

Chapter VI

Causes of Death

Key Words:

Cardiac deaths

Death rates

Diabetic ESRD

Hemodialysis

Infection in ESRD

Malignancy in dialysis

Peritoneal dialysis

Transplant deaths

Withdrawal from dialysis

More than a quarter of a million ESRD patients have died in the United States since the first USRDS Annual Data Report in 1989. This chapter focuses on the specific causes of their high mortality and may serve as a source to help decrease the death rates of ESRD patients through further in-depth epidemiological and clinical research. The distributions for specific causes of death for various subgroups of prevalent dialysis and transplant patients are described. Withdrawal from dialysis therapy prior to death is also analyzed.

Analytical Methods

The high prevalence of cardiac disorders in ESRD patients has been noted previously and has been shown to be associated with an elevated risk of mortality (USRDS 1992; Churchill 1992; Foley 1995). The main source of information on causes of death among the ESRD population is the HCFA ESRD Death Notification Form, which was revised in 1990. The Death Notification Form contains 59 causes of death, including categories for “other known” and “unknown” cause. The prior form listed 22 causes of death including “withdrawal from dialysis” as one of the causes of death. The new form inquires whether “withdrawal from dialysis” occurred prior to death, as a question separate from “cause of death”. Thus for each death, the patient’s physician reports both the cause of death and whether the patient withdrew from dialysis prior to death. In this chapter, the USRDS reports on data for deaths that occurred during 1994-1996.

The USRDS files include a “missing” cause of death category for those patients who, by means of the Social Security Death Benefits files and hospital discharge records, are known to have died but for whom no Death Notification Form was received. Analyses of these sources reveal that the Death Notification Form was missing or incomplete in about 14 percent of total reported ESRD deaths, 12 percent of dialysis deaths, and 51 percent of transplant deaths. The percent distribution among the reported causes of death is likely valid despite missing forms since unknown causes are also reported. For completeness, the death rates for patients with missing cause are also shown as a category in Reference Tables D.4-D.6. For the purpose of this report, the 59 causes on the HCFA Death Notification Form plus the “missing” category were collapsed into 9 cause of death categories as shown in Table VI-1. More detailed information is provided in Reference Table D.4, where the death causes are reported in 22 categories and D.5, where the death rates for all 59 cause of death categories are given by age group.

Death rates were analyzed by primary cause of death among patients who were prevalent at the beginning of, or incident (defined as 90 days following start of ESRD) during, the years 1994, 1995 and 1996. Patients were followed through each year and the days at risk were calculated for each patient by year, so that patients dying during a year contribute only the days from January 1 (if prevalent) or day 90 of ESRD (if incident) to date of death. On this basis, statistics for patient years at risk were calculated. A patient prevalent at the beginning of

Collapsed Categories from Causes of Death on Death Notification Form (HCFA-2746)*

Acute Myocardial Infarction (Acute MI)

Cardiac Arrest, cause unknown

Cardiac, other

- Atherosclerotic heart disease
- Cardiac arrhythmia
- Cardiomyopathy
- Pericarditis, including cardiac tamponade
- Pulmonary edema, due to exogenous fluid
- Valvular heart disease

Cerebrovascular (CVD)

- Cerebrovascular accident
- Ischemic brain damage

Infection

- AIDS
- Fungal peritonitis
- Hepatitis B
- Infection, other
- Other viral hepatitis
- Pulmonary infection, bacterial
- Pulmonary infection, fungal
- Pulmonary infection, other
- Septicemia, due to peritonitis
- Septicemia, due to PVD/gangrene
- Septicemia, due to vascular access
- Septicemia, other
- Tuberculosis
- Viral infection, CMV
- Viral infection, other

Malignancy

- Malignant disease, Hx of immunosupp. Rx
- Malignant disease, other

Other Known Causes

- Accident related to treatment
- Accident unrelated to treatment
- Air embolism
- Bone marrow depression
- Cachexia
- Chronic obstructive pulmonary disease
- Cirrhosis
- Complications of surgery
- Dementia
- Diabetic coma, hypo/hyperglycemia
- Drug overdose
- Drug overdose-street drugs
- GI hemorrhage
- Hemorrhage from dialysis circuit
- Hemorrhage from ruptured vascular access
- Hemorrhage from surgery
- Hemorrhage from transplant site
- Hemorrhage from vascular access
- Hyperkalemia
- Liver failure, cause unknown
- Liver-drug toxicity
- Mesenteric infarction/Ischemic bowel
- Other hemorrhage
- Other identified cause
- Pancreatitis
- Perforation of bowel
- Perforation of peptic ulcer
- Polycystic liver disease
- Pulmonary embolus
- Seizures
- Suicide

Unknown

Missing (Cause of death not recorded or no Death Notification Form)

