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Prevalence of anemia in erythropoietin-treated pediatric as compared to adult chronic dialysis patients

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Prevalence of anemia in erythropoietin-treated pediatric as compared to adult chronic dialysis patients.

Background. Recent guidelines recommend a target hemoglobin range of 11 to 12 g/dL in pediatric and adult dialysis patients. We compared anemia prevalence in United States Medicare pediatric and adult dialysis patients.

Methods. Prevalent hemodialysis patients (0 to 19 years, pediatric: $N = 1692$; adult: $N = 352{,}291$) and peritoneal dialysis patients (pediatric: $N = 597$; adult: $N = 39{,}136$) treated with recombinant human erythropoietin (rHuEPO) from 1996 to 2000 were selected. Mean annual hemoglobin values were calculated by modality, age, sex, and race.

Results. Among hemodialysis patients, mean annual hemoglobin values less than 11 g/dL were present in pediatric and adult patients during 54.1% versus 39.8% patient years, respectively ($P < 0.0001$); for peritoneal dialysis patients, 69.5% versus 55.1% ($P < 0.0001$). Mean hemoglobin values increased over time and were 11.2, 11.5, 10.8, and 11.2 g/dL for pediatric and adult hemodialysis and peritoneal dialysis patients, respectively, in 2000. Pediatric hemodialysis patients received intravenous iron less frequently than adults (66.3% vs. 82.5% patient years; $P < 0.0001$).

Conclusion. Hemoglobin values in rHuEPO-treated pediatric dialysis patients lagged behind those of adult patients, with pediatric patients achieving target hemoglobin values only a minority of the time (45.9% and 30.5% patient years, respectively, for hemodialysis and peritoneal dialysis). Trends show recent improvement in anemia treatment of children on dialysis. Still, further attention to and analysis of rHuEPO and iron therapy in pediatric dialysis patients is warranted.

Anemia is a major consequence of chronic kidney disease. When severe, it is associated with cardiovascular dysfunction, cardiomyopathy, and death [1–4]. As we recently reported, cardiomyopathy incidence is increasing in pediatric chronic dialysis patients in the United States [5]. These findings led us to our current study of anemia in children receiving dialysis.

The major cause of anemia in patients with chronic kidney disease and end-stage renal disease (ESRD) is erythropoietin deficiency resulting from decreased production of the kidneys [6, 7]. In 1989, recombinant human erythropoietin (rHuEPO) became available in the United States for the treatment of anemia due to ESRD [8]. Correction of anemia in children with ESRD improves cardiac dysfunction and exercise tolerance and reduces left ventricular hypertrophy [9–11]. In 1997, the National Kidney Foundation recommended a hemoglobin range of 11 to 12 g/dL (hematocrit, 33% to 36%) for chronic dialysis patients [12]. The updated guidelines include similar recommendations and some discussion of treatment to higher hemoglobin values, provided that evidence is published showing that such treatment further reduces the potential for cardiac complications [13].

Detailed data are not available on the frequency and extent to which anemia is present over time in pediatric dialysis patients. Therefore, we investigated hemoglobin values in these patients, and in adult Medicare dialysis patients receiving rHuEPO to determine the prevalence of anemia.

METHODS

Data and sources

Using data from the United States Renal Data System, we studied the 1996 to 2000 period prevalent Medicare hemodialysis and peritoneal dialysis patients. The period prevalent cohort for each year included both point prevalent patients (who received ESRD treatment on January 1 of the year and whose first ESRD service date was ≥90 days before January 1), and incident patients (who reached day 91 of ESRD between January 1 and December 31 of the year). The follow-up period was defined as the time from the start of follow-up until the

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earliest of the following: date of death, modality change, loss to follow-up, or December 31 of the year. Demographic data, including age, sex, race, and primary cause of ESRD, were obtained from the Identification and Medical Evidence sections of the Renal Beneficiary Utilization System of the Centers for Medicare and Medicaid Services. Patients with Medicare as a secondary payer, or coverage from a health maintenance organization, were excluded because data on rHuEPO use, hemoglobin values, or intravenous iron use were incomplete.

Data on patient hematocrit values, rHuEPO dose, and administration of intravenous iron were obtained from institutional outpatient Medicare claims from January 1, 1996, to December 31, 2000. Included patients had at least one rHuEPO claim during the follow-up period. For each patient, the mean annual hematocrit value was calculated from all rHuEPO claims during each year of follow-up. Hemoglobin values were then calculated by dividing the mean hematocrit value by three. Claims occurring during the follow-up period also yielded data on the use of intravenous iron, including iron dextran and ferric gluconate, which became available for use in 2000. However, the use of ferric gluconate in 2000 may be underreported because a national claims code for this product was not available until 2001. Patients were defined as treated with intravenous iron if they had received at least one administration of intravenous iron during each follow-up year.

