Epoetin use and Kidney Disease Outcomes Quality Initiative hemoglobin targets in patients returning to dialysis with failed renal transplants

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Patients with failed renal transplants represent an increasing proportion of the current dialysis population. Although their risk of anemia might be expected to be high, whether these patients receive adequate anemia therapy after returning to dialysis is unknown. We studied intravenous iron use, epoetin doses, and hemoglobin levels in patients with and without failed renal transplants who survived for 6 months after initiation of dialysis in the United States between 1996 and 2001. Of the study population ($n = 220\,557$), 9922 (4.5%) had failed renal transplants. In spite of a greater likelihood of receiving intravenous iron therapy (adjusted odds ratio (AOR) 1.47, $P < 0.0001$) and epoetin (AOR 1.57, $P < 0.0001$), patients with failed transplants were more anemic and had higher epoetin doses in each month of follow-up. During month 6, patients with failed transplants were more likely to have hemoglobin levels below 11 g/dl (AOR 1.50, $P < 0.0001$) and to have epoetin-to-hemoglobin ratios above the population median of 1030 U/week per g/dl (AOR 1.73, $P < 0.0001$). Patients who return to dialysis with failed transplants are at a higher risk of anemia than other patients who start dialysis; the pattern of lower hemoglobin levels and higher ratios of epoetin-to-hemoglobin suggests that relative epoetin resistance may be contributory.

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Transplantation is the renal replacement therapy of choice for most patients with end-stage renal disease. Long-term mortality risks among patients receiving renal transplants are estimated to be about one-third those of otherwise similar dialysis patients remaining on the transplant waiting list.[1] Enhanced quality of life is another clear advantage of renal transplantation.[2–11] However, despite advances in the field of renal transplantation, a substantial proportion of patients experience progressive graft loss and return to dialysis therapy. For example, recent estimates from the United States Organ Procurement and Transplantation Network show a 31.1% 5-year graft loss rate for 1998–2003.[12] Approximately 7% of patients on maintenance dialysis in the United States have had a failed renal transplant.[13]

Anemia treatment guidelines for dialysis patients, such as the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, do not differentiate according to previous transplantation history.[14] Patients with failing renal transplants are often exposed to acute or chronic inflammation, and to medications that suppress erythropoiesis; all things being equal, one might expect patients returning to dialysis therapy with failing renal transplants to show a greater predisposition to anemia than those starting dialysis without previous transplantation. Surprisingly, it is unknown whether patients with failed renal transplants receive adequate anemia therapy after returning to dialysis. The current study attempts to address this issue by enumerating the prevalence of anemia in these patients and investigating the time required to reach K/DOQI-recommended hemoglobin levels.

RESULTS

We compared patients returning to dialysis with failed renal transplants to incident dialysis patients with respect to intravenous iron use, epoetin use, hemoglobin levels, and epoetin dose. The study population included patients aged 18 years and older with Medicare as primary payer who began or returned to dialysis between 1 January 1996, and 31 December 2001, and survived without transplantation for the

following 6 months. Patients with failed transplants had an interval of at least 1 year between transplantation and return to dialysis.

During the study period, 38 325 patients aged 18 years and older returned to dialysis with failed renal transplants. Of these, 25 984 had Medicare as primary payer when they returned to dialysis; of these, 21 476 had an interval of at least 1 year between transplantation and return to dialysis; and of these, 9922 survived for 6 months without another kidney transplant after returning to dialysis. Of the 338 147 patients who began dialysis without prior transplantations, 260 111 had Medicare as primary payer when they began and of these, 210 635 survived for 6 months after beginning dialysis. The study population ($n = 220\,557$) thus included 9922 patients with failed renal transplants and 210 635 with no prior transplantations.