* Revised, in use since September 1990

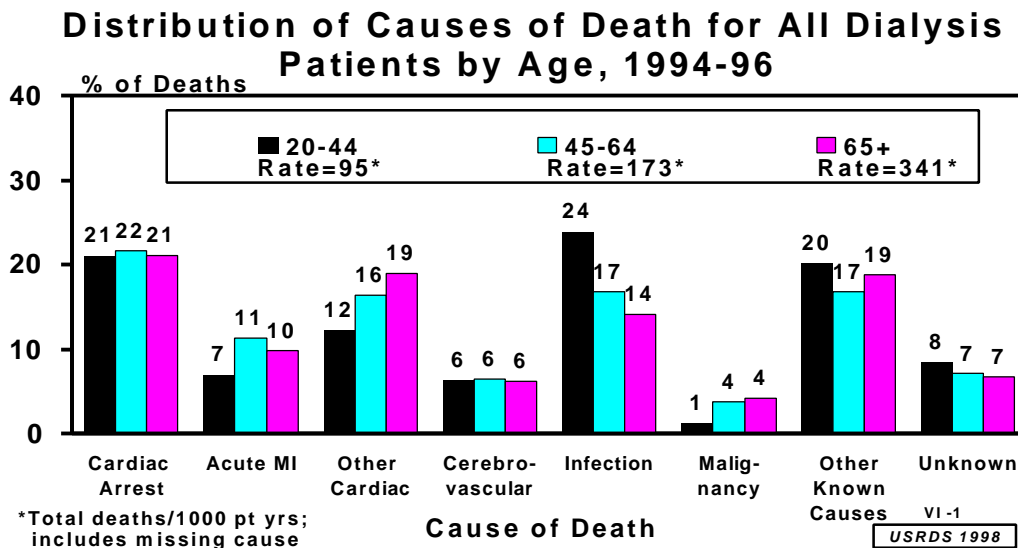
USRDS 1998

Table VI-1

1994, 1995, and 1996 contributed data to all three years. In all analyses, patients were censored at loss-to-followup or end of the calendar year, and in analyses of dialysis groups, patients were censored at transplantation. Patient followup was characterized by age (0-19, 20-44, 45-64, 65+), race (Asian, Black, Native American, White), sex, and modality (hemodialysis, peritoneal dialysis, transplant) at the beginning of each cohort year for prevalent patients or at 90 days of ESRD for incident patients. This

method better reflects the effect of modality, which may change in a given patient from one year to the next. The total number of patient deaths by cause and years at risk for each year were aggregated to enhance the stability of the estimated death rates.

Cause-specific death rates for various patient subgroups presented in this chapter are unadjusted. Numerous other stratified unadjusted death rates by cause of death for a variety of subgroups are



Distribution of causes of death for all dialysis patients by age, 1994-96. The categories are collapsed from the Death Notification Form as per Table VI-1. Patients < 20 are excluded. Missing cause of death is included in the total death rate and excluded from the distribution. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4

presented in the Reference Tables D.4-D.6. While death rates per patient year at risk tend to be more informative, it is also of interest to analyze the distribution of causes of death among patients who died. This allows comparisons with other studies and data from other registries that present the percent distribution of cause of death. The figures in this chapter show the distribution for causes by death for various subgroups of prevalent dialysis and transplant patients. The total death rate for each subgroup is also shown so that death rates by cause can be easily calculated. Since the total death rate includes missing cause, this calculation would assume that deaths with a missing death report have a similar percent distribution of causes of death as that shown. More detailed percentages can be calculated for various subgroups from death rates in the reference tables by dividing the cause-specific death rate by the overall reported death rate (total death rate minus the missing as the denominator).

Causes of Death Among Dialysis Patients

Death rates by cause of death were analyzed for prevalent and incident ESRD patients treated with hemodialysis (HD) or peritoneal dialysis (PD). Patients transplanted during the year of observation

were censored (removed from the analysis) on day of transplantation. The distribution of causes of death for dialysis patients aged 20-44 years, 45-64 years, and 65 years and older is shown in Figure VI-1. Cardiac causes (cardiac arrest, acute myocardial infarction, and other cardiac) account for almost half of the reported causes of dialysis patient deaths in each of the three age groups. A USRDS study of new and established dialysis patients, pointed out that cardiac disorders were already present in a large fraction of patients when they began dialysis (Bloembergen, 1997).

