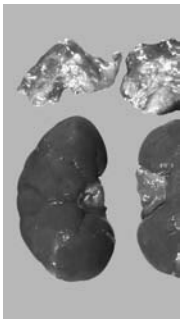

Chapter **36**

Diseases of the Kidney and the Urinary System

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CAUSES AND CHARACTERISTICS OF THE BURDEN OF DISEASES

Estimates of the global burden of disease indicate that diseases of the kidney and urinary tract account for approximately 830,000 deaths and 18,467,000 disability-adjusted life years annually, ranking them 12th among causes of death (1.4 percent of all deaths) and 17th among causes of disability (1.0 percent of all disability-adjusted life years). This ranking is similar across World Bank regions (table 36.1).

Recent research suggests that the data shown in table 36.1 underestimate the global prevalence of kidney disease. Chronic kidney disease (CKD) patients often suffer from cardiovascular or cerebrovascular disease, and their deaths may be attributed to either complication (Hostetter 2004). Altered kidney function is often found in patients with hypertensive and ischemic heart disease, both of which are associated with increased cardiovascular morbidity and mortality. Approximately 30 percent of patients with diabetes have diabetic nephropathy, with higher rates found in some ethnic groups (King, Aubert, and Herman 1998). Table 36.2 shows that both genders are similarly affected by kidney disease (Coresh and others 2003).

Generally, renal diseases progress to a final stage as end-stage renal disease (ESRD) and function is substituted by renal replacement therapy (RRT), hemodialysis, peritoneal dialysis, or transplantation. National and international registries of patients on RRT are useful for providing information on the prevalence of renal diseases in a given country. Data combined from different sources show that more than 1.5 million people worldwide are on RRT, 80 percent of whom live in Japan, Europe, and North America (Weening 2004).

The percentage of patients on regular dialysis varies across countries as a consequence of the capacity of health care systems to provide treatment. Europe is an example. Whereas in the 15 countries of the European Union (before 2004) the prevalence rate of RRT was approximately 650 patients per 1 million people, in Central and Eastern Europe it was only 160 patients per 1 million people, reflecting differences in gross national product.

Much less is known about the prevalence of earlier stages of CKD, when symptoms may be mild, ignored, or undiagnosed. A lack of standardization of the stages of CKD has hampered assessments of the burden of CKD. In an attempt to carry out such an assessment, the National Center for Health Statistics of the Centers for Disease Control and Prevention in the United States conducted a survey from 1988 to 1994. The center analyzed a sample of 15,625 noninstitutionalized individuals age 20 and older and defined five stages of renal dysfunction according to estimates of renal function and urine albumin level. Coresh and others (2003) found that the estimated prevalence of CKD in the United States is 11 percent of the adult population, or 19.8 million people. Nationally representative data on U.S. adults older than 20 show that 6.3 percent, or 11 million people, have stage 1 CKD, or kidney damage (proteinuria) with normal kidney function (Glomerular Function Rate (GFR) at least 90 milliliters per minute in 1.73 per meter squared) or stage 2 CKD, that is, mildly reduced kidney function (60 to 89 ml/min/1.73 m^2). Furthermore, 4.3 percent, or 7.6 million people, exhibit stage 3 CKD, or moderately

Table 36.1 Contribution of Diseases of the Kidney and Urinary System to the Global Burden of Disease by Gender and Region *(thousands)*

Gender and region	Population	Deaths	Disability-adjusted life years	Years lived with disability	Years of life lost
Females	3,056,384	397	8,008	2,546	5,450
Males	3,093,849	433	10,459	4,493	5,960
World	6,150,233	830	18,647	7,039	11,415
East Asia and the Pacific	1,850,775	233	5,400	1,858	3,530
Europe and Central Asia	447,180	53	1,417	623	793
Latin America and the Caribbean	526,138	70	1,667	779	888
Middle East and North Africa	309,762	57	1,283	460	823
South Asia	1,387,873	156	3,991	1,373	2,619
Sub-Saharan Africa	667,663	107	2,623	1,046	1,576

Source: Mathers and others 2006.

Table 36.2 Global Deaths Caused by Diseases of the Genitourinary System by Gender and Age

	Age (years)							
Gender	Birth–4	5–14	15–29	30–44	45–59	60–69	70–79	80+
Male deaths								
Number (thousands)	11	7	24	43	80	86	110	88
Percent	3	2	5	10	18	19	24	20
Female deaths								
Number (thousands)	10	6	21	29	61	66	85	98
Percent	3	2	5	8	16	18	23	24

Source: WHO 2002.

reduced kidney function (30 to 59 ml/min/1.73 m^2), and 0.2 percent, or 400,000, have stage 4 CKD, or severely reduced kidney function (15 to 29 ml/min/1.73 m^2) (Coresh and others 2003; Coresh, Astor, and Sarnak 2004; National Kidney Foundation 2002). A sizable proportion (360,000) of these patients eventually progress toward ESRD (stage 5, or less than 15 ml/min/1.73 m^2) and require RRT. Early detection of CKD is, therefore, important to retard or arrest the loss of renal function. Late detection of CKD is a lost opportunity for making lifestyle changes and initiating therapeutic measures.