Data analysis

By treatment modality (hemodialysis, peritoneal dialysis), characteristics of 1996 to 2000 combined prevalent patients were analyzed by year, age (on January 1 of the year), sex, race, primary cause of ESRD, and hemoglobin value. Patients who appeared in multiple years were counted only once in the characteristic totals. The exceptions were totals by year and by modality, where one patient may contribute to multiple years or modalities (e.g., a 1998 and 1999 peritoneal dialysis patient who became a 2000 hemodialysis patient).

Using 1996 to 2000 combined patients, the proportion of time that patients had a hemoglobin value of $\geq$11 g/dL was assessed by modality and age. To account for patients appearing in multiple years, a patient-year method was used. The follow-up time ($\leq$1 year) was computed annually for each patient. Total patient years were then calculated as the total number of years (or fraction of a year) of follow-up time for each modality and age group. Each year, patients were classified as to whether or not they attained a mean hemoglobin value of $\geq$11 g/dL. For each modality and age, the total percentage of patient years with a mean hemoglobin value of $\geq$11 g/dL was computed. Values for pediatric (younger than age 20 years) and adult patients (20 years old or older) within each modality were compared with a test based on assumption of a Poisson distribution. Methods were repeated to compute and compare the percentage of patient years with intravenous iron. For patients with and without intravenous iron, the distribution of patient years with a hemoglobin value of $\geq$11 g/dL also was computed and comparisons by treatment modality were made. In addition, the percentage of patient years with a mean hemoglobin value of $\geq$11 g/dL was computed for adult subgroups (20–44, 45–64, and $\geq$65 years). Because pediatric patients may have greater similarity to younger adults, values for pediatric patients were compared to those of adults in the 20- to 44-year-old age group.

Trends in mean hemoglobin values were also identified by age and year. For each year and treatment modality, Bonferroni *t* tests were used to compare the pediatric patients with adults. For 2000, mean hemoglobin values were also calculated for the 20- to 44-, 45- to 64-, and $\geq$65-year-old adult groups, and pediatric and 20- to 44-year-old adult patients were compared using a *t* test.

For the year 2000, trends in mean hemoglobin values were also identified by age and sex. Within each modality, the mean hemoglobin value was computed for each sex and age group. Within each sex, Bonferroni *t* tests were used to compare pediatric patients with adults. Methods were repeated to compare whites with blacks (for other races, the sample size was insufficient).

Within the period prevalent hemodialysis and peritoneal dialysis cohorts, the subset of incident patients was analyzed. These patients were evaluated separately using data from the Medical Evidence Report (Centers for Medicare & Medicaid Services Form 2728) completed at initiation of dialysis. These data included hematocrit value, body weight, and if the patient had received rHuEPO before initiation of dialysis. We calculated the mean hemoglobin value at initiation of dialysis for pediatric and adult patients (1996 to 2000) who did and did not receive rHuEPO after initiation of dialysis during the incident year of ESRD. Also, among unique patients included in the 1996 to 2000 cohorts, we compared the percentages of pediatric and adult patients who were incident during the 5-year study period.

In 1996 to 2000 hemodialysis and peritoneal dialysis patients, the use of rHuEPO before initiation of dialysis was evaluated in the subset of incident patients with complete Medical Evidence Report data. The percentages of pediatric and adult patients who received predialysis rHuEPO were compared. The weekly rHuEPO dose per kg of body weight (rHuEPO/kg) was also evaluated for the subset of incident patients with a valid body weight measurement (1 to 175 kg) recorded on the Medical Evidence Report at initiation of dialysis. For each patient, rHuEPO dose per week was calculated as the total units of rHuEPO received during the follow-up time divided by the total outpatient weeks. Because outpatient rHuEPO claims are not generated during hospitalizations, outpatient

Table 1. Percentages of 1996 to 2000 period-prevalent rHuEPO-treated hemodialysis and peritoneal dialysis patients by sex, race, and primary cause of ESRD[a]