Infection accounts for almost a quarter of all deaths in the 20-44 year age group, but only 17 percent and 14 percent of deaths in the 45-64 years and 65 years and older age groups, respectively. Septicemia makes up more than 75 percent of the infection category. ESRD patients are known to have a high incidence of infection due to defects in cellular immunity, neutrophil function, and complement activation (Khan 1993; Vanholder 1993). Additionally, dialysis patients have an elevated risk of infection due to the vascular or peritoneal access. Cerebrovascular disease make up about 6 percent of the deaths in each age group, while 1 to 4 percent of the cause of death for dialysis patients is attributable to malignancy. Previous studies have suggested an increased risk of certain malignancies in the dialysis

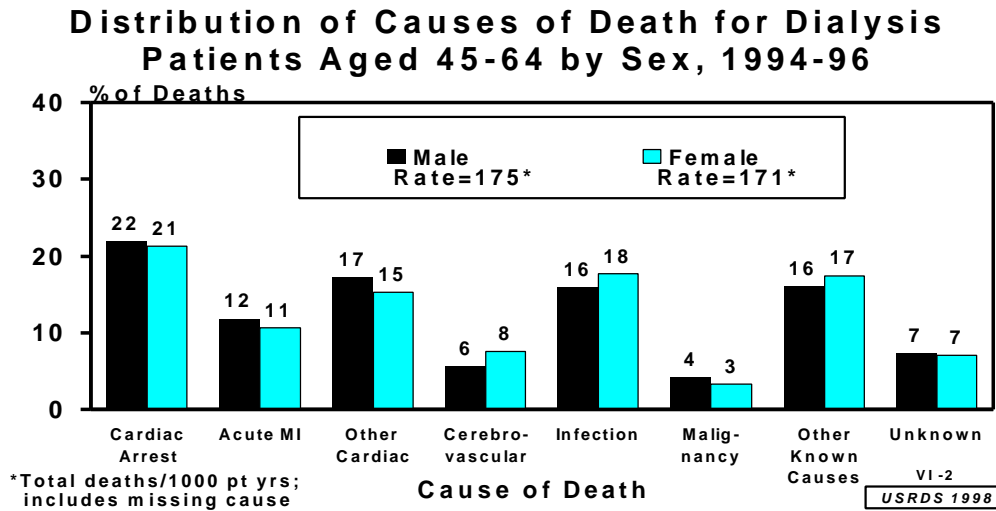


Figure VI-2

Distribution of causes of death for all dialysis patients aged 45-64 by sex, 1994-96. The categories are collapsed from the Death Notification Form as per Table VI-1. Missing cause of death is included in the total death rate and excluded from the distribution. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4

(Port, 1989a; Kantor 1987; Inamoto 1991) population compared to the general population. Although this may be due to the effect of uremia or a side-effect of dialytic therapy, the USRDS Case Mix studies found a diagnosis of malignancy in 9 percent of patients at

initiation of therapy (USRDS 1992), suggesting that acceptance of patients with malignancy is not uncommon.

Other known causes account for almost 20 percent

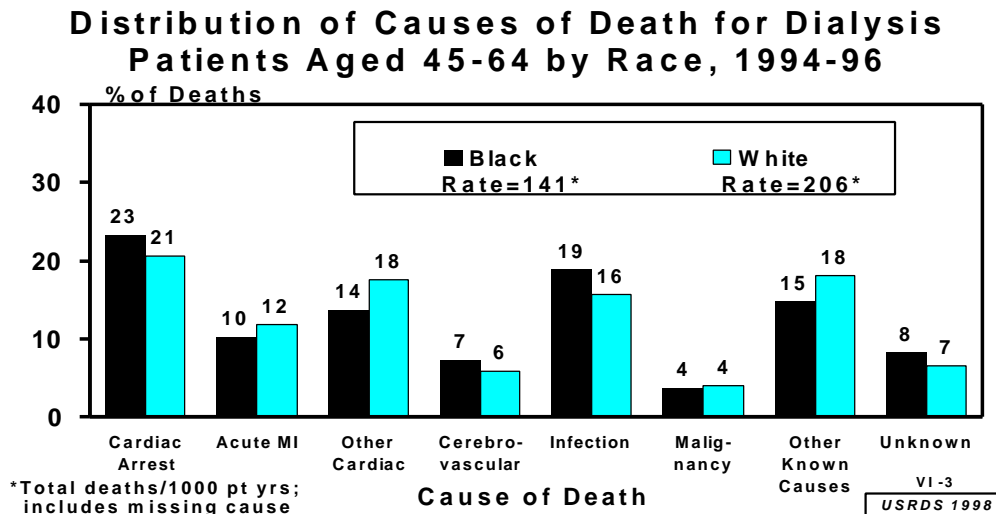
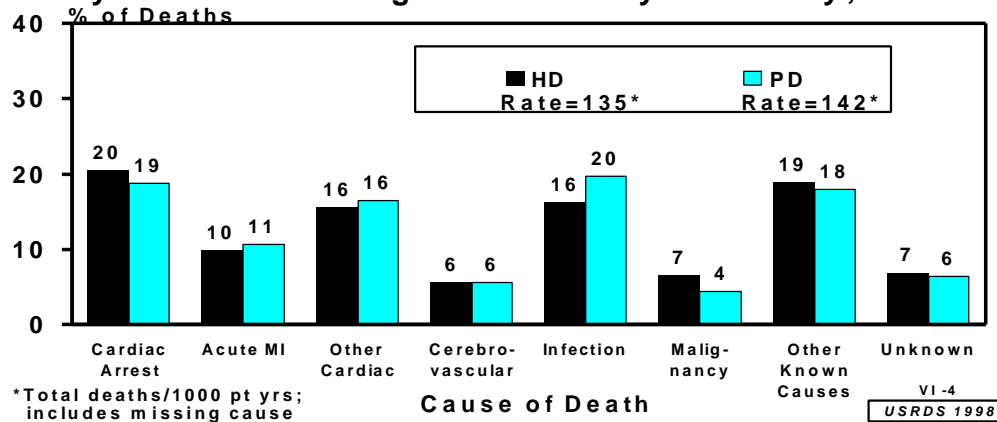