CAUSES OF DISEASES OF THE KIDNEY AND URINARY SYSTEM

Kidney disease leading to ESRD has many causes. The prevalence varies by country, region, ethnicity, gender, and age.

Genetic Diseases

Knowledge of inherited kidney disease has changed radically with advances in molecular biology and gene-sequencing technology. The characterization of inherited kidney diseases has improved, and novel mutations leading to selective renal defects have been described. Inherited kidney diseases are rare, with the exception of autosomal dominant polycystic kidney disease, the fourth most common cause of ESRD in developed countries. This disease has a prevalence of 1 in 1,000 people and affects approximately 10 million people worldwide (Grantham 1997). Autosomal recessive polycystic kidney disease is less frequent, with an incidence of 1 in 40,000, but is an important hereditary disease of childhood (Guay-Woodford, Jafri, and Bernstein 2000). Many other inherited diseases can lead to ESRD, but together they account for only a small percentage of all people with ESRD.

Glomerulonephritis

Glomerulonephritides are a group of kidney diseases that affect the glomeruli. They fall into two major categories: *glomerulonephritis* refers to an inflammation of the glomeruli and can be primary or secondary, and *glomerulosclerosis* refers to scarring of the glomeruli. Even though glomerulonephritis and

glomerulosclerosis have different causes, both can lead to ESRD. Glomerulonephritis ranks second after diabetes as the foremost cause of ESRD in Europe. (Stengel and others 2003) and is the second leading cause of ESRD in the United States, according to the United States Renal Data System (http://www.ifrr.net/). Approximately 20 to 35 percent of patients requiring RRT have a glomerular disease.

Glomerular diseases are more prevalent and severe in tropical regions and low-income countries (Seedat 2003). A common mode of presentation is the nephrotic syndrome, with the age of onset at five to eight years. Estimates indicate that 2 to 3 percent of medical admissions in tropical countries are caused by renal-related complaints, most resulting from glomerulonephritis.

A number of kidney diseases that result from infectious diseases, such as malaria, schistosomiasis, leprosy, filariasis, and hepatitis B virus, are exclusive to the tropics. HIV/AIDS can be complicated by several forms of kidney disease; however, patient data are sparse (Seedat 2003).

Acute poststreptococcal nephritis following a throat or skin infection caused by Group A streptococcus has almost disappeared in high-income countries because of improved hygiene and treatment but remains an important glomerular disease in India and Africa, where epidemics have been reported (Seedat 2003).

The eradication of endemic infections, along with improvements in socioeconomic status, education, sanitation, and access to treatment, is a crucial step toward decreasing the incidence of glomerular diseases in developing countries.

Infections, Stones, and Obstructive Uropathy

Infections of the urinary tract are a common health problem worldwide and can be categorized as either uncomplicated or complicated. Uncomplicated infections include bladder infections such as cystitis, seen almost exclusively in young women (Hooton 2000). Among sexually active women, the incidence of cystitis is 0.5 episodes per person annually, and recurrence develops in 27 to 44 percent of cases. Acute, uncomplicated pyelonephritis, involving the kidney, is less frequent in women than is cystitis. Males are less susceptible to acute, uncomplicated infections of the bladder or the kidney, with an incidence of five to eight episodes per 10,000 men annually. Even though uncomplicated urinary tract infections are considered benign, they have significant medical and financial implications estimated at approximately US$1.6 billion per year (Foxman 2003).

As for complicated urinary tract infections, hospitalization results in almost 1 million such infections per year in the United States. Bladder catheterization is the most important cause.

Developing countries exhibit a different pattern of urinary tract infection. Obstructive or reflux nephropathy is often attributed to urinary schistosomiasis (Barsoum 2003). Worldwide, 200 million people are affected and an estimated 300 million are at risk. The disease causes lesions in the bladder and predisposes those with the condition to secondary infections, bladder cancers, and chronic pyelonephritis.

Some 15 to 20 million people have tuberculosis (TB) worldwide, of whom 8 million to 10 million are infectious. Genitourinary TB is a common form of extrapulmonary TB and is always secondary to the primary lesion, which usually occurs in the lung (Pasternak and Rubin 1997). Lesions referred to as *ulcero-cavernous* or *miliary* affect the kidneys. If left untreated, such lesions may progress to kidney destruction. Early recognition of and effective therapy for TB substantially decrease the consequences in relation to kidney function.

In the industrial countries, kidney stones are a common problem (Morton, Iliescu, and Wilson 2002), affecting 1 person in 1,000 annually, and the incidence is increasing in tropical developing countries (Robertson 2003). Factors such as age, sex, and ethnic and geographic distribution determine prevalence. The peak age of onset is in the third decade, and prevalence increases with age until 70.

Although largely idiopathic, the following risk factors are associated with stone disease: low urine volume, hyperuricosuria, hyperoxaluria, hypomagnesuria, and hypocitraturia. Diarrhea, malabsorption, low protein, low calcium, increased consumption of oxalate-rich foods, and low fluid intake may play a role in the genesis of stone disease. In developing countries, 30 percent of all pediatric urolithiasis cases occur as bladder stones in children. The formation of bladder stones in children is caused by a poor diet high in cereal content and low in animal protein, calcium, and phosphates.