	Hemodialysis		Peritoneal dialysis	
Age *years*	0–19	≥20	0–19	≥20
Sex				
Male	54.3	51.6	48.1	50.9
Female	45.7	48.4	51.9	49.1
Race				
White	49.3	56.9	62.3	66.7
Black	40.8	37.0	25.6	26.7
Native American	2.2	1.7	2.0	1.7
Asian	4.0	3.1	5.0	3.7
Other	3.7	1.2	5.0	1.3
Primary cause of ESRD				
Diabetes	1.3	40.4	–	36.0
Hypertension	6.0	29.1	3.5	24.4
Glomerulonephritis	34.9	10.7	38.0	17.4
Cystic kidney disease	2.1	2.4	4.7	3.4
Other urologic	5.6	1.9	6.0	1.7
Hemolytic uremic syndrome	1.8	0.1	2.5	0.2
Chronic interstitial nephritis	1.8	1.6	1.8	2.2
Lupus erythematosus	6.8	1.2	3.9	2.4
Renal hypoplasia, dysplasia, oligonephronia	7.9	0.1	10.7	0.3
Congenital obstructive uropathy	7.3	0.3	5.7	0.3
Hereditary nephritis, Alport's syndrome	2.1	0.1	–	0.4
Other/unknown/missing	22.3	12.1	21.1	11.4

Abbreviations are: rHuEPO, recombinant human erythropoietin; ESRD, end-stage renal disease.

[a]Values represent percentages of 0- to 19- and ≥20-year-old hemodialysis patients ($N = 1692$ and $N = 352,291$) and peritoneal dialysis patients ($N = 597$ and $N = 39,136$).

– Values for cells with fewer than 10 patients are suppressed.

weeks were computed as the total weeks of follow-up, excluding hospital days, which were obtained from Medicare institutional inpatient claims data. Weekly rHuEPO/kg was then computed as rHuEPO dose per week divided by body weight in kg. For hemodialysis and peritoneal dialysis patients, mean weekly rHuEPO/kg was calculated and compared between pediatric and adult patients. Patient percentages were compared with the Pearson chi-square test, hemoglobin values were compared with the *t* test, and weekly rHuEPO/kg was compared with the Wilcoxon rank-sum test.

RESULTS

Patient distributions

For the years 1996 to 2000 combined, 353,983 period-prevalent hemodialysis and 39,733 peritoneal dialysis patients were rHuEPO-treated and included in the study (Tables 1 and 2). Of these, 1692 (0.5%) and 597 (1.5%) were pediatric hemodialysis and peritoneal dialysis patients, respectively. For the year 2000, among pediatric patients, the included rHuEPO-treated patients represented 89.5% and 36.2% of all period-prevalent pediatric hemodialysis and peritoneal dialysis patients, respectively; among adults, 94.1% and 57.6%.

The by-age distribution of patient years with a hemoglobin value of ≥11 g/dL varied by modality (Fig. 1). For hemodialysis patients, the percentage of patient years with a hemoglobin value of ≥11 g/dL was lowest for patients aged 0 to 4 years and increased with age. However, for peritoneal dialysis patients, the percentage had a U-shaped appearance, decreasing from ages 0 to 4 years to 15 to 19 years, and then increasing in adults. Overall, for pediatric and adult hemodialysis patients, the percentages of patient years with a hemoglobin value of ≥11 g/dL were 45.9% and 60.2%, respectively ($P < 0.0001$); for peritoneal dialysis patients, 30.5% and 44.9% ($P < 0.0001$). For 1996 to 2000 patients combined, the percentage of patient years with a hemoglobin value of ≥11 g/dL was lowest for pediatric patients, and increased with increasing age in the adult groups. Respectively, for 20- to 44-, 45- to 64-, and ≥65-year-old adults, the percentages of patient years with a hemoglobin value of ≥11 g/dL were 55.3%, 59.3%, and 62.5% for hemodialysis patients, and 34.7%, 44.0%, and 54.0% for peritoneal dialysis patients. Percentages were significantly lower for pediatric patients than for 20- to 44-year-old adults among hemodialysis ($P < 0.0001$) and among peritoneal dialysis patients ($P = 0.038$).

The percentage of patient years with intravenous iron was low, especially for younger patients and peritoneal dialysis patients, and generally increased with age (Fig. 2). Among pediatric and adult hemodialysis patients, intravenous iron was administered in 66.3% and 82.5% of the patient years, respectively ($P < 0.0001$); among peritoneal dialysis patients, 14.7% and 20.3% ($P = 0.001$). Also, for patients with and without intravenous iron, the distribution of patient years with a hemoglobin value of ≥11 g/dL varied by modality. Among adult patients with and without intravenous iron, respectively, the percentages of patient years with a hemoglobin value of ≥11 g/dL were 61.5% and 54.0% among hemodialysis patients ($P < 0.0001$), and 39.7% and 46.3% among peritoneal dialysis patients ($P < 0.0001$). Among pediatric patients, for those with and without intravenous iron, respectively, the percentages of patient years with a hemoglobin value of ≥11 g/dL were 49.1% and 39.6% among hemodialysis patients ($P = 0.31$), and 21.1% and 32.1% among peritoneal dialysis patients ($P = 0.03$).