Table 1 compares characteristics of incident dialysis patients with those of patients with failed renal transplants. The discriminating characteristics of patients with failed transplants include initiation of dialysis in later calendar years, younger age, male sex, black race, and the absence of each comorbid condition investigated. Table 1 also shows that within 6 months of returning to dialysis, 64% of patients with failed transplants received intravenous iron therapy and 82% received epoetin. The corresponding percentages were marginally higher ($P<0.001$) for incident dialysis patients

Table 1 | Comparison of incident dialysis patients and patients with failed renal transplants

	Percent incident dialysis patients (*n*=210 635)	Percent failed transplant patients (*n*=9922)	*P*	AOR[a] (95% CI)			
				i.v. iron by month 6[b]	*P*	Epoetin by month 6[c]	*P*
Incident dialysis patients	100	0		Reference		Reference	
Failed transplant patients	0	100		1.47 (1.40, 1.55)	<0.0001	1.57 (1.48, 1.67)	<0.0001
Received IV iron by dialysis month 6	67	64	<0.0001				
Received epoetin by dialysis month 6	85	82	<0.0001				
Year of dialysis							
1996	16	14		Reference		Reference	
1997	16	15		1.44 (1.39, 1.48)	<0.0001	1.15 (1.10, 1.20)	<0.0001
1998	16	16		1.86 (1.80, 1.92)	<0.0001	1.43 (1.37, 1.49)	<00001
1999	17	17		1.83 (1.77, 1.89)	<0.0001	1.29 (1.23, 1.34)	<0.0001
2000	17	18		1.79 (1.74, 1.85)	<0.0001	1.27 (1.22, 1.33)	<00001
2001	18	19	<0.0001	3.05 (2.95, 3.16)	<0.0001	1.96 (1.87, 2.05)	<0.0001
Female sex	49	41	<0.0001	1.05 (1.03, 1.07)	<0.0001	1.04 (1.01, 1.07)	0.0024
Age (years)							
18–44	6	51		Reference		Reference	
45–64	19	41		1.25 (1.20, 1.30)	<0.0001	1.04 (0.99, 1.09)	0.1173
⩾65	75	8	<0.0001	1.91 (1.84, 1.99)	<0.0001	1.85 (1.77, 1.93)	<0.0001
Race							
White	68	61		Reference		Reference	
Black	27	35		1.16 (1.14, 1.19)	<0.0001	1.09 (1.06, 1.12)	<0.0001
Other/unknown	5	4	<0.0001	0.85 (0.81, 0.88)	<0.0001	0.98 (0.93, 1.04)	0.4525
Comorbid conditions							
Atherosclerotic heart disease	37	15	<0.0001	1.04 (1.01, 1.06)	0.0025	1.15 (1.11, 1.19)	<0.0001
Congestive heart failure	44	21	<0.0001	1.17 (1.14, 1.20)	<0.0001	1.35 (1.30, 1.40)	<0.0001
Stroke or transient ischemic attack	12	5	<0.0001	0.99 (0.96, 1.02)	0.5481	1.15 (1.08, 1.21)	<0.0001
COPD	17	7	<0.0001	1.13 (1.09, 1.16)	<0.0001	1.22 (1.16, 1.28)	<0.0001
Gastrointestinal bleeding	9	6	<0.0001	0.97 (0.94, 1.01)	0.0876	1.16 (1.09, 1.23)	<0.0001
Diabetes mellitus	50	31	<0.0001	1.40 (1.37, 1.43)	<0.0001	1.66 (1.61, 1.72)	<0.0001
Hypertension	73	66	<0.0001	2.66 (2.60, 2.72)	<0.0001	4.37 (4.24, 4.51)	<0.0001
Infectious hospitalizations							
0	62	61		Reference		Reference	
1–3	36	37		1.04 (1.02, 1.07)	0.0001	1.50 (1.44, 1.55)	<0.0001
4 or more	2	2	0.0068	0.63 (0.59, 0.68)	<0.0001	1.19 (1.05, 1.35)	0.0072

AOR, adjusted odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; i.v., intravenous.

[a]With logistic regression, adjusted for incident dialysis or failed transplant, year of dialysis initiation, sex, race, and comorbid conditions.