Kidney stones can have different clinical presentations, ranging from asymptomatic to large obstructing calculi in the upper urinary tract that can severely impair renal function and lead to ESRD. Although specific causes of kidney stones should be treated appropriately, general treatment includes increased fluid intake, limited daily salt intake, moderate animal protein intake, and medical treatment with alkali and thiazides.

The Afro-Asian stone-forming belt stretches from Sudan, the Arab Republic of Egypt, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, and Indonesia to the Philippines. The disease affects all age groups from less than 1 year old to more than 70, with a male to female ratio of 2 to 1. The prevalence of calculi ranges from 4 to 20 percent (Hussain and others 1996). Urolithiasis accounts for some 50 percent of the urological workload and the bulk of urological emergencies. Patients may present with major complications leading to eventual ESRD and resulting in significant morbidity and mortality. In developed countries, only about 1 percent of patients are on dialysis because of obstructive uropathy, whereas in developing countries such as Indonesia and Thailand, obstructive uropathy is often the leading cause of ESRD, accounting for 20 percent or more of patients on dialysis. The availability of appropriately

trained medical and surgical personnel and of equipment essential for treating stone disease promptly would reduce the incidence of obstructive uropathy and ESRD. Cost analyses indicate that the medical prevention of stones saves more than US$2,000 per person annually (Parks and Coe 1996).

Benign Prostatic Hypertrophy

Benign prostatic hypertrophy is a major cause of lower urinary tract symptoms and leads to obstructive renal failure and ESRD. By age 80, 80 percent of men have benign prostatic hypertrophy. The World Health Organization quotes a mortality rate of 0.5 to 1.5 per 100,000 (La Vecchia, Levi, and Lucchini 1995). The actual incidence of benign prostatic hypertrophy is difficult to assess because of the lack of epidemiological data. In the developed world, the incidence varies between 0.24 and 10.90 per 1,000 annually from age 50 to 80, and the probability of prostate surgery for benign prostatic hypertrophy ranges from 1.4 to 6.0 percent (Oishi and others 1998).

Acute Renal Failure

Acute renal failure refers to a sudden and usually temporary loss of kidney function that may be so severe that RRT is needed until kidney function recovers. Even though acute renal failure can be a reversible condition, it carries a high mortality rate. Acute renal failure is a prominent feature of major earthquakes, where many suffer from crush syndrome accompanied by severe dehydration and rapid release of muscle cell contents, including potassium. Kidney function shuts down unless body fluid and blood pressure are rapidly corrected and frequent hemodialysis is available. Recent earthquake rescues in the Islamic Republic of Iran and Turkey have demonstrated the benefits of rapid hydration and dialysis (Sever and others 2001).

Diabetes

Diabetes is one of the most common noncommunicable diseases (see chapter 30). With the serious complication of nephropathy, diabetes has become the single most important cause of ESRD in the United States and Europe, according to Stengel and others (2003) and the United States Renal Data System (http://www.ifrr.net/). Diabetes may account for one-third of all ESRD cases.

Family-based studies and segregation analyses suggest that inherited factors play a major role in people's susceptibility to diabetic renal complications (Seaquist and others 1989). In the United States, the burden of ESRD is threefold to fivefold greater among African Americans, Mexican Americans, and Native Americans than other Americans, and Imperatore and others (2000) find a 200 percent greater possibility of the occurrence of inherited diabetic nephropathy. A family history of hypertension has also been associated with an increased risk of diabetic nephropathy. When specific markers of risk are found, high-risk individuals can be identified early and monitored for the development of proteinuria and kidney dysfunction.

The earliest sign of diabetic nephropathy is the appearance of small amounts of protein in the urine (*proteinuria*). As proteinuria increases and blood pressure rises, kidney function declines. The complete loss of kidney function occurs at different rates among type 2 diabetes patients, but it eventually occurs in 30 percent of proteinuria cases. The latter have a 10-fold increased risk of dying from associated coronary artery disease, which may obviate the progression of diabetic nephropathy to ESRD. As therapies and interventions for coronary artery disease improve, patients with type 2 diabetes may survive long enough to develop kidney failure.

Hypertension

Hypertension and kidney disease are closely related. Most primary renal diseases eventually produce hypertension. Arterial hypertension accelerates many forms of renal disease and hastens the progression to ESRD (Luke 1999). Recent studies have firmly established the importance of continuous blood pressure reduction to slow the progression of many forms of renal injury, particularly glomerular disease (Agodoa and others 2001; Peterson and others 1995). Over the long term, damage to the heart and cardiovascular system resulting from hypertension represents the major cause of morbidity and mortality among ESRD patients (Martinez-Maldonado 1998).

Before the development of effective antihypertensive agents, 40 percent of hypertensive patients developed kidney damage and 18 percent developed renal insufficiency over time (Johnson and Feehally 2000). Elevated serum creatinine develops in 10 to 20 percent of hypertensive patients, with African Americans and Africans at particularly high risk. In 2 to 5 percent of hypertensive patients, progression toward ESRD will occur in 10 to 15 years. Despite the relatively low rate of progression, hypertension remains the most common cause of ESRD after diabetes in the United States, is the foremost cause of death in all developed countries, and is a likely primary cause in developing countries given its high global prevalence rate. Native Americans and Hispanic Americans are disproportionately affected relative to Caucasian Americans.