Trends in mean hemoglobin value by modality, year, and age

Within each modality and year, the mean hemoglobin value for pediatric patients was significantly lower than that for adults (Fig. 3). However, hemoglobin values improved in pediatric hemodialysis patients from 1996 to 2000 and in pediatric peritoneal dialysis patients after 1998.

Table 2. Distributions of 1996 to 2000 period-prevalent rHuEPO-treated hemodialysis and peritoneal dialysis patients by hemoglobin, age, and year[a]

	Hemodialysis				Peritoneal dialysis			
	0–19		≥20		0–19		≥20	
Age *years*	N	%N	N	%N	N	%N	N	%N
Hemoglobin *g/dL*								
<9	99	5.9	9,695	2.8	106	17.8	2,786	7.1
9–9.9	209	12.4	27,587	7.8	124	20.8	6,042	15.4
10–10.9	541	32.0	107,270	30.4	205	34.3	13,920	35.6
11–11.9	657	38.8	164,502	46.7	113	18.9	12,265	31.3
≥12	186	11.0	43,237	12.3	49	8.2	4,123	10.5
Age *years*								
0–4	56	3.3	–	–	65	10.9	–	–
5–9	95	5.6	–	–	53	8.9	–	–
10–14	281	16.6	–	–	142	23.8	–	–
15–19	1,260	74.5	–	–	337	56.4	–	–
20–44	–	–	53,005	15.0	–	–	10,090	25.8
45–64	–	–	114,210	32.4	–	–	14,736	37.7
≥65	–	–	185,076	52.5	–	–	14,310	36.6
Year[b]								
1996	570	33.7	146,190	41.5	224	37.5	15,715	40.2
1997	587	34.7	160,869	45.7	202	33.8	15,573	39.8
1998	615	36.3	171,058	48.6	177	29.6	13,232	33.8
1999	603	35.6	181,575	51.5	137	22.9	12,098	30.9
2000	599	35.4	190,467	54.1	134	22.4	11,149	28.5

rHuEPO is recombinant human erythropoietin.

[a]Values represent the number and percentage of 0- to 19- and ≥20-year-old hemodialysis patients ($N = 1692$ and $N=352,291$) and peritoneal dialysis patients ($N = 597$ and $N = 39,136$).

[b]Percentages across years sum to >100 because some patients appear in multiple years.

– Values for cells with fewer than 10 patients are suppressed.

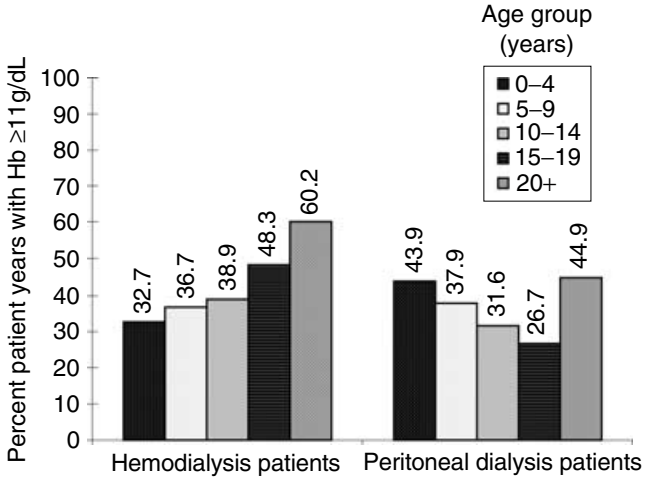

Fig. 1. Percentage of patient years with a hemoglobin (Hb) value of ≥11 g/dL by modality and age, 1996 to 2000 (combined) period-prevalent hemodialysis and peritoneal dialysis patients treated with recombinant human erythropoietin (rHuEPO). Each patient may contribute <1 to 5 total patient years to a maximum of two age groups.

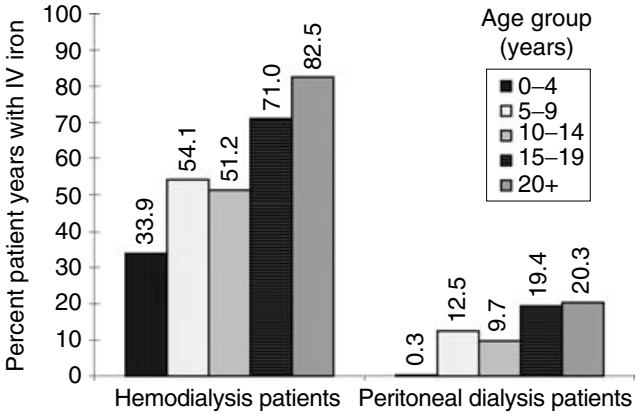

Fig. 2. Percentage of patient years with intravenous (IV) iron by modality and age, 1996 to 2000 (combined) period-prevalent hemodialysis and peritoneal dialysis patients treated with recombinant human erythropoietin (rHuEPO). Each patient may contribute <1 to 5 total patient years to a maximum of two age groups.