[b]Interaction terms analysis showed that the following associations differed in patients with and without failed transplants: female ($P<0.0001$, AOR 0.87 with failed transplant, 1.06 without failed transplant), age 45–64 ($P=0.0001$, AOR 1.06, 1.30), hypertension ($P<0.0001$, AOR 2.11, 2.69), and the years 1997–2001 (all $P<0.0001$; AOR with failed transplant 1.19, 1997; 1.40, 1998; 1.46, 1999; 1.45, 2000; 2.07, 2001; without failed transplant 1.45, 1997; 1.89, 1998; 1.85, 1999; 1.81, 2000; 3.12, 2001).

[c]Interaction terms analysis showed that the following associations differed in patients with and without failed transplants: age 45–64 ($P=0.0142$, AOR 1.19 with failed transplant, 1.01 without failed transplant), other race ($P=0.0296$, AOR 0.75, 0.99), diabetes ($P=0.0174$, AOR 1.39, 1.67), hypertension ($P<0.0001$, AOR 3.14, 4.46), and the years 1998, 1999, and 2001 ($P<0.0001$, 1998; 0.0084, 1999; <0.0001, 2001; AOR with failed transplant 0.97, 1998; 0.996, 1999; 1.22, 2001; without failed transplant 1.46, 1998; 1.30, 1999; 1.99, 2001).

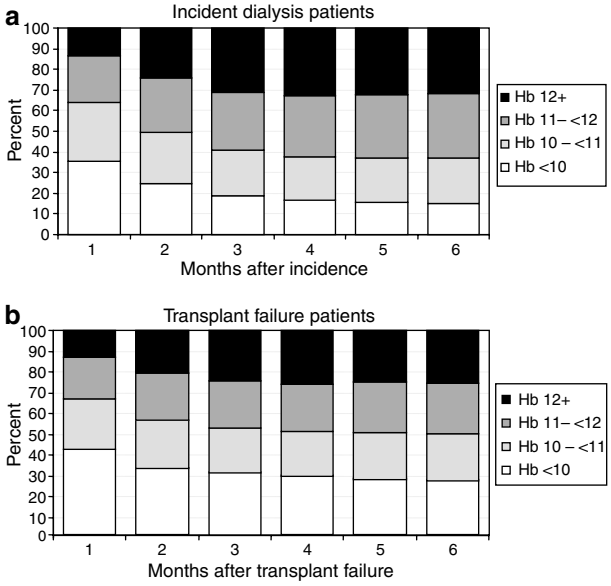

Figure 1 | Mean hemoglobin levels, dialysis months 1-6. $P<0.001$ for each month for the comparison of patients with and without failed transplants. Hb, hemoglobin, in g/dl.

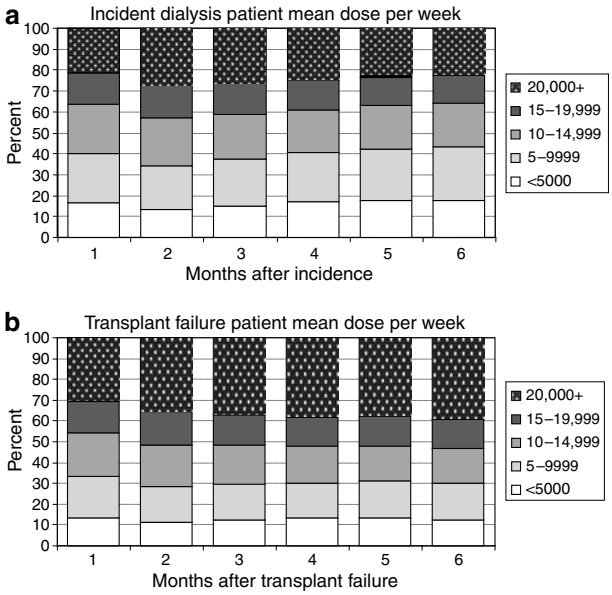

Figure 2 | Epoetin doses, dialysis months 1-6. $P<0.001$ for each month for the comparison of patients with and without failed transplants.

with no prior transplants, of whom 67% received intravenous iron therapy and 85% received epoetin. When adjustment was made for year of dialysis initiation, sex, race, comorbid conditions, and infectious hospitalizations, patients with failed transplants were 1.47 times more likely than incident dialysis patients to receive intravenous iron therapy and 1.57 times more likely to receive epoetin in the first 6 months after returning to dialysis.