GLOBAL PERSPECTIVES IN RELATION TO RRT

Despite the lack of uniform data worldwide, the medical community is aware that the total number of patients requiring RRT is growing in all high- and middle-income countries. In the United States, for example, 360,000 people with ESRD were on RRT in 2003, compared with 150,000 in 1994, and

according to a recent forecast, by 2014 the figure will have increased to 650,000 (Xue and others 2001). This increase represents a linear growth in new cases combined with longer survival by existing patients.

Levels in middle-income countries are lower, but rising. In Eastern Europe between 1990 and 1996, following economic changes, the number of hemodialysis and peritoneal dialysis centers increased by 56 and 296 percent, respectively (Rutkowski 2002), and the number of patients rose by 78 and 306 percent, respectively.

Overall, the incidence of ESRD is increasing worldwide at an annual growth rate of 8.0 percent, far in excess of the annual population growth rate of 1.3 percent. Nearly 1.6 million people, or only 15 percent of those affected, are receiving RRT, 80 percent of them in developed countries. The remaining 20 percent are treated in more than 100 developing countries, whose populations account for more than 50 percent of the world's population. A large proportion of people living in the poorest countries die of uremia because of a complete lack of RRT.

Risk Factors for Kidney Disease

The identification of risk factors can prevent or limit disease through lifestyle modifications or specific therapeutic interventions (Appel 2003; McClellan and Flanders 2003). For example, familial predisposition for a disease, which is not amenable to modification, can be used to identify high-risk populations for future monitoring.

Low socioeconomic status and limited access to health care are strong risk factors for kidney failure but account for only part of the excess of ESRD among African Americans (Perneger, Whelton, and Klag 1995), whereas racial and social factors account for most ESRD incidence (Pugh and others 1988; Rostand 1992). Factors associated with the progression of CKD include the following:

- unmodifiable variables
  - old age
  - gender
  - genetics
  - ethnicity
- risk factors susceptible to social and educational interventions
  - low birthweight
  - smoking
  - alcohol abuse
  - illicit drug abuse
  - analgesic abuse and exposure to toxic substance such as lead
  - sedentary lifestyle
- risk factors susceptible to pharmacological interventions
  - hypertension
  - dyslipidemia
  - poor glycemic control in diabetic patients
  - proteinuria
- biological markers
  - hemoglobin
  - insulin-resistant syndrome
  - proteinuria
  - serum creatinine.

Growing evidence suggests that fetal exposure to an abnormal intrauterine environment leads to an increased risk of chronic disease later in life. For example, children of diabetic mothers are prone to obesity and diabetes at a young age, and intrauterine growth retardation can lead to ischemic heart disease, diabetes, hypertension, and kidney disease. Disadvantaged racial minorities in developed countries and the impoverished in developing countries are at risk of intrauterine growth retardation caused by malnutrition (Nelson 2001; Nelson, Morgenstern, and Bennett 1998). Attention to maternal nutrition and other factors that would reduce low birthweight and impaired nephron development may have long-term implications for the development of CKD.

In low-income countries, poverty is associated with increased exposure to infectious diseases that increase susceptibility to CKD, including glomerulonephritis and parasitic diseases. Obesity caused by a diet rich in saturated fats and high in salt are risk factors for diabetic nephropathy and hypertensive kidney disease. Change in dietary habits and physical activity can reduce the overall incidence of diabetes (see chapter 44). Smoking and excessive alcohol consumption increase the risk of ESRD (McClellan and Flanders 2003), and analgesic abuse and exposure to toxic substances such as lead may affect progressive renal insufficiency (Lin and others 2001).

Interventions to Delay CKD

During the past 20 years, human and animal research has developed our understanding of CKD and led to preventive measures. The notion of renoprotection has resulted in a dual approach to renal diseases based on effective and sustained pharmacological control of blood pressure and reduction of proteinuria. Lowering blood lipids, stopping smoking, and maintaining tight glucose control for diabetes form part of the multimodal protocol for managing renal patients monitored by specific biological markers (Ruggenenti, Schieppati, and Remuzzi 2001).

Abnormal urinary excretion of protein is strongly associated with the progression of CKD in both diabetic and nondiabetic renal diseases. Clinical studies have established that a reduction in proteinuria is associated with a decreased rate of kidney function loss. A specific category of drugs that lower blood pressure, the angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, appear to be more effective than

other antihypertensive drugs in slowing the progression of both diabetic and nondiabetic CKDs (Brenner and Zagrobelny 2003). The administration of an ACE inhibitor (or of an angiotensin receptor blocker) is an important treatment for controlling blood pressure and slowing the rate of progression of chronic kidney failure. Other drugs to lower blood pressure are added as necessary to achieve current targets of 120/80 to 130/80 millimeters of mercury. Concurrent diuretic therapy is often necessary in patients with renal insufficiency, because fluid overload is an important determinant of hypertension in such cases.

