Comorbid Conditions and Special Problems in Dialysis Patients

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Renal failure seldom exists as an isolated clinical entity. Rather, renal patients usually manifest other non-renal medical conditions. These comorbid conditions greatly modify clinical outcomes and medical resource utilization, as do major demographic characteristics such as age, race, sex, and socioeconomic status. The distribution of comorbid conditions and demographic characteristics among patients describes the case mix of a population (e.g. all dialysis patients, all end-stage renal disease (ESRD) patients, all patients in a dialysis unit).

Comorbidity generally refers to the additional (non-renal) illnesses present in a patient or population at a given time, such as start of ESRD or start of a year. Comorbidity can obviously change over time. In the specific context of ESRD, comorbid conditions may be present when renal replacement therapy (RRT) is initiated. Such baseline comorbid conditions may have caused or contributed to the development of kidney failure. Diabetes mellitus (DM) and systemic vasculitis illustrate comorbid conditions of this type. Alternatively, comorbid conditions may develop after the onset of kidney disease, perhaps as a direct or indirect consequence of renal failure and its treatment. Renal osteodystrophy and anemia exemplify this pattern of comorbidity. The relationship between renal disease and a comorbid condition may be bi-directional. For example, conditions such as hypertension may both contribute to and result from renal failure. All comorbid conditions can potentially influence mortality, morbidity, quality of life, and utilization of medical resources. This chapter considers some of the most common comorbid conditions associated with ESRD, without regard for causality.

Comorbid conditions are important for several reasons. Comorbidity should be considered for epidemiologic research and quality improvement activities. Important clinical outcomes, such as mortality, hospitalization, and quality of life, are greatly influenced by patient comorbidity in addition to demographic characteristics and treatment practices. Thus, comorbidity adjustment is potentially needed for proper assessment of outcomes and clinical performance. Comorbidity is also a major determinant of the resources required to care for patients with ESRD. On average, comorbid illnesses require additional medical services such as hospitalization, procedures, and specialty care. Patient comorbidity can be important for understanding the causes and consequences of renal failure. Finally, the provision of medical care to ESRD patients largely entails the treatment of comorbid conditions. Modern dialysis and transplantation techniques can usually control the direct clinical consequences of renal failure such as fluid overload, hyperkalemia, and the uremic syndrome. Most of the major medical problems faced by ESRD patients

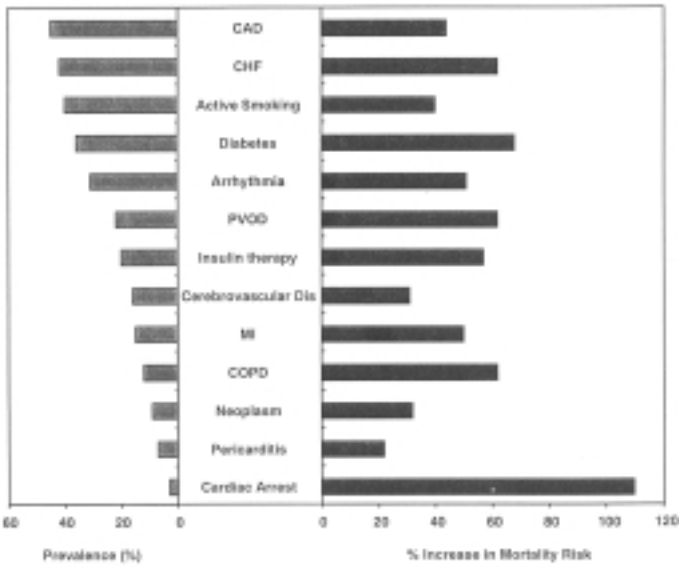

Figure 1. Prevalence (left panel) and mortality risk (right panel) associated with selected comorbid conditions in ESRD patients. Data taken from USRDS 1995 Annual Data Report.

arise from comorbid diseases rather than renal failure. Consequently, most hospitalizations and deaths among ESRD patients are attributable to comorbid conditions. A similar accounting of comorbidity from other countries might reveal interesting contrasts in the nature and consequences of comorbidity among different groups of ESRD patients.

Among a defined group of patients, the proportion with a given comorbid condition is expressed as the prevalence. The rate at which a comorbid condition appears among individuals previously lacking the condition is expressed as incidence. For renal patients, considerably more is known about the prevalence than the incidence of most comorbid conditions. Although the severity of a given comorbid condition can vary greatly in clinical terms, uniform and validated severity measures are poorly developed at this time. The degree to which an outcome, such as mortality, is associated with a baseline comorbid condition is measured by the relative risk. The deviation of relative risk above 1.0 indicates the excess mortality associated with the attribute as compared to the group of individuals lacking the attribute. For example, a relative risk of 1.2 indicates a 20% increase in mortality. If the baseline death rate is 25%, then a relative risk of 1.2 translates into an absolute risk of 30%.