Figure VI-3

Distribution of causes of death for all dialysis patients aged 45-64 by race, 1994-96. The categories are collapsed from the Death Notification Form as per Table VI-1. Black and White patients only. Missing cause of death is included in the total death rate and excluded from the distribution. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4

Distribution of Causes of Death for Nondiabetic Dialysis Patients Aged 45-64 by Modality, 1994-96



Distribution of causes of death for all nondiabetic dialysis patients aged 45-64 by treatment modality, 1994-96. The categories are collapsed from the Death Notification Form as per Table VI-1. HD and PD patients only. Missing cause of death is included in the total death rate and excluded from the distribution. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4

of deaths in all three age groups. Mesenteric infarction/ischemic bowel and dementia are the largest causes in this category (1-2 percent each). The cause of death is reported unknown for 7 to 8 percent of adult dialysis patient deaths in the three age groups. Death rates for 44-64-year-old patients are almost two fold higher than 20-44-year-old patients. Death rates for patients 65 years and older are almost twice as high as for 44-64-year-old dialysis patients.

Figure VI-2 shows the distribution of cause of death among all dialysis patients aged 45-64 years by sex. The distribution of causes of death for males and females show only small differences. Males have slightly higher cardiac causes (51 percent for males and 47 percent for females) and females have higher infection causes (16 percent for males and 18 percent for females) and cerebrovascular disease (6 percent for males and 8 percent for females). Malignancy and other known and unknown causes show minor differences by sex that are within one percentage point. The total death rate is somewhat higher for males rate (175 deaths per 1000 patient years) than females (171 deaths per 1000 patient years).

The distribution of causes of death for Blacks and Whites aged 45-64 is shown in Figure VI-3. Whites have an almost 50 percent higher death rates than Blacks (206 and 141 deaths per 1000 dialysis patient years in this unadjusted analysis). Cardiac causes account for the largest percentage of deaths for both

rates (47 percent and 51 percent for Blacks and Whites, respectively). Infection accounts for 19 percent of deaths for Blacks and 16 percent of deaths for Whites. Blacks and Whites have similar proportions of causes of death due to cerebrovascular disease (7 percent and 6 percent, respectively), malignancy (4 percent each), and unknown causes (8 percent and 7 percent, respectively). Whites have a higher proportion of other known causes (18 percent) than Blacks (15 percent).

Figures VI-4 and VI-5 show the cause of death for dialysis patients aged 45-64 by dialytic modality for nondiabetic and diabetic patients, respectively. There is a small difference in the death rates of nondiabetic HD and PD patients. Nondiabetic HD patients have a death rate of 135 per 1000 patient years and nondiabetic PD patients have a death rate 142 per 1000 patient years. However, diabetic PD patients have a substantially higher death rate than diabetic HD patients (278 and 202 deaths per 1000 patient years, respectively). Nondiabetic HD and PD patients have similar proportions for all cardiac causes. Cardiac arrest accounts for 20 percent of nondiabetic HD patients and 19 percent of nondiabetic PD patients. Acute MI accounts for 10 and 11 percent of nondiabetic HD and PD patients, respectively. Sixteen percent of nondiabetic HD and PD patients die of other cardiac causes. Larger proportions of diabetic HD patients (24 percent) die of cardiac arrest than diabetic PD patients (20

Distribution of Causes of Death for Diabetic Dialysis Patients Aged 45-64 by Modality, 1994-96