Dyslipidemia accelerates atherosclerosis and may promote the progression of renal disease. Careful control of the blood glucose level in diabetic patients can be beneficial and may limit other complications. Obesity has not been directly linked to the progression of CKD but is an important risk factor for diabetes and cardiovascular morbidity and mortality. Many patients and health care professionals do not appreciate the benefits of smoking cessation, an important measure in protecting the kidneys from progressive disease resulting from cardiovascular disease (CVD). Additional elements of secondary prevention measures include the treatment of anemia and of abnormal calcium and phosphorus metabolism.

The International Society of Nephrology is developing a program that can be implemented according to the specific needs of a given developing country. The program has two objectives: (a) to identify the prevalence of renal disease among seemingly healthy subjects using a communitywide screening program, especially among populations at risk, and (b) to initiate interventions to prevent the progression of renal disease and affect both renal and CVD outcomes in subjects with or at risk of developing renal disease based on the screening program (Weening 2004). The Kidney Help Trust of Chennai, India, has undertaken a screening program for a population of 25,000. All those who tested positive for high blood pressure, diabetes, or both (about 15 percent) were further studied and then treated with inexpensive antihypertensive and antidiabetic drugs. The cost of the one-year program was Rs 300,000 (US$7,500) or a per capita cost of US$0.27, well within the limits of the Indian government's per capita annual health expenditure of US$7.67 (Mani 2003). A similar program in Bolivia examined a population of 14,000 and also found that 15 percent were hypertensive, diabetic, or both.

An extremely successful program of detection and treatment of renal and cardiovascular diseases among Australian Aborigines was conducted from 1995 to 2000. The ESRD rate among Aborigines is 3 to 10 times that in developed countries. Treatment consisted of long-acting ACE inhibitors to lower blood pressure. After an average of 3.4 years of follow-up, the incidence of ESRD was reduced by 63 percent and nonrenal deaths were reduced by 50 percent. Hoy and others (2003) estimate that this two-year program may have saved US$500,000 to US$2.7 million in avoided or delayed dialysis costs.

Trained staff members can carry out screening programs inexpensively. Economic analysis, however, suggests that large-scale programs should be restricted to screening and treating only specific high-risk populations. Screening programs can be implemented using simple, cheap, and reliable tests consisting of measurements of bodyweight, blood pressure, blood glucose, and creatinine. Screening includes testing urine for hemoglobin, glucose, leukocytes, and protein (repeat tests may be necessary on a spot urine sample); calculating albumin to creatinine ratios; testing positive results for increased serum creatinine and fasting glucose (or glycosylated hemoglobin A1c test); and reassessing the urine protein excretion rate, a cornerstone of kidney assessment. Resulting albumin to creatinine ratio categories would indicate a scale of severity of glomerular disease, with a cardiovascular risk score based on body mass index, hypertension, fasting glucose level, microalbuminuria or gross albuminuria, and serum creatinine. Patients with positive markers for kidney disease would receive the best treatment available at the screening center. Incorporating screening for kidney disease within screening programs developed for CVD and diabetes is important because proteinuria and renal dysfunction are early sensitive markers of vascular dysfunction and CVD patients are at significantly higher risk of kidney disease than the general population.

Resultant medical treatment would focus on the use of ACE inhibitors or angiotensin receptor blockers with a target blood pressure of 120/80 to 130/80 millimeters of mercury. The greater the level of proteinuria, the more treatment is required; thus, the ACE inhibitor dose would be titrated up as proteinuria levels increased. Diuretics and other antihypertensives would be added to meet blood pressure targets. Efforts should be made to obtain low-cost (off-patent) ACE inhibitors or other low-cost antihypertensives. Such treatment should delay or stop the progression of kidney disease and reduce the risk of CVD. Other preventive measures include serum glucose and lipid control and low-dose aspirin if a risk of CVD exists (see chapter 44).

ECONOMIC BENEFITS OF INTERVENTION

An abundance of literature is available on the economics of ESRD. In the industrial world, treatment is usually readily available and is covered by government or private health insurance. Previous restrictions—for example, treatment being limited to certain age groups—have been removed (Chugh and Jha 1995). Dialysis treatment accounts for 0.7 to 1.8 percent of health care budgets in European countries, even though dialysis patients account for only 0.02 to 0.05 percent of the population (Schiepatti, Perico, and Remuzzi 2003).

The most cost-effective option is prevention. Population screening is not particularly cost-effective, given the low incidence of ESRD—namely, 100 to 200 per million population

worldwide (Kher 2002)—and given that testing is not highly accurate. According to Kiberd and Jindal (1998), screening costs around US$20 per test, but the positive predictive value for a single test is only 0.3. Even repeat testing does not improve predictive value dramatically. Screening strategies have, therefore, focused on specific populations at higher risk of ESRD than the general population. Whereas only 2 to 5 percent of more than 1 billion hypertensive patients will ultimately develop nephropathy, approximately 30 percent of type 1 and type 2 diabetic patients will develop overt nephropathy (Satko and Freedman 2001). The conclusion is that treating all diabetics in developed countries with ACE inhibitors is a cost-saving strategy. The modest outlay for ACE inhibitors, which amounts to US$320 per year in the United States and is likely to come down as more ACE inhibitor treatments come off patent, offsets the much larger future costs of dialysis and transplant (Golan, Birkmeyer, and Welch 1999; Kiberd and Jindal 1998).