Comorbid Conditions Associated with ESRD

Figure 1 shows the prevalence of several important comorbid conditions associated with ESRD from a randomly selected, nationally representative group of hemodialysis (HD) patients in the U.S. [1]. The list, while not exhaustive, is useful for prioritizing the many specific comorbid conditions that are seen in ESRD patients. The figure also illustrates the relative mortality risk associated with each comorbid factor, as derived from a multivariate regression model of survival. Subject to several assumptions, the model estimates the independent effect of each comorbid condition on mortality under the addi-

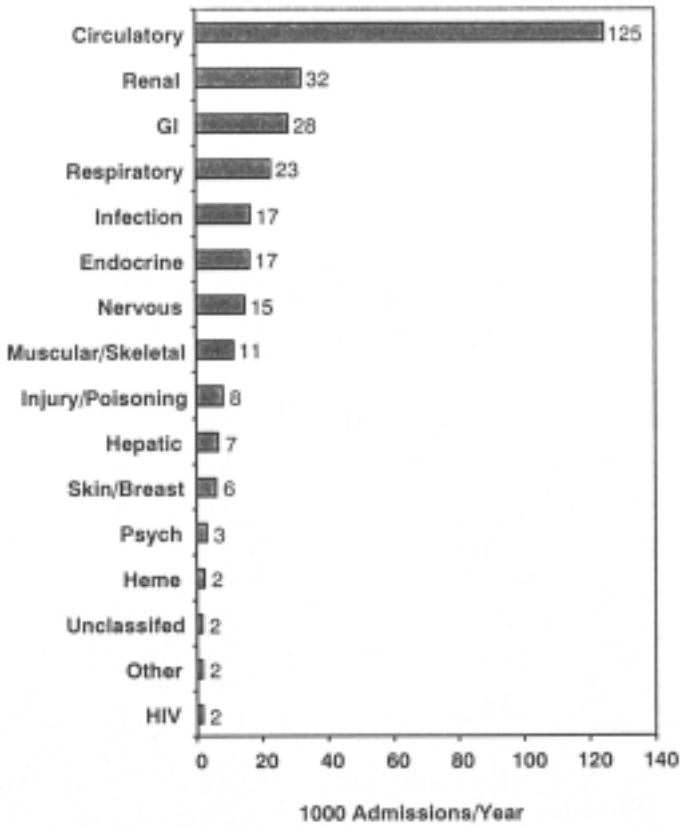

Figure 2. Hospital admission rates for ESRD patients by selected disease categories. Data taken from USRDS 1997 Annual Data Report.

tional assumption that all other modeled characteristics (demographic and comorbid factors) are held constant. For example, coronary artery disease (CAD) was present in 45% of the patient sample. As a group, the patients with CAD had a 44% higher chance of death compared to patients lacking a baseline diagnosis of CAD. The prevalence and risk of any given comorbid condition tends to vary among studies, reflecting differences in case-mix. The comorbidities described in Figure 1 are broadly applicable to all HD patients in the U.S. The impact of comorbid conditions is further illustrated by Figure 2, which shows the major reasons for hospitalization, and by Figure 3, which shows the most common causes of death among U.S. dialysis patients [2]. These figures highlight the importance of comorbidity from a clinical outcomes viewpoint.

The prevalence of most comorbid conditions has increased over time, even after adjustment for differences in race, sex, and, especially, age [3, 4]. Increasing comorbidity among new ESRD patients could be explained by liberalization over time of the implicit criteria for referral and acceptance of patients for RRT. Another explanation for this trend is that survival has been increasing for patients at risk for developing ESRD but prior to the actual onset of ESRD. Improved patient survival in the pre-ESRD phase is plausibly attributable to improvements in the treatment of comorbid conditions, primarily cardiovascular diseases. The extended survival of patients with atherosclerotic CAD and other ill-

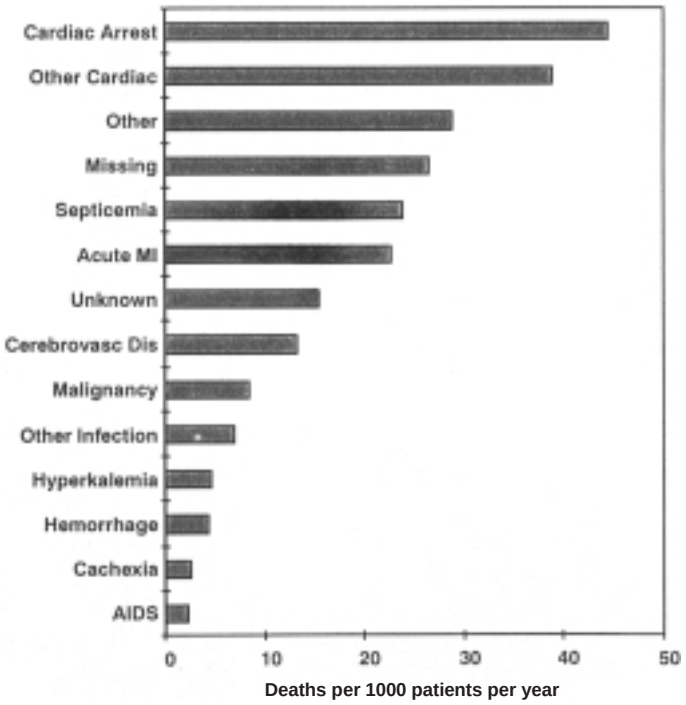

Figure 3. Distribution of deaths by cause for dialysis patients. Data taken from USRDS 1997 Annual Data Report..