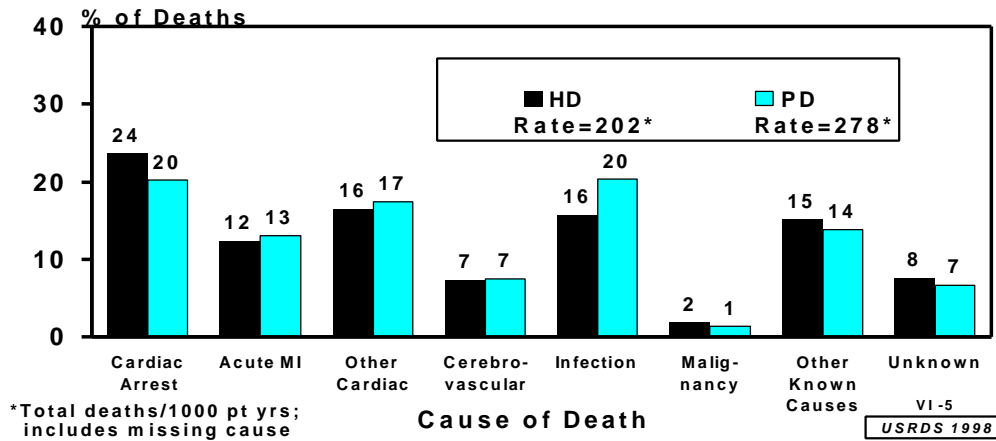


Figure VI-5

Distribution of causes of death for all diabetic dialysis patients aged 45-64 by treatment modality, 1994-96. The categories are collapsed from the Death Notification Form as per Table VI-1. HD and PD patients only. Missing cause of death is included in the total death rate and excluded from the distribution. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

percent). However, diabetic HD patients have slightly fewer acute MI and other cardiac causes than diabetic PD patients. PD patients have a substantially higher percentage of deaths due to infection (20 percent) than HD patients (16 percent) for both nondiabetics and diabetics.

The higher infection deaths among PD patients may be related to several factors including: poor technique, peritoneal access, less overall clearance of small uremic toxins, possible deleterious effects of the PD fluid on macrophage function, malnutrition, or differences in baseline comorbidity between HD and PD patients (Bloembergen, 1996). Further discussion of the distribution of specific cardiac and infectious causes among all deaths are presented in the USRDS 1997 Annual Data Report. Nondiabetic patients have larger proportions of deaths due to malignancy among patients on HD (7 percent) and PD (4 percent) than do diabetic patients on HD (2 percent) and PD (1 percent). Of note is the higher fraction of HD patients deaths due to malignancy than the fraction for PD patients. There are slightly higher proportions of other and unknown causes for HD patients than PD patients for nondiabetics and diabetics.

The differences in cause-specific mortality among PD and HD treated patients may be due to the technical differences of these dialysis modalities,

differences in compliance, medical care, or dose of dialysis. As a result of studies showing a relationship of dose of dialysis and mortality, dose of dialysis has increased substantially on a national level among the hemodialysis population (USRDS 1996). However, a similar relationship has also been found among PD treated patients, and has stimulated an interest in increasing the dialysis dose in this population as well (Canada-USA). Differences in case-mix severity among these patient groups may also play a role although a previous study has shown relatively small differences in comorbidity between PD and HD treated incident patients (USRDS 1992 ADR; Held 1994). The results presented here refer mostly to prevalent patients. Overall mortality during the first year of ESRD was very similar for HD and PD patients (Held 1997).

Causes of Death among Transplant Recipients

Prevalent patients with a functioning transplant on January 1 of 1994, 1995, or 1996 were classified as such and are followed through the remainder of each year independent of transplant failure that may have occurred in some patient during the year. The distribution of causes of death for all patients with a functioning transplant aged 0-19, 20-44 and 45-64

Distribution of Causes of Death for All Transplant Patients by Age, 1994-96

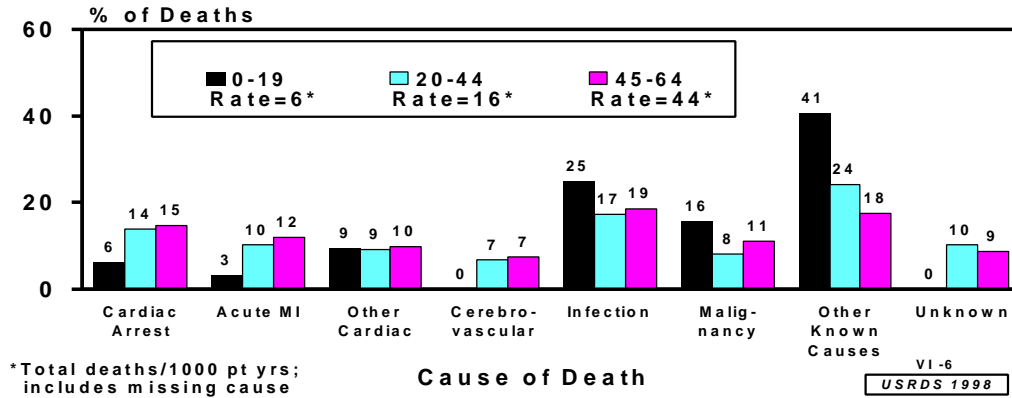


Figure VI-6

Distribution of causes of death for all transplant patients by age, 1994-96. The categories are collapsed from the Death Notification Form as per Table VI-1. Patients ≥ 65 are excluded. Missing cause of death is included in the total death rate and excluded from the distribution. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4

years is given in Figure VI-6. The death rate for transplanted pediatric patients (age 0-19 years) was more than two fold lower than transplanted adult patients aged 20-44 and about 7 times lower than adult transplanted patients aged 45-64. In contrast to dialysis patients, cardiac causes accounted for a

smaller proportion of deaths for transplanted patients with approximately 18 to 37 percent of all deaths for each age group. About a quarter of all transplanted pediatric patients died due to infection, whereas 17 and 19 percent of transplanted patients aged 20-44, and 45-64 years died due to infection. Malignancy