We undertook a crude cost-effectiveness calculation for treating diabetics in developing countries with ACE inhibitors in those cases in which no treatment of ESRD is undertaken. If we use Clark and others' (2000) assumptions, 82 percent of diabetic patients not using ACE inhibitors would survive for 11 years from the onset of macroproteinuria to ESRD, whereas 72 percent of those using ACE inhibitors would survive for 18 years from the onset of macroproteinuria to ESRD (the annualized death rate for both groups is 1.8 percent). If we make the gross assumption that all patients with ESRD in poor developing countries die, this assumption suggests that, at a discount rate of 3 percent and an annual cost for ACE inhibitors of US$320, the cost per quality-adjusted life year (QALY) saved would be about US$1,100 for treating diabetic patients with macroproteinuria. Because of the lack of data, these calculations apply survival rates in developed countries to developing countries; thus, the rates are likely too high. Using survival rates in developing countries would probably increase the cost per QALY saved, but treatment with ACE inhibitors is nevertheless likely to be an attractive investment (table 36.3).

Satko and Freedman (2001) suggest that screening first- and second-degree relatives of ESRD patients may be cost-effective. They cite one study that found 38 percent of first-degree relatives of African-American patients with hypertensive ESRD had some form of renal disease (Bergman and others 1996). Satko and Freedman also cite a study by Freedman, Soucie and McClellan (1997) revealing that in 4,365 incident ESRD patients in the southeastern United States, 14 percent of white patients and 23 percent of black patients had first- or second-degree relatives with ESRD (the rates would probably have been higher if subclinical nephropathy had been included). Satko and Freedman (2001) recommend annual screening for blood pressure, urinalysis, measurement of serum creatinine and blood urea nitrogen concentration, and testing for diabetes mellitus, when appropriate, for first- and second-degree relatives of ESRD patients. They did not calculate any formal cost-effectiveness results (table 36.3).

Table 36.3 Cost-Effectiveness of Selected Interventions for Kidney Disease

Intervention	Alternative	Outcome (2000 US$)
Center hemodialysis[a]	No RRT	55,000–80,000/life year 79,000–114,000/QALY
Home hemodialysis[a]	No RRT	33,000–50,000/life year 47,000–71,000/QALY
Kidney transplant[a]	No RRT	10,000/life year 11,000/QALY
ACE inhibitors for all type 1 diabetics with macroproteinuria[b]	No RRT	1,100/QALY
Screening diabetic relatives of nephropathy patients[c]	No screening	Screening potentially cost saving
Treat all type 2 diabetics with ACE inhibitors[d]	Screening for microalbuminuria and treating those who test positive	Incremental cost-effectiveness ratio is 7,500/QALY for treating all type 2 diabetics
Treat all insulin-dependent diabetics with ACE inhibitors[e]	Screening for microalbuminuria or macroproteinuria and treating those who test positive	Treating all insulin-dependent diabetics dominates under a plausible range of parameters

Sources: [a]Winkelmayer and others 2002 (review); [b]authors' rough estimates; [c]Satko and Freedman 2001; [d]Golan, Birkmeyer, and Welch 1999; [e]Kiberd and Jindal 1998.

Kidney transplants are the most cost-effective intervention for ESRD. Transplant costs in developed countries have declined steadily from about US$60,000 in 1970 to about US$10,000 currently (Winkelmayer and others 2002). In addition to facing transplant costs, patients face ongoing costs for immunosuppressive drugs, which start at about US$3,000 per year initially but can decline thereafter to US$300 per year (Kher 2002). Kidney transplants are cheaper in India than in the United States, ranging from US$1,500 in government hospitals to as much as US$7,000 in private hospitals. Such costs, combined with a higher quality of life than obtained with dialysis, make renal transplantation the most cost-effective option (table 36.3). However, the availability of kidneys is a major limiting factor. Developed countries tend to have well-organized organ retrieval programs, and cadaveric donor transplants are more common than they are in developing countries. Japan, with its extremely low transplant rates, is an exception, perhaps because of difficulties in obtaining permission for organ donation.

Developing countries have limited access to cadaveric donor programs but better living donor programs. Unrelated living donors are more common than in developed countries because poverty increases the willingness of donors to offer kidneys in

exchange for payment. The Philippines recently restricted donations to "emotionally related" donors, but that limitation does not prevent abuses, such as men marrying women of the appropriate blood type in the hope of obtaining a kidney. Developing countries face particular transplantation problems, such as patients' inability to continue paying for immunosuppressive drugs and the transmission of hepatitis B and C, malaria, and TB through organ transplant (Kher 2002).

Long-term hemodialysis was introduced in 1960 and is the most costly treatment option at approximately US$60,000 per year at a center and US$40,000 at home in developed countries. It is most cost-effective if used as an interim measure before kidney transplant. Peritoneal dialysis—for example, continuous ambulatory peritoneal dialysis—was developed in the late 1970s and is less expensive—approximately US$20,000 per year (Winkelmayer and others 2002). Most economies continue to rely on hemodialysis for dialysis patients, except for those mandating that continuous ambulatory peritoneal dialysis be the first choice—that is, Hong Kong (China), Mexico, New Zealand, and the United Kingdom. Switching to continuous ambulatory peritoneal dialysis has the potential of reducing costs for developing countries, especially if they manufacture the consumables domestically rather than importing them. Nevertheless, dialysis remains costly and is not a viable long-term solution in places where health budgets are limited.

