, serum prealbumin, transferrin, or even insulin-like growth factor I have been used to monitor a patient's nutritional status.[8] One of the most accurate ways to monitor a patient's nutritional status is regular determination of the serum albumin and 24-hour urinary content of creatinine, urea nitrogen, and protein excretion. The urinary studies can help to quantify the urinary normalized protein nitrogen appearance, which is an indirect indictor of DPI. Urinary normalized protein

Table 2.—**General Dietary Guidelines for Patients With Chronic Renal Failure*†**

Degree of renal failure	Protein (g/kg/day)	Sodium (mEq/day)	Potassium (mEq/day)	Phosphorus (mg/day)	Fluid (mL/day)
Mild (GFR 30-40 mL/min)	1.0	90	NL	NL	NL
Moderate (GFR 20-30 mL/min)	0.8-1.0	90	60-90	1,000	NL‡
Severe (GFR <20 mL/min)	0.6-0.8§	60-90	60	800	24-h urinary output + 1,000 mL//
Dialysis	1.0-1.2	90	60-90	800-1,000	24-h urinary output + 1,000 mL//

*GFR = glomerular filtration rate; NL = normal dietary intake, usually no limit.
†Calories, 30 to 35 kcal/kg/day for all patients.
‡May need restriction in some patients.
§Severe restriction of 0.6 g/kg/day is difficult for patients to follow and may cause protein malnutrition. Prolonged use of such a diet is usually not feasible.
//Sodium and potassium restrictions may differ for patients with good urinary output or "salt-wasting."

nitrogen appearance of less than 0.8 g/kg per day is also an important indicator of a DPI of less than 0.8 g/kg per day and possible malnutrition. The average of the clearances of creatinine and urea can be used to estimate the GFR. In general, initiation of long-term dialysis therapy is indicated when the GFR declines below 10.5 mL/min per 1.73 m^2 of body surface area, the urea clearance decreases below 7 mL/min per 1.73 m^2, or the creatinine clearance declines below the level of 9 to 14 mL/min per 1.73 m^2.[8]

Other nutritional aspects in the care of patients with CRF include attention to metabolic acidosis, phosphorus control, and vitamin supplements.[9] The serum bicarbonate level should be monitored regularly, and oral vitamin supplements may be necessary when the serum bicarbonate level decreases below 20 mEq/L. At this level of serum bicarbonate, protein catabolism and bone resorption increase and other adverse effects on metabolic processes are noted. Oral vitamin supplements should be used that provide 1 mg/day of folic acid plus all other B vitamins and water-soluble vitamins. Supplementation of vitamins A, D_2, and C should be avoided. Phosphorus control is an important element of a nutritional program that is designed to reduce the development of secondary hyperparathyroidism. In order to improve control of serum phosphorus levels, dietary phosphorus should be limited to 800 to 1,000 mg/day. Phosphate-binding antacids are administered with meals. Currently, the preferred phosphate-binding agent is a calcium salt such as calcium acetate or calcium carbonate. In the future, phosphorus-binding resins and other non-calcium-containing compounds will probably be used to retard the intestinal absorption of dietary phosphorus. The phosphorus level should be maintained in the range of 3.5 to 5.0 mg/dL.

S = Specialist Referral

At some point, the patient with advanced renal failure should be referred to a nephrologist. Obviously, some patients with nephrotic syndrome, acute glomerulonephritis, or other renal disease may benefit from referral to a nephrologist for diagnostic purposes before renal failure occurs. Patients with CRF who have been regularly seeing a nephrologist (for example, at least two visits in the 6 months before the initiation of long-term dialysis) have a less frequent need for hospitalization and have an improved survival rate in comparison with patients who have never undergone assessment by a nephrologist before the initiation of dialysis therapy.[10] Early referral to a nephrologist facilitates provision of a permanent dialysis access before the development of uremic symptoms, timely initiation of dialysis, and involvement of other health-care professionals—renal dietitians, social workers, nurse educators, and surgical teams—who are crucial to the management of patients with ESRD. In addition, patients are also more likely to be educated about their renal disease, maintain rehabilitation, and receive an earlier referral for renal transplantation. Patients should be referred to a nephrologist in the following circumstances: GFR is less than 30 mL/min per 1.73 m^2 (serum creatinine, approximately 3.0 mg/dL); dialysis seems imminent within the next year; patient is a potential renal transplant recipient; or patient's primary physician wants help with many of the medical issues associated with CRF (for example, control of hypertension and anemia, nutritional care, provision of dialysis access, and education).

I am hopeful that, if clinicians can remember to "take care of the BEANS" (Table 1), we can substantially improve the pre-ESRD care of all patients with chronic renal disease and help them to live longer, fuller lives.

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Questions About Management of Patients With Chronic Renal Failure

(*See article, pages 269 to 273*)

1. Which *one* of the following patients has *significant* renal failure (that is, an estimated creatinine clearance lower than 25 mL/min) (use the Cockcroft-Gault formula to estimate the creatinine clearance)?
   a. An 18-year-old male football player who weighs 120 kg and whose serum creatinine level is 1.9 mg/dL
   b. An 80-year-old woman who weighs 60 kg and whose serum creatinine level is 1.8 mg/dL
   c. A 75-year-old man who weighs 60 kg and whose serum creatinine level is 2.1 mg/dL
   d. A 45-year-old woman who weighs 40 kg and whose serum creatinine level is 1.9 mg/dL
   e. A 32-year-old woman who weighs 65 kg and whose serum creatinine level is 1.8 mg/dL

2. Which *one* of the following is the *currently recommended* level for blood pressure control in patients with chronic renal failure?
   a. 150/95 mm Hg
   b. 140/90 mm Hg
   c. 130/85 mm Hg
   d. 100/60 mm Hg
   e. 160/95 mm Hg

3. Which *one* of the following would be a *reasonable initial* dosage of erythropoietin in a patient with a serum creatinine level of 3.8 mg/dL, hemoglobin concentration of 9.1 g/dL, and normal iron values?
   a. 20 to 30 U/kg, administered weekly
   b. 40 to 60 U/kg, administered twice weekly
   c. 150 U/kg, administered twice weekly
   d. 100 U/kg, administered every 10 days
   e. 150 U/kg, administered monthly

4. Which *one* of the following patients should be *referred* for creation of permanent vascular access for dialysis?
   a. A patient with diabetes whose serum creatinine level is 1.2 mg/dL and proteinuria is 2.0 g/day
   b. A 65-year-old patient with hypertensive nephrosclerosis whose serum creatinine level is 4.0 mg/dL
   c. A 58-year-old woman with adult-onset diabetes whose creatinine clearance is 42 mL/min
   d. A 45-year-old man with IgA nephropathy whose serum albumin level is 4.2 g/dL and serum creatinine level is 3.1 mg/dL
   e. A 32-year-old woman in the intensive-care unit who has acute renal failure and a creatinine level of 3.8 mL/min

5. Which *one* of the following nutritional factors is *not* important in assessing the nutritional status of a patient with chronic renal failure?
   a. Serum albumin
   b. 24-hour urinary creatinine clearance
   c. 24-hour urinary urea nitrogen excretion and clearance
   d. 24-hour urinary protein excretion
   e. Prescribed dietary protein restriction

Correct answers:
1. *a*, 2. *c*, 3. *b*, 4. *b*, 5. *e*