Distribution of Causes of Death for Transplant Patients Aged 20-44 by Race, 1994-96

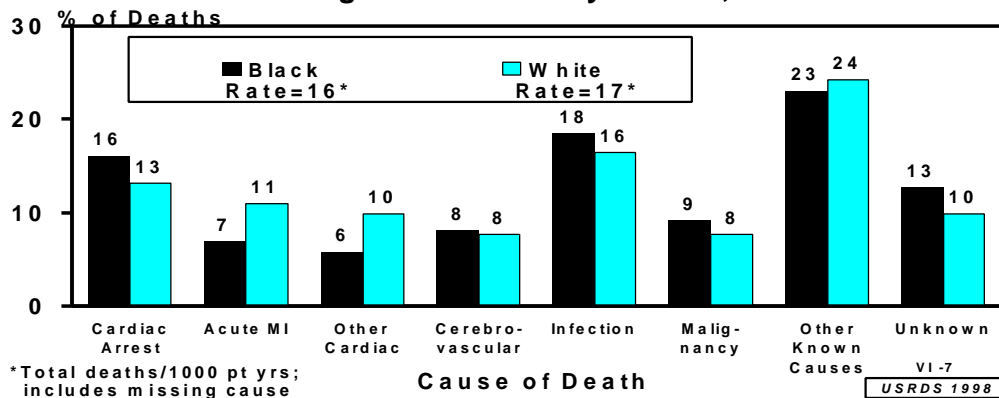


Figure VI-7

Distribution of causes of death for all transplant patients aged 20-44 by race, 1994-96. The categories are collapsed from the Death Notification Form as per Table VI-1. Black and White patients only. Missing cause of death is included in the total death rate and excluded from the distribution. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4

accounted for 16 percent, 8 percent, and 11 percent of transplanted patients aged 0-19, 20-44, 45-64 years, respectively. Previous studies have suggested an increased risk of certain malignancies in the transplant population (Penn 1988) compared to the general population. Other known causes make up a large proportion of transplant patient deaths. The most common known causes were hyperkalemia and GI hemorrhage.

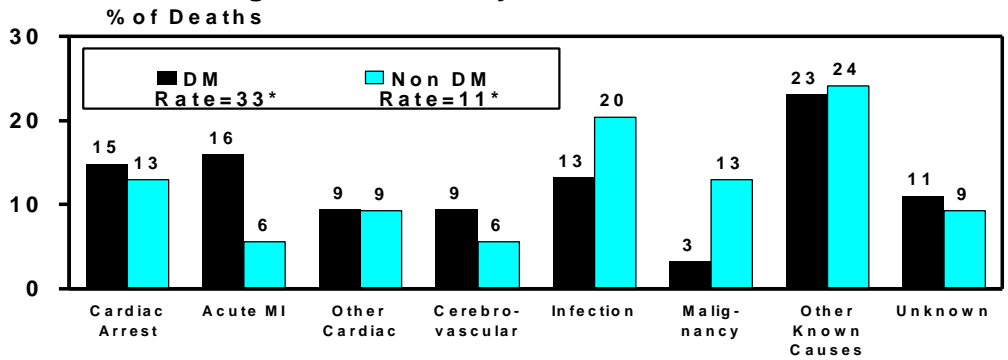
A comparison of patients with similar age reveals a substantially lower death rate for transplant patients than for dialysis patients. Transplant patients aged 20-44 years had a sixth of the death rate of dialysis patients aged 20-44 years, while transplant patients aged 45-64 years had a quarter of the death rate of dialysis patients aged 45-64 years. This is likely due in part to selection of healthier patients to transplantation (Gaylin 1993; Wolfe 1997). In addition to patient selection, other factors such as the greater level of renal functional replacement with transplantation may be playing a role in the better long-term outcomes with transplantation.

Figure VI-7 shows the distribution of causes of death by race. Black transplant patients aged 20-44 years have a slightly lower death rate than White transplant patients aged 20-44. The death rate due to cardiac arrest for Black transplant patients is higher than White transplant patients, while Blacks had lower rates of acute MI and other cardiac causes than Whites. Blacks and Whites have similar distributions of cerebrovascular, infection,

malignancy, and other known causes. In the older age groups, Black transplant patients have a higher rate of death than White transplant patients (see Reference Table D.4) which is in direct contrast to the dialysis population where death rates due to most causes were higher among Whites. Despite these higher death rates among Black transplant recipients the benefit of cadaveric renal transplantation for dialysis patients on the transplant waiting list is large and similar to that observed in Whites (Ojo, 1994).