nesses allows more time for the development of ESRD. This reduction in competing risk factors may partially explain the steady growth in new ESRD cases over the past 10 – 20 years [1].

The topic of comorbid conditions associated with renal failure encompasses nearly all of medicine. This chapter presents a brief discussion of selected comorbid conditions that are particular common or noteworthy. The discussion emphasizes prevalence, risk associations, and topical or evolving clinical information.

Diabetes Mellitus (DM)

DM is the single most common attributed cause of ESRD and a major comorbid condition. In a recent large national study of ESRD patients, DM was reported as a comorbid factor in 36% of patients whereas it was the attributed cause of ESRD in 27% of patients (Figure 1) [1]. Thus, DM is present or develops in a substantial number of patients in whom renal failure is caused by another disease. This point notwithstanding, the designation of DM as a comorbid condition is based on attributed cause of ESRD in many studies.

DM is clearly associated with increased mortality (Figure 1) and is an important adjustment factor (along with age, race, and other major causes of ESRD) for calculating the standardized mortality rate (SMR) for a dialysis unit [5]. DM disposes to accelerated atherosclerosis, a major factor in diseases of both large and small blood vessels. DM is also associated with excess formation of advanced glycosylation products, glycoproteins than bind to tissues in a non-enzymatic irreversible

fashion and disrupt cell functions. DM also disposes to infections, due in part to vascular disease and impairment of integumentary barriers and other host defense mechanisms. Retinopathy, peripheral vascular disease, and peripheral neuropathy often precede ESRD in diabetic patients. In general, the very fact of ESRD underscores the impact and severity of the disease in a diabetic individual.

Treatment considerations for patients with DM are discussed elsewhere. It is important to realize that insulin requirements may decrease with progressive kidney failure and ESRD due to loss of normal renal insulin elimination. The fall in insulin requirements in no way signifies any improvement in the underlying disease. Also, good glucose control should remain a goal even after initiation of dialysis. Although the goal of preventing renal injury may seem moot, it remains important to protect against further injury at other sites such as the eyes. Glycemic control may also be important for preserving residual renal function for as long as possible.

Hypertension

The prevalence of hypertension exceeds 70% among ESRD patients [6]. Hypertension often precedes the onset of ESRD. In the absence of other known renal diseases, renal failure is often attributed to hypertensive nephrosclerosis although it is realized that a variety of other etiologically important but otherwise nondescript diseases could be misdiagnosed as hypertension [7, 8]. Furthermore, renal failure usually stimulates blood pressure elevation in previously normotensive individuals and exacerbates hypertension in patients with pre-existing high blood pressure.

The etiology and pathogenesis of essential hypertension remains incompletely understood and classified at this time despite intensive investigation of this common condition. However, hypertension in renal patients is thought to be mediated by volume expansion in as many as 50 – 90% of cases [9, 10]. Hypertension is specifically associated with markers of long-term volume expansion, such as the diameter of the inferior vena cava and total body water [11, 12]. In accordance with this observation, aggressive ultrafiltration (UF) programs based on long (e.g. 8 hours) dialysis sessions have been associated with a decreased prevalence and severity of hypertension [13, 14]. Despite the apparent benefits of aggressive UF associated with long dialysis sessions, it is usually not practical to perform 8-hour treatments on a routine basis and methods have not been fully developed for achieving excellent UF and blood pressure control in large numbers of ESRD patients. Short, daily, home HD has been advocated as a practical method of lowering dry weight, blood pressure, and mortality. However, enthusiasm for such approached must be tempered by the studies that have found only small or negligible blood pressure elevations associated with intra-dialytic fluid gains and short-term volume loading [15, 16]. Discrepancies among current studies regarding the relationship between volume status and blood pressure may be explained by varying sensitivity of the techniques used to measure volume.

Nonetheless, the current body of evidence does not uniformly support the conventional assumption that hypertension is directly associated with adverse clinical outcomes in ESRD patients. In non-ESRD patients, blood pressure is clearly associated with increased cardiovascular morbidity and mortality. Furthermore, multiple randomized controlled trials have shown benefit from lowering blood pressure. In contrast, while some studies show

that increased blood pressure is associated with higher mortality in the ESRD population [4, 17], a surprising number of studies (some involving large numbers of patients) have not found this expected relationship [18 – 20]. While low blood pressure could plausibly be associated with high mortality due to cardiac dysfunction or coronary ischemia, it is difficult to explain the lack of association between high blood pressure and mortality. The expected relationship may be obscured by the frequent use of antihypertensive drugs in ESRD patients or by the variability in blood pressure throughout the interdialytic period but the issue requires further study.