Figures 1 and 2 show hemoglobin levels and epoetin doses for patients treated with epoetin in the first 6 months of dialysis. Compared with incident dialysis patients with no prior transplants, patients with failed transplants were more anemic and had higher epoetin doses in each month of follow-up. Table 2 shows multivariate associations of hemoglobin levels <11 g/dl and epoetin-to-hemoglobin ratios above the 6-month population median of 1030 U/week per g/dl. When adjustment was made for year of dialysis initiation, sex, race, comorbid conditions, and infectious hospitalizations, patients with failed transplants were 1.50 times more likely than incident dialysis patients to have hemoglobin levels <11 g/dl and 1.73 times more likely to have epoetin-to-hemoglobin ratios >1030 U/week per g/dl in month 6 of dialysis.

Other factors that could influence hemoglobin levels and epoetin resistance within the transplant population (including duration of graft survival, transplant nephrectomy after the return to dialysis, and mode of immunosuppression) were analyzed separately with models including only the transplant group. Longer graft survival was associated with receiving iron (adjusted odds ratio (AOR) $=1.16$, $P=0.0469$) and a lower likelihood of hemoglobin <11 g/dl (AOR $=0.82$, $P=0.0188$). Nephrectomy within 3 months of returning to dialysis (16%) was associated with epoetin (AOR $=2.12$, $P<0.0001$) and iron (AOR $=1.62$, $P<0.0001$) use, a lower likelihood of hemoglobin <11 g/dl (AOR $=0.73$, $P<0.0001$), and a high epoetin-to-hemoglobin ratio (AOR $=1.35$, $P<0.0001$).

For the subset of transplant patients for whom United Network of Organ Sharing transplant follow-up forms could be found (65% of 9922), the most recent follow-up form before a graft failure was used to determine use of corticosteroid (7%), calcineurin inhibitors (cyclosporine or tacrolimus, 83%), azathioprine (34%), or mycophenolate mofetil (36%). Using a model with the same adjustors as above, only mycophenolate mofetil was associated with a study outcome (a high epoetin-to-hemoglobin ratio, AOR $=1.29$, $P=0.0018$).

Of patients with failed transplants, 5840 (59%) had epoetin claims at month 12. Of these, 46% had hemoglobin levels <11 g/dl at month 6 and at month 12, and 72% had epoetin-to-hemoglobin ratios >1030 U/week per g/dl at month 6 and at month 12. Among non-transplant patients, 127 802 (61%) had epoetin claims at month 12. Of these, 43% had hemoglobin levels <11 g/dl at month 6 and at month 12, and 63% had epoetin-to-hemoglobin ratios >1030 U/week per g/dl at month 6 and at month 12.

DISCUSSION

Graft-failure patients have a higher mortality rate than incident dialysis patients.[15] When case-mix was taken into account, we found that patients returning to dialysis after failed renal transplantation were much more likely to start therapy with intravenous iron and epoetin; nevertheless, they were much less likely to attain K/DOQI hemoglobin targets, and the observation of substantially higher epoetin-to-hemoglobin ratios suggests that lower hemoglobin targets may have resulted, in part, from epoetin resistance.

Table 2 | Associations of hemoglobin <11 g/dl and epoetin-to-hemoglobin ratio >1030 at dialysis month 6