The distribution of causes of death for transplant patients aged 20-44 years by diabetic status is shown in Figure VI-8. Deaths rates were about three fold higher among diabetic than nondiabetic transplanted patients. Forty percent of deaths were due to cardiac causes for diabetic transplant patients with a relatively high fraction dying of acute myocardial infarction. Twenty percent of nondiabetic transplant patients had infection as their cause of deaths, while only 13 percent of diabetics transplant patients did. Additionally, only 3 percent of diabetic transplant patients died of a malignancy in contrast to 13 percent of nondiabetic transplant patients. Nearly a quarter of both nondiabetic and diabetic transplanted patients died of other known causes. Hyperkalemia and hemorrhage make up about 20 percent of the other known cause category for this age group.

Distribution of Causes of Death for Transplant Patients Aged 20-44 by Diabetic Status, 1994-96



*Total deaths/1000 pt yrs; includes missing cause

Cause of Death

Figure VI-8

VI-8
USRDS 1998

Distribution of causes of death for all transplant patients aged 20-44 by diabetic status, 1994-96. The categories are collapsed from the Death Notification Form as per Table VI-1. Missing cause of death is included in the total death rate and excluded from the distribution. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.4.

Rate of Withdrawal from Dialysis by Age, Diabetes, Sex, and Race, 1994-96

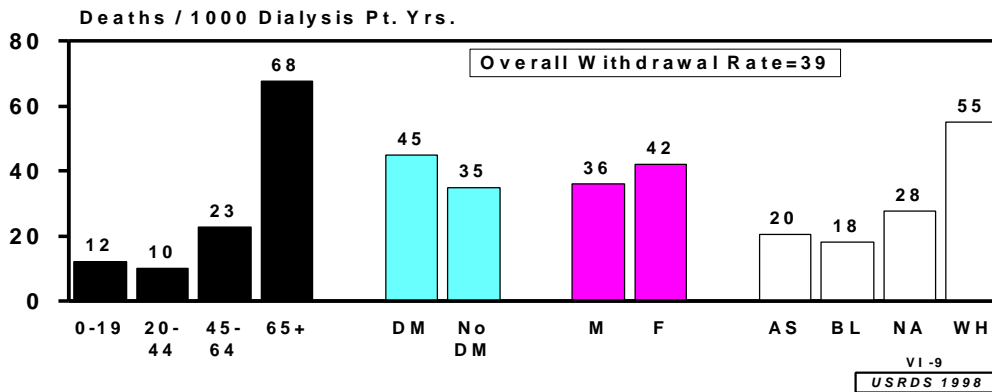


Figure VI-9

Death rate due to withdrawal among dialysis patients by age, diabetic status, sex, and race, 1994-96. Patients with missing cause of withdrawal are excluded. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.6.

Withdrawal from Dialysis

Approximately one out of every five dialysis patients withdraws from dialysis before death. (This does not include patients who have stopped dialysis because of a return of renal function.) Figure VI-9 shows the rate of withdrawal from dialysis by age group, diabetic status, sex, and race and Figure VI-10

shows the percentage of deaths with prior withdrawal from dialysis by age, diabetic status, sex, and race. The overall withdrawal rate was 39 deaths per 1000 dialysis patient years. Older patients (age 65 years and older) have a much higher rate of withdrawal than do younger patients. Almost a quarter of all 65 years and older dialysis patient deaths were preceded by withdrawal from dialysis. Sixteen percent of

Percentage of Deaths* with Prior Withdrawal by Age, Diabetic Status, Sex, and Race, 1994-96