There has been growing interest in the use of ambulatory blood pressure monitoring (ABPM) for ESRD patients. This technique is especially attractive for HD patients who experience potentially large fluctuations in blood pressure between dialysis treatments. In a recent study, the prevalence of hypertension was over 70% by ABPM compared to 25% using conventional measurements [21]. Furthermore, ABPM results were strongly correlated with the echocardiographic presence of left ventricular hypertrophy. ABPM has generally revealed a loss of the normal diurnal blood pressure pattern in patients treated with both HD [21] and peritoneal dialysis (PD) [22]. The use of ABPM may clarify the relationship between blood pressure and clinical outcomes. However, until ABPM measurement are convincingly associated with outcomes and clinical management decisions, the technique will probably be used primarily as a research tool.

Despite efforts to maximize UF, hypertension is still very prevalent in most dialysis units. Furthermore, despite the confusion about the nature of the association between blood pressure and cardiovascular outcomes in ESRD patients and the lack of controlled studies supporting the efficacy of treating ESRD patients, most experts believe that hypertension should be treated in this group of patients. At this time, pharmacologic approaches are recommended for patients whose blood pressure cannot be controlled through dialytic UF. The overwhelming body of epidemiologic and clinical trial evidence in non-ESRD patients supports this position until more definitive information emerges for ESRD patients. However, it is important to recognize that antihypertensive medications can be surprisingly ineffective in fluid-overloaded patients, whether due to inadequate dialysis or dietary non-compliance. There is very little information in ESRD patients on which to base the selection of antihypertensive medications. Beta antagonists are attractive because they have been shown to improve survival in patients with coronary artery disease, a very common comorbidity in the ESRD population. It has been argued that beta antagonists have been underutilized because of exaggerated concerns that they mask the symptoms of insulin reactions in diabetic patients [23]. Angiotensin converting enzyme (ACE) inhibitors have been claimed to decrease inter-dialytic weight gain through suppression of the central thirst mechanism [24] but this compelling finding has not been replicated [25]. However, this class of drug provides a survival advantage in non-ESRD patients with DM as well as congestive heart failure (CHF) [26]. Calcium channel blockers have enjoyed popularity because they are well tolerated but they have not undergone long-term studies and have been linked to increased coronary events [26, 27]. Blood pressure in ESRD patients is also modified by a wide variety of other dietary and treatment-related factors including salt intake, calcium intake, phosphate balance, erythropoietin administration, and red cell mass [28].

Coronary Artery Disease (CAD)

Atherosclerotic CAD is one of the most common and important comorbid conditions in ESRD patients. For classification purposes, CAD includes the current or historical presence of angina, myocardial infarction (MI), abnormal coronary angiogram, or coronary bypass surgery or angioplasty. Approximately 30 – 45% of new ESRD patients carry a diagnosis of some form of CAD, depending on the specific definition and series [1, 29]. As in the non-renal population, virtually all CAD is caused by atherosclerosis, which is associated with well known risk factors including hypertension, hyperlipidemia, smoking, and family history. These risk factors can also cause or contribute to the development of renal failure. Thus, ESRD and CAD are associated on the basis of underlying risk factors. In addition, renal disease has been hypothesized to accelerate the development and progression of atherosclerosis, leading to excess CAD in the ESRD population [30, 31]. Among ESRD patients, the presence of CAD has been associated with an increased mortality risk in some [1] but not all studies [29]. However, CAD, manifest as acute MI and cardiac arrest, is the single most common cause of death among ESRD patients, accounting for > 30% of deaths [2]. The mortality risk of CAD is augmented in patients with concomitant CHF [29].

The clinical presentation of CAD in ESRD patients is usually similar to non-renal patients. However, atypical presentations may occur, particularly in diabetic patients who are prone to silent ischemia and painless myocardial infarctions [32]. The sensitivity of non-invasive stress testing appears to be lower in renal patients than in non-renal patients [33]. Dobutamine stress echocardiography may be more sensitive than other techniques for inducing stress and detecting ischemia [34]. All else being equal, the clinical threshold for performing coronary angiography should be lower for ESRD patients than for non-renal patients.

Coronary ischemia can be treated either medically or through revascularization procedures. The usual factors should dictate the decision. Medical therapy with nitrates, beta antagonists, calcium antagonists and correction of anemia should be fully explored. The evidence that beta antagonists lower mortality from coronary disease is especially strong and it has been suggested that these agents are underutilized in ESRD patients [23]. In contrast, calcium antagonists have been less well studied altogether and, although attractive drugs in terms of patient tolerability, may be used more often than justified by current evidence. In some centers, there is a reluctance to perform revascularization procedures in ESRD patients because of their poor average survival and perceived high risk status. An individualized approach that considers the patients overall status should be used. The available evidence indicates that ESRD patients accrue similar benefits from revascularization procedures [35]. A growing body of evidence suggests that angioplasty is less effective than coronary bypass surgery, particularly in diabetic renal patients [36].