	Hemoglobin <11 g/dl			Epoetin/hemoglobin ratio >1030 units/week per g/dl		
	AOR[a,b]	95% CI	*P*	AOR[a,c]	95% CI	*P*
Incident dialysis patients	Reference			Reference		
Failed transplant patients	1.50	1.42, 1.59	<0.0001	1.73	1.63, 1.83	<0.0001
Year of dialysis						
1996	Reference			Reference		
1997	0.98	0.95, 1.02	0.2793	0.99	0.95, 1.02	0.5086
1998	0.59	0.57, 0.61	<0.0001	1.21	1.17, 1.25	<0.0001
1999	0.47	0.45, 0.49	<0.0001	1.30	1.25, 1.34	<0.0001
2000	0.39	0.38, 0.41	<0.0001	1.21	1.17, 1.25	<0.0001
2001	0.34	0.33, 0.35	<0.0001	1.30	1.26, 1.35	<0.0001
Female sex	1.09	1.07, 1.12	<0.0001	1.00	0.98, 1.02	0.9994
Age (years)						
18–44	Reference			Reference		
45–64	0.81	0.77, 0.85	<0.0001	1.01	0.96, 1.06	0.6402
⩾65	0.68	0.65, 0.71	<0.0001	0.83	0.79, 0.87	<0.0001
Race						
White	Reference			Reference		
Black	1.17	1.14, 1.20	<0.0001	1.36	1.33, 1.39	<0.0001
Other/unknown	1.07	1.02, 1.13	0.0067	0.84	0.80, 0.88	<0.0001
Comorbid conditions						
Atherosclerotic heart disease	1.00	0.98, 1.02	0.9697	1.04	1.01, 1.06	0.0033
Congestive heart failure	1.04	1.02, 1.07	0.0017	1.14	1.11, 1.17	<0.0001
Stroke or transient ischemic attack	1.07	1.04, 1.11	<0.0001	0.98	0.95, 1.01	0.1192
COPD	1.05	1.03, 1.09	0.0003	1.02	0.99, 1.04	0.2393
Gastrointestinal bleeding	1.23	1.18, 1.27	<0.0001	1.30	1.26, 1.35	<0.0001
Diabetes mellitus	1.03	1.01, 1.05	0.0188	1.04	1.01, 1.06	0.0014
Hypertension	1.01	0.98, 1.04	0.4501	1.16	1.12, 1.19	<0.0001
Infectious hospitalizations						
0	Reference			Reference		
1–3	1.24	1.22, 1.27	<0.0001	1.28	1.25, 1.31	<0.0001
4 or more	2.24	2.08, 2.43	<0.0001	1.54	1.43, 1.67	<0.0001

AOR, adjusted odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
[a]With logistic regression, adjusted for incident dialysis or failed transplant, year of dialysis initiation, sex, race, and comorbid conditions.
[b]Interaction terms analysis showed that the following association differed in patients with and without failed transplants: age 45–64 (*P*=0.0114, AOR 0.91 with failed transplant, 0.78 without failed transplant) and four or more infectious hospitalizations (*P*=0.0130, AOR 1.47, 2.29).
[c]Interaction terms analysis showed that the following association differed in patients with and without failed transplants: female (*P*=0.0007, AOR 1.19 with failed transplant, 0.99 without failed transplant), one to three infectious hospitalizations (*P*=0.0161, AOR 1.12, 1.29), and four or more infectious hospitalizations (*P*=0.0032, AOR 0.93, 1.58).

Few studies have examined anemia management in patients with failed renal transplants. Thus, a PubMed search on 15 September 2006, using the terms *transplant failure*, *dialysis*, *hemoglobin*, and *epoetin* yielded 21 citations, of which only one was relevant to the question addressed in our study. That report, by Almond *et al.*[16] in 1994, was a cross-sectional examination of epoetin doses in 60 dialysis patients. Epoetin doses were approximately 70% higher in patients with failed transplants than in patients with no prior transplantation.

Anemia is relatively common in patients with functioning renal transplants. One study of 4263 patients from 72 centers in Europe[17] reported that approximately one in three transplant patients develops anemia (defined as hemoglobin levels <13 g/dl in male and <12 g/dl in female subjects) at some stage after engraftment. Impaired glomerular filtration was the dominant association; other associations included the use of angiotensin-converting enzyme inhibitors and known myelosuppressant agents such as azathioprine and mycophenolate, kidneys from older donors, and recent infections. It is tempting to suggest that some of these factors may have been involved in the apparent epoetin resistance we observed in patients returning to dialysis with failed transplants. Also, conceivably, ongoing chronic allograft nephropathy and recurrence of a primary renal disease of an inflammatory nature may account for some of our findings.