Hemoglobin values also increased with increasing age among the adults. In 2000, the mean hemoglobin values for 0- to 19-, 20- to 44-, 45- to 64-, and ≥65-year-old prevalent patients were 11.16, 11.42, 11.47, and 11.51 g/dL for hemodialysis patients, and 10.76, 10.79, 11.13, and 11.43 g/dL for peritoneal dialysis patients, respectively. Although the mean hemoglobin value in 2000 was lower among pediatric patients than among 20- to 44-year-old adult hemodialysis patients ($P < 0.0001$), the difference between pediatric and 20- to 44-year-old adult peritoneal dialysis patients was not significant ($P = 0.81$). Among adult hemodialysis and peritoneal dialysis patients in 2000, the mean hemoglobin value was significantly lower in 20- to 44-year-olds than in 45- to 64-year-olds, and in 45- to 64-year-olds than in ≥65-year-olds ($P < 0.0001$).

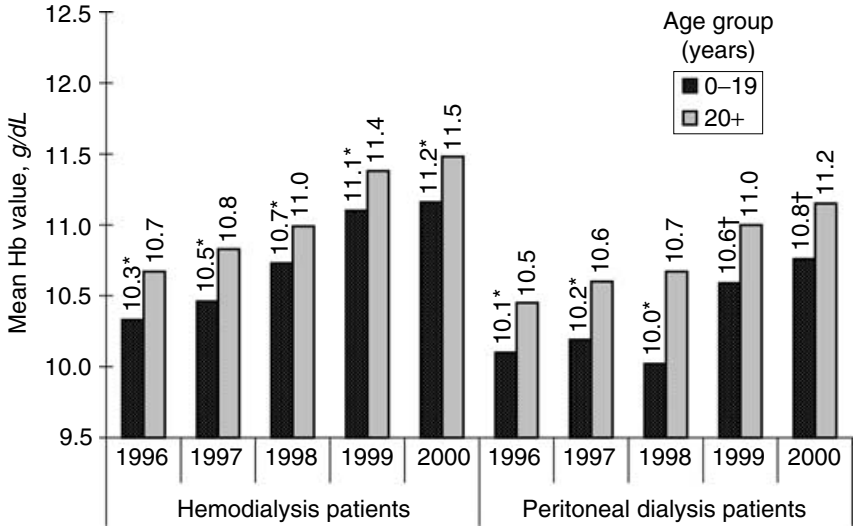

Fig. 3. Mean hemoglobin (Hb) value by modality, year, and age, 1996 to 2000 period-prevalent hemodialysis and peritoneal dialysis patients treated with recombinant human erythropoietin (rHuEPO). *$P < 0.0001$ in comparison with that year's group aged ≥20 years; †$P = 0.0001$ to <0.005 in comparison with that year's group aged ≥20 years. With use of the Bonferroni t test, a P value of <0.005 was required for significance to maintain an overall P value of 0.05.