Congestive Heart Failure (CHF) and Cardiomyopathy

CHF commonly develops as a consequence of coronary disease and other types of organic heart disease. Although patients with renal

failure and ESRD are disposed to fluid accumulation on the basis of decreased capacity to excrete salt and water, pulmonary edema is unusual in the absence of decreased heart pumping function. However, the occurrence of flash pulmonary edema in the setting of relatively well preserved systolic cardiac function suggests the possibility of diastolic dysfunction or functionally significant bilateral renal arterial occlusive disease. A clinical diagnosis of CHF is associated with a > 60% increased mortality risk in ESRD patients.

For ESRD patients, PD is sometimes preferred over HD because of continuous UF and avoidance of continuous shunting of cardiac output through a vascular access [37]. PD is effective for controlling CHF symptoms and ventricular function [38] but it has not been clearly shown to be superior to other modalities. CHF management is centered on dietary restriction of salt and water and fluid removal through dialysis. Diuretic therapy is not usually helpful except for new ESRD patients who still produce urine or the occasional patient with preserved residual urine output. Afterload reduction with ACE inhibitors should be considered but may compromise residual renal function and dispose to hyperkalemia. Close monitoring is recommended when using these drugs. Digitalis preparations may be effective but the most common preparation, digoxin, is normally excreted by the kidneys, necessitating dose adjustment and close monitoring of blood levels in renal patients. As with any patient with CHF, the underlying cause of the pump failure should be explored and treated to the extent possible.

CHF indicates the presence of cardiomyopathy, broadly defined as a pathologic alteration of the cardiac muscle. Cardiomyopathy may also be manifest as arrhythmia or it may be subclinical. Several types of cardiomyopathy have been characterized in ESRD patients [39].

The high prevalence of CAD among ESRD patients gives rise to ischemic cardiomyopathy, manifest by regional wall motion abnormalities, decreased ejection fraction, and clinical symptoms and signs of CHF. Ischemic cardiomyopathy and regional wall motion abnormalites imply the presence of prior myocardial infarction. Angina may or may not be present, depending on patient characteristics and the presence of ischemic myocardium. Patients should be assessed for at-risk myocardium and possible revascularization. However, the risk of bypass procedures is generally elevated in patients with pump failure.

Dilated cardiomyopathy is characterized echocardiographically by increased chamber volume and decreased left ventricular pumping function. Typically, the left ventricular ejection fraction is < 40%. Patients may present with CHF or arrhythmia. Dilated cardiomyopathy appears to be distinct from ishcemic cardiomyopathy in that regional wall motion abnormalities are lacking and coronary artery disease may be absent. The etiology of the dilatation is unclear but may be associated with the uremic state or uremic toxins.

Hypertrophic hyperkinetic cardiomyopathy is characterized echocardiographically by thickened ventricular wall, normal chamber volume, and relatively preserved pump function. These patients are usually considered to have cardiac symptoms on the basis of diastolic dysfunction. Left ventricular systolic dysfunction and the CHF syndrome can arise as a late manifestation. Hypertrophic cardiomyopathy confers substantial mortality above and beyond hypertension. LVH is associated with CHF and arrhythmia is an independent risk factor for mortality. The pathogenesis of hypertrophic cardiomyopathy has been related primarily to hypertension [21] but factors such as anemia, obesity, valvular

heart disease, sympathetic overactivity, certain antihypertensive medications, and anemia may also play an important role [40 – 42]. These associated conditions should be identified and rectified to the extent possible. The complications associated with LVH should be addressed as required by clinical circumstances.

Arrhythmia

Cardiac arrhythmias are an independent risk factor in ESRD patients (Figure 1). Mild rhythm disturbances are extremely common in ESRD patients. When sought by Holter monitoring, ventricular and supraventricular arrhythmias were found in 30 – 90% of dialysis patients [43, 44]. The frequency of these largely assymptomatic arrhythmias increased during or following HD treatments. The prevalence of arrhythmias increased with age of the patient and longer duration of ESRD. Arrhythmias may be less common in continous ambulatory peritoneal dialysis (CAPD) patients than HD patients [45].

Arrhythmias can arise from electrolyte disturbances, as a reaction to the dialysis and UF procedure, and heart disease. More serious arrhythmias usually arise secondary to underlying organic heart disease. The relative risk of death is increased 51% in ESRD patients with a recorded clinical history of arrhythmias, without regard for the nature or success of treatment. Treatment should be initiated with pharmacologic, electrical, or surgical techniques as for non-renal patients. Drugs such a procainamide are normally excreted by the kidneys, necessitating careful dose adjustment and monitoring of drug and metabolite levels.