Several limitations of our study should be noted. This was a retrospective analysis using claims to define the study subjects and their outcomes. The study entry criteria, reflecting the twin pressures of wishing to study patients immediately from inception of dialysis and reliance on Medicare claims for longitudinal data points, produced a subset of all patients returning to dialysis with failed transplants. The available data did not allow us to determine whether allograft loss was due to chronic allograft nephro-

pathy, calcineurin nephrotoxicity, or recurrence of a primary renal disease; which patients used fistulas, grafts, and catheters for dialysis vascular access; or medication use, historical and current. The hemoglobin levels of patients not receiving epoetin were unknown. Iron store measures were unavailable, as were standard indicators of nutritional anemia, such as B_{12} and folate levels. Similarly, serological measures of inflammatory and oxidative stress could not be determined. Information on the route of epoetin application was not available; however, current data from the Centers for Medicare and Medicaid Services End-stage Renal Disease Clinical Performance Measures Project show that less than 10% of epoetin is given subcutaneously.[18]

Despite its limitations, we believe this study has useful features. The sample size is large and reflective of clinical practice at a national level. On a relative basis, loss of renal allograft function may be the most rapidly increasing cause of end-stage renal disease requiring dialysis. As was apparent in this study, patients with failed transplants are considerably younger and healthier than the typical newcomer to dialysis therapy. The possibility of a repeat transplant may be considered in many of these patients. Suggesting that hemoglobin targets should be similar in dialysis patients with failed transplants and those with no prior transplants seems reasonable. Our study suggests that current management of anemia in patients with recently failed renal transplants may be suboptimal.

MATERIALS AND METHODS

Patients

Patients with failed transplants were identified from the United States Renal Data System (USRDS) data set, which incorporates data from the United Network of Organ Sharing. These patients had the following characteristics:

1. returned to dialysis between 1 January 1996, and 31 December 2001;
2. aged $\geqslant$18 years at transplant failure date;
3. had Medicare as primary payer at time of return to dialysis;
4. had $\geqslant$1 year interval between engraftment and return to dialysis;
5. survived for 6 months after returning to dialysis.

Incident dialysis patients were identified from the USRDS data set. They had the following characteristics:

1. initiated dialysis between 1 January 1996, and 31 December 2001;
2. aged $\geqslant$18 years at first dialysis service date;
3. had Medicare as primary payer at time of dialysis initiation;
4. survived for 6 months after initiating dialysis.

Measurements

Epoetin claims and associated hemoglobin levels in the first 6 months after dialysis initiation were identified from the USRDS data set, using the following criteria:

1. hematocrit between 10 and 50%;
2. dose per epoetin administration between 500 and 80 000 U;
3. epoetin administrations between 1 and 20 per month.

We made an *a priori* decision that values outside these ranges were more likely to represent claim error than clinical reality.

We also determined, on a monthly basis, whether intravenous iron was used.

Analysis

We reasoned that 6 months after the start of dialysis therapy would be a sufficient amount of time to establish clinical stability and to gauge therapeutic approaches to anemia treatment. Accordingly, we report findings on patients who survived for 6 months after the initiation of dialysis. Our findings were very similar, however, when 6-month survival was not required. *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* and *Physicians' Current Procedural Terminology* codes were used to define comorbid conditions and infectious hospitalizations, based on claims made in the first 3 months of dialysis therapy. We used the χ^2 test to compare proportions of patients with mean hemoglobin levels $<$10, 10 to $<$11, 11 to $<$12, and $\geqslant$12 g/dl in each of the first 6 months after initiation of dialysis therapy. In addition, we used logistic regression to identify associations of intravenous iron use and epoetin use among all patients, mean hemoglobin levels above 11 g/dl, epoetin doses above the median, and epoetin-to-hemoglobin ratios above the median in month 6. Finally, to determine whether associations were similar in subgroups of patients with failed transplants and with no prior transplantation, all associations in multivariate analyses were repeated with interaction terms made between candidate associations and the presence or absence of a failed transplant.

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