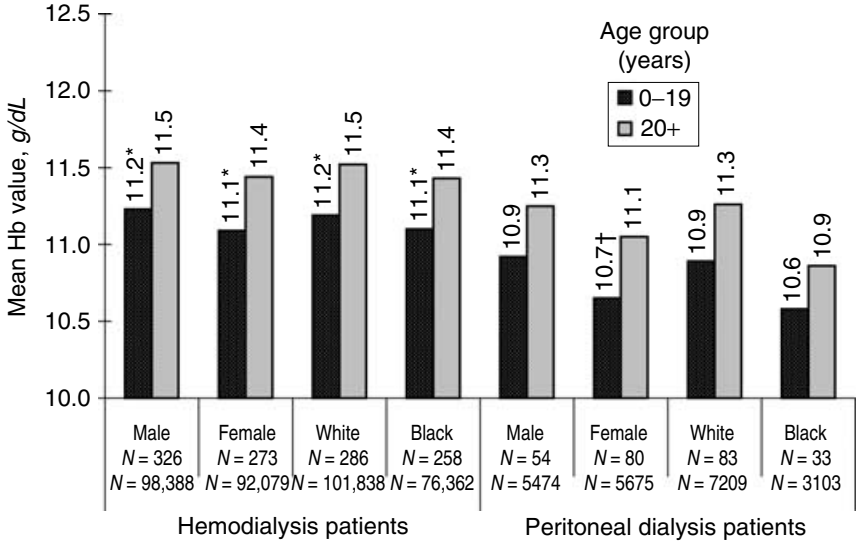

Fig. 4. Mean hemoglobin (Hb) value by modality, sex, race, and age, 2000 period-prevalent hemodialysis and peritoneal dialysis patients treated with recombinant human erythropoietin (rHuEPO). *$P < 0.0001$ in comparison with that sex's or race's group aged ≥20 years; †$P = 0.0061$ in comparison with females aged ≥20 years. With use of the Bonferroni t test, a P value of <0.0063 was required for significance to maintain an overall P value of 0.05. "N" provides the number of patients aged 0 to 19 and ≥20 years, respectively, in each group.

Trends in mean hemoglobin value by age and sex and by age and race

Among hemodialysis patients in 2000, pediatric patients had a significantly lower mean hemoglobin value than that of same-sex and same-race adults ($P < 0.0001$) (Fig. 4). Among peritoneal dialysis patients grouped by sex and race, the trend of lower hemoglobin among pediatric patients than adults appeared consistent; however, only the pediatric females had a significantly lower hemoglobin value than that of female adults ($P = 0.0061$). Among pediatric hemodialysis and peritoneal dialysis patients, respectively, mean hemoglobin values were 0.1 and 0.2 g/dL lower in females than in males, and 0.1 and 0.3 g/dL lower in black than in white patients. Mean hemoglobin values were lowest in female pediatric peritoneal dialysis patients (10.7 g/dL) and in black pediatric peritoneal dialysis patients (10.6 g/dL). The sex and racial differences were not statistically significant (results not shown).

Distributions in the subset of incident patients

In incident Medicare dialysis patients (1996 to 2000 combined) with and without rHuEPO during the incident year of ESRD, respectively, the mean hemoglobin values at initiation of dialysis were as follows: for pediatric hemodialysis patients, 8.7 and 8.3 g/dL ($N = 421$ and $N = 78$; $P = 0.10$); for adult hemodialysis patients, 9.5 and 9.7 g/dL ($N = 146{,}948$ and $N = 24{,}621$; $P < 0.0001$); for pediatric peritoneal dialysis patients, 8.4 and 9.0 g/dL ($N = 135$ and $N = 270$; $P = 0.007$); and for adult peritoneal dialysis patients, 9.7 and 10.1 g/dL ($N = 9352$ and $N = 9547$; $P < 0.0001$). Among included rHuEPO-treated patients (1996 to 2000 combined), the percentage of patients who were incident sometime during the 5-year study period was smaller for pediatric than for adult hemodialysis patients (28.7% vs. 45.1%; $P < 0.0001$); percentages were similar for pediatric and adult peritoneal dialysis patients who were incident (25.8% vs. 25.7%; $P = 0.94$).

We evaluated rHuEPO use before initiation of dialysis in the subset of incident patients (1996 to 2000 combined) with complete Medical Evidence Report data ($N = 451$ pediatric and $N = 156{,}793$ adult hemodialysis patients; $N = 147$ pediatric and $N = 9901$ adult peritoneal dialysis patients). For pediatric and adult patients, respectively, predialysis rHuEPO was received in 24.6% and 24.9% of hemodialysis patients ($P = 0.88$) and 27.9% and 35.0% of peritoneal dialysis patients ($P = 0.07$). Also, we computed the weekly rHuEPO/kg body weight during the incident year of dialysis for the subset of incident patients with a valid body weight measurement recorded on the Medical Evidence Report ($N = 442$ pediatric and $N = 154{,}739$ adult hemodialysis patients; $N = 123$ pediatric and $N = 8837$ adult peritoneal dialysis patients). For pediatric and adult patients, respectively, the mean weekly rHuEPO/kg body weight was 208 and 181 U/kg for hemodialysis patients ($P = 0.009$), and 121 and 77 U/kg for peritoneal dialysis patients ($P < 0.0001$).

DISCUSSION

Our data show that a target hemoglobin value of ≥11 g/dL was achieved a low percentage of the time among Medicare pediatric patients receiving rHuEPO treatment while on chronic dialysis. Among pediatric hemodialysis patients, 0- to 4-year-old patients attained a target hemoglobin value the lowest percentage of time, followed by 5- to 9-year-olds. Among pediatric peritoneal dialysis patients, 10- to 14-year-old and 15- to 19-year-old patients achieved a target hemoglobin value the lowest percentage of time. Among pediatric patients within each modality, slightly lower mean hemoglobin values were found among blacks than whites, and among females than males.