Cerebrovascular Disease

Cerebrovascular disease arises from the same metabolic, environmental, and genetic risk factors that promote atherosclerosis in other vascular beds. The prevalence of cerebrovascular disease of any type is approximately 16% in ESRD patients. Approximately 13% of deaths in ESRD patients are attributed to cerebrovascular disease. Among ESRD patients, the risk of death from stroke (as for other causes of death) is inversely related to the delivered dose of dialysis [46].

The clinical manifestations, diagnosis, and treatment of cerebrovascular disease are similar in the renal and non-renal populations. The major cerebrovascular syndromes are transient ischemic attack (TIA) and cerebrovascular accident (CVA). In addition, hemodialysis patients are susceptible to subdural hematomas, in part related to platelet dysfunction and regular exposure to heparin. The incidence of stroke is > 4-fold higher among ESRD patients than the general population [47]. Among ESRD patients, the risk of carotid atherosclerosis is associated with age, coroanry disease, and the plasma concentration of lipoprotein (a).

Carotid endarterectomy prevents subsequent stroke in patients with high grade carotid stenosis or symptomatic TIAs. However, patients with renal failure have been found to have poorer outcomes than non-renal patients in terms of operative mortality and subsequent stroke [48, 49]. At this time, an individualized assessment of risks, benefits, and patient preferences related to surgical intervention should be undertaken.

Peripheral Vascular Disease (PVD)

PVD is reported in approximately 36% of dialysis patients and is associated with increased mortality risk. The risk and pathogenic factors are fundamentally similar for PVD and CAD. Many of the important risk factors for atherosclerosis are commonly present in renal patients, including hypertension, diabetes, and a history of smoking. The problem may be compounded to the extent that renal failure independently promotes atherogenesis.

Dialysis patients experience the same clinical manifestations of PVD as non-renal patients including intermittent claudication, rest pain, and ulceration of the extremities. Physical findings may include diminished or absent peripheral pulses, skin atrophy, decreased hair growth, and ulcers. The diagnosis is confirmed and staged using non-invasive vascular studies and angiography. The lower extremities are preferentially affected. However, upper extremity arterial inflow is particularly important for hemodialysis patients with permanent vascular accesses in the upper extremities. It is likely that upper extremity arterial occlusive disease contributes to vascular access problems including failed maturation, low flow, thrombosis, and steel syndromes. Upper extremity disease that might otherwise be assymptomatic can manifest itself in HD patients in this way. Hand weakness, digital ulceration, and amputations can be unfortunate complications of the combination of upper extremity vascular disease and vascular access devices.

The treatment of PVD is graded to the severity of illness. Mild disease can be managed by life style changes. Smoking cessation will often yield some symptom relief. Elimination of medications that impede peripheral dilation should be considered. Patients with more advanced disease can be considered for revascularization procedures, either surgery or angioplasty. Many ESRD patients progress to amputation, particularly diabetic patents who tend to have microvascular disease that is not amenable to revascularization. PVD is a marker for increased cardiovascular morbidity and risk. Higher mortality has been reported for revascularization surgery than for primary amputation, suggesting the need to carefully select patients for aggressive revascularization procedures [48].

Hyperlipidemia and Hyperhomocysteinemia

The high prevalence of atherosclerotic vascular disease among ESRD patients is potentially explained by several prominent risk factors including hypertension, cigarette smoking, DM, and hyperlipidemia. A variety of lipid abnormalities have been described in ESRD patients including hypertriglyceridemia and low high density lipoprotein (HDL) cholesterol. The pathogenesis of these abnormalities is partly related to decreased lipoprotein lipase activity, possibly as a consequence of accumated cytokines and other toxins [50]. The independent association between lipid abnormalities and either cardiovascular complications or outcomes has not been extensively studied in patients with renal failure. Based on extensive studies in non-renal patients, hyperlipidemia should be sought and treated in ESRD patients but definitive proof of efficacy is lacking at this time.

Homocysteine is an amino acid that has been found to be associated with athero-

sclerosis in the general population. Homocysteine levels are substantially elevated in ESRD patients [51]. Hyperhomocysteinemia is associated with the low concentrations of folate and pyridoxine and exogenous administration of these vitamins appears to lower homocysteine levels.

Anemia

Some degree of anemia develops in the majority of patients with ESRD, often beginning in the pre-ESRD phase of renal failure. The predominant reason for the anemia of renal failure is erythropoietin deficiency. Erythropoietin is produced in the kidney and the synthetic capacity declines with progressive renal failure. In addition, direct bone marrow suppression and shortened red blood cell survival have been reported for ESRD patients. The HD procedure is also associated with mild blood loss although this has been minimized with modern techniques.