More than 120 countries have dialysis programs (Moeller, Gioberge, and Brown 2002). The following data from India highlight the stark economics of dialysis (Kher 2002). Government hospitals will provide hemodialysis only for acute renal failure or pretransplant stabilization (Li and Chow 2001), and with an incidence of 100 per million population, approximately 100,000 patients develop ESRD each year. Of the 10,000 who consult a nephrologist, RRT is initiated for 9,000. Of the 8,500 who begin hemodialysis, about 60 percent are lost to follow-up within three months, probably because of the costs involved. Few remain on dialysis after 24 months. Between 17 and 23 percent of those on dialysis for two to three months receive transplants.

IMPLEMENTATION OF CONTROL STRATEGIES: LESSONS OF EXPERIENCE

Measures for primary and secondary prevention of CKD are now well documented and will eventually reduce the number of patients requiring dialysis. Until recently, the focus has been on RRT to save lives, and considerable efforts are being made to improve the quality of dialysis. In the United States, guidelines derived from the Kidney Disease Outcomes Quality Initiative have added greatly to the quality of dialysis in terms of access (graft or fistula), adequacy, treatment of anemia, treatment of secondary hyperparathyroidism, and—more recently—greater emphasis on CVD, all of which contribute to quality-of-life outcomes, but at an increased cost (National Kidney Foundation 2002).

The high mortality rate of dialysis approximates 10 percent per year and has changed little over the past decade; however, new approaches are emerging for dealing with CVD in RRT facilities. More patients with kidney disease die before they get to the point at which they need treatment for renal failure, because early kidney disease is a major marker for CVD and reinfarction, congestive heart failure, and stroke.

In middle-income countries such as Thailand and Turkey and in middle-income countries in Latin America (Zatz, Romão, and Noronha 2003), extensive dialysis facilities are available, as they are in some low-income countries. For example, in 2003, Pakistan had 110 centers with 2,400 patients on hemodialysis; India had 100 centers with 6,000 patients mostly on hemodialysis; and China had 75,000 patients on dialysis. Those figures show that needs and markets for dialysis are expanding. However, in poorer countries, such as Nicaragua and Tanzania, options for RRT are limited because of the lack of equipment, trained staff, and costly consumables. In addition, many low-income countries lack health insurance to defray treatment expenditures, keeping dialysis out of reach. In such countries—for example, Nigeria—dialysis directed at preparation for renal transplantation is the best policy. Recent findings concerning primary prevention through lifestyle changes and secondary prevention by means of pharmaceutical treatment should eventually reduce, but not eliminate, the burden of ESRD.

The acknowledgment by the World Bank and the World Health Organization that chronic conditions, particularly those resulting from diabetes and hypertension, will increase to become a leading cause of death by 2028 has intensified the need for prevention and RRT programs. The need to increase awareness, launch targeted screening and intervention studies, provide training for staff, maintain education for physicians in kidney and urological disease, and assist centers for RRT is urgent.

Developed nations have well-established nephrology and urology centers attached to academic medical institutions and regional public and private secondary and tertiary referral hospitals. They have training programs to meet national requirements for health professionals—including renal physicians, primary care physicians, and nurses—specializing in kidney and urological disorders. Their centers incorporate the results of up-to-date research developments pertaining to kidney disease and clinical applications of the latest advances in care and technology. Numerous publications arise from academic endeavors, and a close association exists between health care delivery and pharmaceutical industries. Each country and region has societies of nephrology and urology for adults and children.

Middle-income countries may have both public academic centers and private hospitals that offer specialized equipment,

such as lithotripters and imaging technology, and dialysis and transplant programs. Although facilities and trained staff for RRT are more limited than in developed countries, some developing countries, such as Turkey, have excellent facilities.

In lower-income countries, facilities and staff are in short supply, and assistance is needed. Large countries, such as China, India, and Pakistan, have kidney centers available but have considerable unevenness in development of kidney centers and health care in general. Some lower-income countries possess remarkable institutions; for instance, the Sindh Institute of Urology and Transplantation in Karachi, Pakistan, which is supported mainly by charitable donations, provides every patient who presents with ESRD an opportunity for accessing RRT. Overall, however, centers of excellence are urgently needed in developing countries. All the "players," from governments and international organizations to societies and foundations, need to be congregated in conjunction with national institutions to focus on the continued advantages—through treatment—that can be delivered to those developing cardiovascular, diabetic, and kidney disease.

RESEARCH AND DEVELOPMENT AGENDA

Significant progress in knowledge about the geographic burden of kidney and urological diseases has taken place during the past three or four decades as a result of more accurate registries. An international kidney disease data center, in partnership with the World Bank and the World Health Organization, is now required to progressively increase the amount and quality of data collected worldwide.

Basic Knowledge of Kidney Disease

Recent research findings have advanced the understanding and treatment of kidney disease. A continuing emphasis on understanding the basic mechanisms of glomerulonephritic, vasculitic, and autoimmune disease and the detailed mechanisms of the progression of kidney disease to kidney failure is required, as well as research into improved therapies. Well-developed research centers are best equipped to deal with these requirements, aided by national governments, charitable organizations and foundations, international organizations, and centers in the developing world.