All patients in our study received rHuEPO after initiation of dialysis, which has been shown to correct anemia in pediatric dialysis patients [10, 11, 14–16]. However, the target hemoglobin value was achieved in pediatric hemodialysis patients in only 46% of patient years, compared with 55% of patient years in young adults and 60% of patient years in adults overall. The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) has reported findings very similar to ours. The 2001 NAPRTCS annual report showed that 63% of 1855 pediatric chronic dialysis patients who were receiving rHuEPO at 6 months of dialysis had hematocrit values of ≤33% (≤11 g/dL) [17]. This report, however, did not include hemoglobin data, hematocrit data by type of dialysis, or data on children under the age of 6 years who were treated with hemodialysis and were receiving rHuEPO. We did observe improvement in mean hemoglobin values between 1996 and 2000 for pediatric hemodialysis patients and adult hemodialysis and peritoneal dialysis patients. Pediatric peritoneal dialysis patients showed improvement between the years 1998 and 2000. However, mean hemoglobin values in children lagged behind those in adults at all time periods during the study. NAPRTCS found that mean hematocrit values at 6 months of dialysis improved with time, increasing from 31.2% in patients who initiated dialysis between 1992 and 1996 to 32.3% in patients who initiated dialysis between 1997 and 2000 ($P < 0.001$) [17]. Both our study and the NAPTRCS report show that a significant percentage of pediatric patients are below the National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) target hemoglobin value of 11 g/dL.

The recommended starting dosage of rHuEPO is 50 to 150 U/kg, given three times weekly. We could not determine the dosage given based on body weight for the prevalent dialysis patients in this study because body weight data were available only at initiation of dialysis. However, in the small subset of incident patients with a valid body weight measurement at initiation of dialysis, we showed that pediatric hemodialysis and peritoneal dialysis patients received mean weekly rHuEPO doses of 208 and 121 U/kg, respectively, and that these doses were significantly higher than those received by adults. Although the NAPRTCS report did not include rHuEPO/kg, these results are consistent with the results of smaller pediatric studies showing higher rHuEPO dose requirements in pediatric patients of small body weight [14, 16, 18–21]. In the subset of incident patients with an indication on the Medical Evidence Report of rHuEPO use before dialysis, the percentages of patients treated with rHuEPO were similar for pediatric and adult hemodialysis patients, and were slightly, but not significantly, lower in pediatric than in adult peritoneal dialysis patients. In our study, lower rHuEPO use before dialysis did not appear to be a major contributing factor to lower hemoglobin values in pediatric hemodialysis patients. However, these results are limited due to the small subset of incident patients with available data.

Fewer pediatric than adult patients were treated with rHuEPO after initiation of dialysis. Our subset analysis of incident patients showed higher mean hemoglobin values at initiation of dialysis in pediatric and adult peritoneal dialysis patients and adult hemodialysis patients who did not receive rHuEPO during the incident year of ESRD. Still, the mean hemoglobin values for the untreated group were below the target value in the K/DOQI guidelines, suggesting less than optimal management.

The lowest hemoglobin values were observed in young peritoneal dialysis patients. Studies of pediatric dialysis patients have suggested that patient age, size, and dialysis type are factors in the response to rHuEPO[14, 18–21]. A study of 116 pediatric hemodialysis patients found that children weighing less than 30 kg required twice the dose of rHuEPO (225 U/kg per week vs. 107 U/kg per week) as those weighing more than 30 kg to reach a hemoglobin value of 9.6 g/dL[14]. Two studies

of pediatric patients (one of 23 hemodialysis and 30 peritoneal dialysis patients; the other of 9 hemodialysis and 10 peritoneal dialysis patients) found that rHuEPO requirements were nearly three times higher in hemodialysis than in peritoneal dialysis patients [19, 20]. Our finding of lower hemoglobin values in pediatric peritoneal dialysis patients compared to hemodialysis patients could be related to a possible selection bias due to inclusion of only rHuEPO-treated patients. A smaller percentage of peritoneal dialysis (36.2%) versus hemodialysis (89.5%) patients were rHuEPO-treated and included in the study.

Our finding of lower hemoglobin values in pediatric patients could not be attributed to a greater percentage of incident pediatric patients than adult patients in each calendar year. The period-prevalent cohort analysis showed that a smaller percentage of the pediatric hemodialysis patients than adult patients were incident sometime during the 5-year study period. Among peritoneal dialysis patients, similar percentages of pediatric and adult patients were incident.