Anemia is associated with measurable differences in mortality and morbidity. A recent large observational study found that mortality risk was approximately 2-fold higher in patients with a hemoglobin concentration < 8 g/dL as compared with a concentration of 10 g/dL [52]. The majority of patients were being treated with recombinant human erythropoietin (rHu-EPO). The study could not reliably distinguish among the effects of anemia per se, rHu-EPO treatment, and comorbid conditions, such as infection, that might induce rHu-EPO resistance. Anemia was also associated with left ventricular dilation, clinical heart failure, and increased mortality [42]. The treatment of anemia with recombinant rHu-EPO was also associated with a reduction in hospitalization [53]. Anemia also influences individual patients as revealed by the effects of rHu-EPO treatment. The correction of anemia using rHu-EPO was associated with improvements in exercise capacity, oxygen consumption, appetite, nutritional status, and quality of life [54, 55, 56].

The anemia of renal failure is characterized by normochromic normocytic red blood cell morphology. rHu-EPO levels are inappropriately low for the degree of anemia but it is seldom necessary to measure hormone levels in order to make a secure diagnosis. In the absence of other causes of anemia or treatment with rHu-EPO, the blood concentrations of iron, ferritin, vitamin B_{12}, and folate are usually in the normal range. Patients exhibit variable degrees of fatigue and anorexia. The symptoms of any underlying cardiovascular disease may be exacerbated by anemia. However, the onset of the anemia is often so insidious so that the patient does not perceive the functional decline.

The treatment of anemia has been greatly facilitated by the availability of rHu-EPO. Current guidelines call for initiation of therapy at a dose of 80 – 120 U/kg/week administered as 2 – 3 doses. The subcutaneous (SC) route is probably more effective than the intravenous (IV) route. The goal of therapy is to increase hematocrit (HCT) to the range of 33 – 36%. Greater elevations may be associated with worse outcomes for unclear reasons. Iron deficiency often develops in rHu-EPO-treated patients due to the high degree of iron needed to support new erthropoiesis. Iron replacement therapy is usually required. Oral iron preparations are poorly absorbed and iv iron is usually required. Both intermittent replacement regimens and continuous maintenance regimens have been proposed [57, 58]; the ideal regimen remains to be established. Iron should be supplied to maintain the transferrin saturation > 20%. Additional response in

terms of HCT may be seen at even high iron levels but the serum ferritin should remain < 800 ng/mL to avoid iron toxicity. The response to rHu-EPO may be augmented by concomitant use of androgens (nandrolone decanoate) [59]. RHu-EPO responsiveness is also augmented by increased delivered dose of dialysis [56, 60]

Renal Osteodystrophy

Renal osteodystrophy in the broadest sense refers to the alterations in mineral metabolism and bone health associated with kidney disease. This complicated topic is discussed at length elsewhere. However, it is important to mention renal osteodystrophy in the context of comorbid conditions. The consequences of altered mineral metabolism extend beyond the direct features of bone disease, such as fractures, pain, and osteopenia. Altered mineral metabolism can lead to mineralization of soft tissues and blood vessels, and therefore contribute to functional alterations of virtually every organ system. Hyperparathyroidism has been implicated as a major uremic toxin. Altered mineral metabolism has been associated with a variety of clinical conditions and symptom complexes such as impotence, anemia, and weakness. Patients with markers of altered mineral metabolism have increased mortality. The wider implications of renal osteodystrophy and its treatment require further investigation.

Carpal Tunnel Syndrome (CTS)

CTS occurs more often among ESRD patients than the general population. The excess incidence of CTS is generally attributed to β_2-microglobulin (B2M) deposition within the median nerve sheath. The clearance of B2M is compromised in patients with ESRD. B2M deposition also contributes to bone pain and arthropathy. While CTS probably does not confer added mortality risk, it is a significant cause of morbidity, medical expense, and decreased quality of life.

Patients usually complain of numbness and parasthesias of the middle 3 fingers of the affected hand. Initially, the symptoms are worse at night and may interfere with sleep. As the condition progresses, it can cause weakness and muscle atrophy. The clinical diagnosis is confirmed by electromyography. The initial treatment for relatively mild disease consists of wrist splints and non-narcotic analgesics. Often, these measures are inadequate over time and patients will require surgical release of the carpal tunnel. Surgical results are usually highly satisfactory in well-selected patients. The development of CTS in the same hand as a patient's vascular access presents the risk of access failure in that arterial inflow must be mechanically occluded in order to achieve a bloodless operative field.

Infectious Diseases

Infectious deaths are relatively common in ESRD patients, accounting for 31% of deaths annually. The incidence of infectious diseases

is also increased in ESRD. Most infectious complications occur acutely while a patient is receiving dialysis. However, there are several chronic infections that may predate ESRD and can rightly be considered as comorbid conditions. The high infection rate in ESRD patients is attributable to both increased exposure to infectious agents and decreased host defenses. From the viewpoint of this chapter, comorbidity among ESRD patients consists of an increased prevalence of chronic infections and an increased risk of acute infections.