Prevention of Kidney Failure

Prevention of acute and chronic kidney disease should be a global priority. During the past decade, an array of clinical trials has been directed at assessing the benefits of interventional therapy, particularly the success of ACE inhibitors. Such trials can play an important role in increasing knowledge and improving the implementation of prevention of kidney disease in developing countries. Training epidemiologists and physicians to execute screening strategies and clinical trials in their own settings is urgently needed. The cooperation of global funding agencies and training centers; the consistent availability of effective, inexpensive pharmaceuticals; and the assessment of the efficacy and side effects of multiple drug therapy must be coordinated. The priority is to make low-cost drugs available, using as a model the recent process that allowed universal access to inexpensive antiretrovirals for HIV infection.

Renal Replacement Therapy

Successful RRT outcomes depend on reducing morbidity and mortality among dialysis patients. RRT costs escalate in concert with the rising costs of pharmaceuticals—for example, erythropoietin compounds to treat anemia and vitamin D metabolites and calcimimetics to treat secondary hyperparathyroidism and bone disease. Strategies that will result in less expensive dialysis systems and pharmaceuticals are needed (Schieppati, Perico, and Remuzzi 2003). Costs relating to renal transplantation have reached a steady state, but the lack of availability of donor kidneys is a serious—and perhaps irresolvable—limitation.

Establishment of Teaching and Research Centers

Most high-quality training and research centers for kidney and urinary diseases are in the developed world, where training is expensive. Important centers of clinical care have emerged in countries such as Argentina, China, Mexico, South Africa, Thailand, and Turkey. The ability to obtain high-quality training at the local level would be advantageous to developing countries. For example, the International Society of Nephrology has identified and supported a major clinical training center in South Africa that plays a leading role in training nephrologists and urologists for South Africa and other Sub-Saharan African countries to world standards at lower costs than in developed countries and with increased retention of local physicians. Such local centers should be a national priority in developing countries and should be closely linked to international centers for cardiovascular and diabetic disease, meeting approved international standards for training while recognizing national differences in the pattern of kidney disease. Financial assistance is required to enhance the education and training of health professionals, improve baseline infrastructure, and initiate research studies directed at critical clinical questions and at current and new knowledge relating to the prevention of kidney disease. The centers should have excellent data collection methods and a computer infrastructure that would connect them to current knowledge and allow them to communicate freely on a global scale. Major priority should be given to developing leading centers in selected regions.

Cost-Effectiveness of Treatment

More work is needed in the area of screening and treatment in both developed and developing countries. Work on the cost-effectiveness of screening and treating particular subpopulations would be useful, as would the development of better predictive tests for microalbuminuria. In addition, cohort studies of hypertensive and diabetic populations might help develop better indicators that predict susceptibility to progression toward nephropathy.

CONCLUSIONS: PROMISES AND PITFALLS

Kidney disease and kidney failure, especially as a complication of type 2 diabetes mellitus and hypertension, are rising globally and are rising faster in developing countries. Kidney failure patients account for a small fraction of the disease burden but a disproportionately high cost. CKD, along with all chronic diseases, is placing long-term demands on health care. On a global scale, RRT is rising sharply in terms of costs and is usually unavailable in developing countries. Hemodialysis and peritoneal dialysis are life saving, but in the long term they require coupling with newer, proven, interventional pharmacological treatments that frequently delay or stop continuing progression to ESRD. Advances in the past decade have proven that primary and secondary prevention measures can now reduce the burden of ESRD, and if they are not widely disseminated, the need for RRT will increase along with the certainty that the requirements of kidney disease patients cannot be met.

The following guidelines for diseases of the kidney and urinary system are recommended:

- Expand surveillance of the prevalence of various kidney and urological diseases in developing countries. Provide support for further epidemiological studies in selected countries for assessing the prevalence of kidney disease and interventions to address it and for establishing an international kidney disease data center.
- Promote public awareness in developing countries about the nature and early signs of kidney disease along with knowledge of prevention measures and therapies.
- Focus more attention on the increasing prevalence of diabetes and hypertension, and develop kidney disease programs in that context. Measures of kidney function and protein excretion should be taken. The implementation of primary and secondary prevention to reduce the prevalence of ESRD should be expanded.
- Increase coordination and resources for efficient and timely distribution of supplies and equipment, assessment of patients, and frequent dialysis for acute renal failure patients caused by crush injuries during such major disasters as earthquakes. Countries in earthquake-prone regions should develop emergency policies and practices and be linked with the appropriate international agencies.
- Have the World Bank and the World Health Organization establish a policy advisory group with relevant international groups, such as the International Society of Nephrology, to address and advise national and regional health ministries on kidney and urological strategies as requested.
- Make major health and medical education programs available on an annual basis through existing societies and agencies to train and update physicians, nurses, technicians, and other relevant health professionals.
- Develop selected centers of excellence for education, training, clinical care, and prevention of kidney and urological disease and clinical care of renal failure. At least 10 such centers should be developed in the next decade and located in the countries of the former Soviet Union, Africa, Asia, Eastern Europe, and Latin America. Funds should be provided by international and national agencies and national government organizations and be sustained for up to 10 years.

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