Sex and racial differences in rHuEPO responsiveness have been reported in adults [22–24]. In a study of 309 adult hemodialysis patients (165 women, 144 men), women required a 39% higher rHuEPO dose to achieve hematocrit values comparable to those in men; because women and men received equivalent amounts of intravenous iron, the difference in rHuEPO requirement was attributed to the contribution of androgens to erythropoiesis [22]. In our study, mean hemoglobin values were lower in females than in age-matched males and in blacks than in age-matched whites, irrespective of dialysis type, although the differences were not statistically significant.

Iron deficiency (functional or absolute) is common in rHuEPO-treated ESRD patients; accordingly, these patients require iron supplementation [8, 13, 18, 25–29]. Thus, among pediatric hemodialysis and peritoneal dialysis patients, it is of concern that intravenous iron was not administered during 34% and 85% of the patient years, respectively. We found the use of intravenous iron to be lowest in patients aged 0 to 4 years, irrespective of dialysis type. Among patients aged 0 to 4 years, intravenous iron was received during only 33.9% (hemodialysis) and 0.3% (peritoneal dialysis) of the patient years. Although intravenous iron use increased for peritoneal dialysis patients 5 years of age or older, it was used much less than in hemodialysis patients. However, pediatric peritoneal dialysis patients likely received oral iron supplementation. The 2001 NAPRTCS annual report showed that most pediatric chronic dialysis patients at 12 months of dialysis were receiving oral iron supplementation (84% of peritoneal dialysis and 72% of hemodialysis patients) [17]. Attention to iron management provides an opportunity to improve anemia profiles in pediatric chronic dialysis patients.

The current suggested target hemoglobin range in adults and pediatric patients with ESRD is 11 to 12 g/dL [12]. Despite the publication of guidelines in 1997 [12], pediatric peritoneal dialysis patients from 1998 to 2000 and pediatric hemodialysis patients in 1998 did not achieve a mean hemoglobin value in the target range. Recent improvements in mean hemoglobin values in rHuEPO-treated pediatric hemodialysis patients have exceeded those in rHuEPO-treated pediatric peritoneal dialysis patients.

In adult chronic dialysis patients, anemia has been shown to be a risk factor for the development of left ventricular hypertrophy, cardiomyopathy, and death [3, 4, 23, 30–36]. No large, prospective studies in pediatric chronic dialysis patients have linked anemia to outcomes such as cardiovascular disease, the leading cause of mortality in adults and children with ESRD [4, 5, 37, 38]. In a small study of the effects of anemia on cardiovascular abnormalities in 7 children on chronic dialysis, Morris et al [9] found that treatment of anemia with rHuEPO was associated with improvement in left ventricular hypertrophy. After 12 months of treatment the mean hemoglobin had improved from 7.2 g/dL to 11.7 g/dL ($P < 0.01$), left ventricular mass index had decreased from 94 to 81 g/m^2 ($P = 0.02$), and the mean cardiothoracic ratio had decreased from 50% to 46% ($P = 0.005$) [9]. Recent studies show cardiovascular disease is a significant cause of morbidity and mortality in children with ESRD [5, 37, 38]. Thirty-one percent of 1454 pediatric dialysis patients from 1991 to 1996 in the United States developed cardiovascular disease, and it accounted for 38% of the deaths in these patients [5]. In a study of 381 prevalent pediatric chronic dialysis patients from The Netherlands, cardiac disease accounted for 45% of the patient deaths [37]. Parekh et al [38] found that cardiovascular disease accounted for 23% of 1380 deaths in United States pediatric and young adult ESRD patients who died between 1990 and 1996. These findings suggest the need for a large, prospective study of cardiovascular disease risk factors such as anemia in children with ESRD.

Approximately 55% of 1996 to 1998 incident pediatric ESRD patients received a kidney transplant within two years after starting ESRD therapy [24]. Therefore, the pediatric chronic dialysis patients in this study may have represented a pediatric population with comorbid conditions that prevented them from undergoing transplantation in a timely manner. This potential selection bias may in part explain the degree of anemia found in pediatric patients in this study.

CONCLUSION

Pediatric chronic dialysis patients in the United States may be undertreated for anemia despite the use of rHuEPO supplementation. We found this to be especially

true for black and female patients. Intravenous iron may also be underused in pediatric chronic dialysis patients. Although mean hemoglobin values in pediatric patients lagged behind values in adults across years, we saw a definite trend toward improved mean hemoglobin values in children over time. The results of this study indicate the need for continued improvement in the management of anemia in children undergoing chronic dialysis.

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