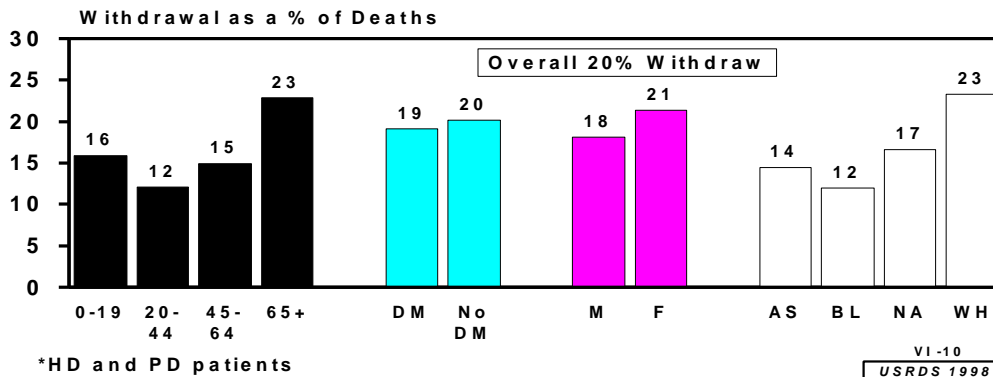
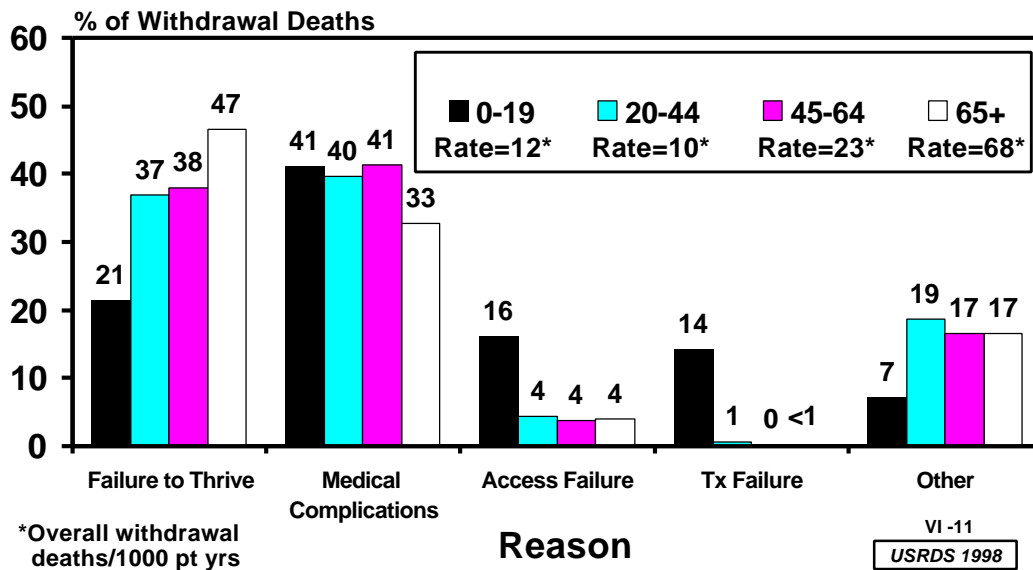


Figure VI-10

Percentage of dialysis deaths with withdrawal from dialysis prior to death by age, diabetic status, sex, and race, 1994-96. Patients with missing cause of withdrawal are excluded. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.6.

Reasons for Withdrawal from Dialysis by Age, 1994-96



Reasons for withdrawal from dialysis by age, diabetic status, sex, and race, 1994-96. Patients with missing cause of withdrawal are excluded. Patients in Puerto Rico and the U.S. Territories are included. Source: Reference Table D.6.

pediatric patients (aged 0-19 years) withdrew, while 12 percent and 15 percent of patients aged 20-44 years and 45-64 years withdrew, respectively. The increase in withdrawal rate with age may be the result of increasing severity of comorbid conditions which may lessen the quality of life of a dialysis patient to the extent that further dialysis may reach questionable benefits (Port 1989; Mailloux 1991; Nelson 1994).

While diabetic patients withdrew at higher rates than nondiabetics (45 versus 35 deaths per 1000 dialysis patient years), a smaller percentage of diabetic deaths (19 percent) were preceded by withdrawal than nondiabetic patient deaths (20 percent). This apparent reversal is explained by the relatively high death rates among diabetic patients. Females withdrew at a higher rate than males (42 versus 35 deaths per 1000 patient years). This accounts for 18 percent of male dialysis deaths and 21 percent of female dialysis deaths.

Withdrawal from dialysis also has marked racial variation. Asians, Blacks, and Native Americans (20, 18, and 28 deaths per 1000 dialysis patient years, respectively) are at half to a third the risk of withdrawal compared to Whites (55 deaths per 1000 dialysis patient years). This is consistent with previous studies which have shown that withdrawal

from dialysis is over twice as commonly reported for White patients than for Black patients (Port 1989; Nelson 1994; Bloembergen 1994; Leggat 1997a). Withdrawal from dialysis preceded 23 percent of all White deaths, while a smaller percentage of deaths for Asians, Blacks, and Native Americans (14, 12, and 17 percent, respectively) followed withdrawal from dialysis. These differences are likely due to sociocultural reasons (Leggat 1997b).

The reported reasons for withdrawal from dialysis are shown in Figure VI-11. Medical complications and failure to thrive made up about sixty to eighty percent of the reasons for withdrawal from dialysis for all four age groups. Access failure accounted for 16 percent of withdrawal in the 0-19 age group, but only four percent of withdrawals in each in the older age groups. Transplant failure (usually refusal to return to dialysis) occurred in 14 percent of withdrawals for pediatric patients. This reason was much lower (1 percent) for patients aged 20-44 years and rarely applies to dialysis patients aged 65 years and older.

It has been stated that withdrawal from dialysis reflects, on the one hand, failure of renal replacement therapy, and on the other hand maintenance of patient

autonomy (Leggat 1997a). In addition, the high rates of withdrawal in the United States (Sehgal) may be due to acceptance of patients for whom benefits from therapy may have been uncertain at initiation of ESRD therapy. As individual patient outcome is not predictable, some have advocated an approach of liberal acceptance policies combined with a willingness to support patients in their decision to withdraw from dialysis (Port 1994).

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