ESRD patients face numerous infectious exposure opportunities. HD patients are vulnerable to infection through the HD procedure which requires regular entry into the circulation. A common nidus for infection can be found in the synthetic materials that are often used for vascular access in the way of temporary catheters or synthetic bridge grafts. Blood products were a historically important source of viral infection although the risks and exposure have been dramatically curtailed by the advent accurate testing for blood borne viruses, hepatitis B vaccine, and rHu-EPO for treatment of anemia. For PD patients, the dialysis catheter affords an efficient mode of entry and the dialysis fluid a rich breeding ground for infections.

The infectious exposure opportunities are magnified by defects in host defense that arise as a consequence of the uremic syndrome. Multiple alterations in host defense mechanisms have been described. Compromised humoral immunity is seen by decreased immunoglobulin responses to specific antigen stimuli. Altered cell-mediated immunity is manifest by decreased delayed hypersensitivity and T cell proliferative responses to specific stimuli, decreased production of interleukin-2, and decreased T cell sub-populations. The role and importance of specific defects in immune function remains unclear. Furthermore, it is difficult to quantitate the role of increased exposure vs. decresed defenses in the high risk of infection among ESRD patients.

Infection control procedures are critical in the dialysis procedure to protect both patients and staff. Universal blood handing precautions must be followed. Blood transfusions should be minimized. When transfusions are required, rigorous blood screening programs should be in place. Native arteriovenous fistulas are preferred over vascular access devices that require synthetic materials, both from the viewpoint of infection control and longevity of the access. Much evidence suggests that synthetic grafts are used more than necessary in the U.S. Patients should be vaccinated against hepatitis B and pneumococcus, preferably prior to the development of ESRD. Increased dose or frequency of hepatitis B vaccine may be required for seroconversion of ESRD patients. In addition, ESRD patients almost always meet the accepted criteria for receiving yearly influenza vaccination. Many units isolate patients with chronic viral infections such as hepatitis B, hepatitis C, and human immuno-deficiency virus (HIV) although the value of this step is questionable if all other recommended precautions are followed.

The clinical manifestations of infection in ESRD patients are as protean as the possible sites and agents. Common infections include bacteremia, endocarditis, osteomyelitis, urinary tract infection, and graft infections. Peritonitis is common among patients treated with PD.

The specific treatment of infectious diseases should be tailored to the presumed or defined organism as well as patient characteristics. When infection is suspected based on fever or other clinical evidence, cultures should be obtained from potentially relevant sites such as blood and urine. However, empiric treatment of strongly suspected infec-

tions should not be delayed while waiting for cultures to grow as even transient bacteremia can lead to seeding of synthetic material, heart valves, or other sites. Dose or interval adjustments are needed for most antimicrobial agents including semi-synthetic penicillins, cephalosporins, aminoglycosides, vancomycin, rifampin, quinalones, acyclovir, and fluconazole. In addition, dose supplementation may be required following dialysis for certain agents such as vancomycin and aminoglycosides. Antibiotic clearance may be strongly influenced by dialyzer specifications. Blood level monitoring is valuable for certain antibiotics such as vancomycin and aminoglycosides. Antibiotic toxicity must be avidly sought and prevented. Although nephrotoxity seems unimportant once patients have reached ESRD, this may not be true for patients who still retain residual renal function. ESRD patients may be especially vulnerable to and affected by vestibular toxicity that can occur with aminoglycosides.

Other Comorbid Conditions

A number of other comorbid conditions are found in ESRD patients including chronic lung disease, smoking, and neoplasms (Figure 1). Although the prevalence of these conditions is relatively low, they are associated with increased mortality risk. Diagnosis and treatment are not materially different from non-ESRD patients.

Management decisions for some comorbid conditions require a judgement about the balance between the short-term risk of treatment and long-term outcomes. Physicians and patients must ask whether the natural history of ESRD justifies the risks of certain intensive treatments such as chemotherapy or bypass surgery. This is a difficult area in ESRD care without definite answers. Although the average survival for ESRD patients is relatively poor, there is tremendous variability and many long-term dialysis survivors exist. Furthermore, average population statistics do not easily translate to individual patients. Formalized decision analysis may provide a framework for discussion. Ultimately, such decisions require careful, individualized discussion of risks, benefits, and preferences among physicians, patients, and families.

Summary

The treatment of patients with ESRD entails both renal replacement therapy and the treatment of comorbid conditions that are associated with renal disease. Largely as a result of comorbid conditions, ESRD patients fare worse than the general population with regard to important clinical outcomes such as mortality, hospitalization, and quality of life. In describing ESRD patient outcomes, and resource utilization at any level, it important to account for variation in comorbidity, particularly for making comparisons. For these reasons, comorbidity is central to both clinical and epidemiologic considerations of ESRD.

Comment

Some of the data reported here were supplied by the United States Renal Data System (USRDS). The interpretation and reporting of the data are the responsibility of the author and in no way should be seen as the official policy or interpretation of the U.S. Government.

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