Evaluation of erythropoiesis and changes in serum erythropoietin concentration in cats after renal transplantation

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Objective—To investigate the clinicopathologic patterns of the erythropoietic response after renal transplantation in cats with chronic renal failure (CRF).

Animals—14 cats with CRF undergoing renal transplantation.

Procedure—Before and at intervals during a 6-month period after transplantation, serum creatinine and erythropoietin concentrations, Hct, erythrocyte indices, aggregate reticulocyte percentage, and iron variables were measured. Additionally, the number of transfusions administered to and any complications that developed in each cat were recorded.

Results—In all cats, preoperative azotemia resolved within 6 days after renal transplantation. Two cats had a temporary increase in serum creatinine concentration secondary to an acute graft rejection episode. Anemia (defined as Hct < 28%) resolved in 10 cats 3 to 49 days after surgery. Resolution of anemia was delayed in 2 cats that had acute rejection episodes. Serum erythropoietin concentration and reticulocyte percentage were low preoperatively; values after surgery were highly variable. Compared with preoperative values, serum erythropoietin concentration increased 1 to 4 days after surgery in 11 cats; between days 5 and 58, another increase was detected in 9 cats. Serum iron concentrations were generally low before and 14 days after transplantation.

Conclusion and Clinical Relevance—The erythropoietic response was highly variable in cats after renal transplantation, but anemia typically resolved within 1 month after surgery. A delay in resolution of anemia in cats may indicate poor graft function and inadequate iron stores, suggesting the need for further evaluation for concurrent illness. (*Am J Vet Res* 2003;64: 1248–1254)

Anemia of **chronic renal failure (CRF)** is complex in origin and causes considerable illness in humans and animals. With regard to the development of this condition, there is experimental and clinical evidence for the supporting roles of nutritional abnormalities, blood loss with iron deficiency, shortened survival time of RBCs, hemolysis, and depression of bone marrow function by uremia associated toxins. However, inadequate production of erythropoietin has clearly emerged as the principle cause of anemia in humans and animals with CRF.[1-11]

After birth, erythropoietin is primarily produced in the kidneys, and its synthesis is regulated by the degree of renal hypoxia. Normally, there is an inverse correlation between a decline in Hct and plasma erythropoietin concentration. However, in humans with CRF, erythropoietin production is drastically impaired; thus the anemia is nonregenerative. In humans who have anemia secondary to CRF, the inadequate production of erythropoietin by the peritubular endothelial cells is thought to be associated with either chronic structural damage to the kidney that has destroyed the cells that normally produce erythropoietin or disturbance of the mechanisms that adjust erythropoietin production in response to changes in oxygen.[12,13] In the latter situation, the capability to produce erythropoietin is preserved.

Although anemia of CRF can be temporarily corrected with transfusions and administration of human or feline recombinant erythropoietin, renal transplantation remains the best physiologic treatment. In humans, successful renal transplantation improves the production of erythropoietin, which subsequently stimulates RBC formation and leads to resolution of the anemia over 1 to 6 months.[1,7,8,10,11,14-16] In humans, patterns of erythropoietin secretion and subsequent erythropoiesis have been well characterized, but are variable.[1-3,6,7,10,14,15,17] The purpose of the study reported here was to assess the erythropoietic response after renal transplantation in cats with CRF.

Materials and Methods

Study population—During a 1-year period (2001), 14 cats with CRF that were candidates for renal transplantation were included in this prospective study. The group of cats comprised 10 domestic shorthair and 2 domestic longhair cats, 1 Tonkinese, and 1 Siamese. Eight cats were female and 6 were male; all were neutered. Mean age ± SD was 8 ± 4.5 years (range, 2 to 16 years). Chronic renal failure was diagnosed on the basis of history and physical-examination, clinicopathologic, and radiographic findings; on the basis of described criteria,[18] all cats were found to be suitable candidates for renal transplantation. Informed consent was obtained from the owners, and the study was approved by the Institutional Animal Care and Use Committee for client-owned animals at the University of Pennsylvania. The owner of each cat that received a transplanted kidney was required to adopt the donor cat.

Fourteen cats were screened for suitability as potential

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donor cats. Twelve of the donor cats were obtained from a pathogen-free colony,[a] and 2 were obtained from an animal shelter.[b] On the basis of physical-examination, clinicopathologic, and radiographic findings, all were considered normal. A donor was selected on the basis of blood type and crossmatch compatibility to the recipient without testing for feline major histocompatability. To induce immunosuppression in the recipients, a combination of cyclosporine[c] (2 to 5 mg/kg, PO, q 12 h) and prednisone (0.5 mg/kg, PO, q 12 h) was administered. Administration of cyclosporine was begun 48 to 72 hours prior to surgery, and prednisone treatment was started the morning of surgery. The cyclosporine dose was adjusted to maintain a 12-hour trough blood concentration of 300 to 500 ng of cyclosporine/mL (measured via high-performance liquid chromatography). Transplantation of a donor's kidney was performed as described.[19] On admission to the hospital, all cats received fluid IV (nutritional supplement solution[d]; 2 to 3 mL/kg/h). Fluid treatment was tapered over a 7-day period after renal transplantation. Briefly, the renal transplantation procedure involved end-to-side anastomosis of the renal artery and vein of the transplanted kidney to the caudal aorta and caudal vena cava, respectively; ureteroneocystostomy was also performed.

Data collection—For each cat, the time and number of transfusions administered were recorded. Each transfusion consisted of 40 mL of stored whole blood anticoagulated in 6 mL of citrate phosphate dextrose adenine solution. The blood was collected from blood type- and crossmatch-compatible cats from a hospital donor colony. During hospitalization, blood samples from the recipient were obtained from a double lumen jugular catheter[e] placed at the time of anesthetic induction. Once the cat was discharged, blood samples were collected via jugular venipuncture. When iron variables were additionally evaluated, a total of 4 mL of blood was obtained (2 time points). At all other time points, 2 mL of blood was collected. Serum erythropoietin and creatinine concentrations, Hct, aggregate reticulocyte percentage, **mean corpuscular volume (MCV)**, and **mean corpuscular hemoglobin concentration (MCHC)** were evaluated before surgery (day 0), daily on days 1 to 7, and on days 14, 28, 56, 84, 112, 140, and 168 if possible. Serum erythropoietin concentration was measured by use of a serum erythropoietin ELISA[f] test kit for feline samples.[20] Serum **total iron binding capacity (TIBC)** and ferritin and iron concentrations were evaluated on days 0 and 14; standard methods were used to measure these variables.[21,g] Additionally, details of postoperative complications, including episodes of acute graft rejection, were also recorded. Additional laboratory testing, including a CBC and serum biochemical analyses, was performed on 2 cats that had acute rejection episodes postoperatively. In cats with acute rejection, treatment consisted of the IV administrations of cyclosporine diluted in physiologic saline (0.9% NaCl) solution (6.6 mg/kg administered during 6 hours, q 24 h) and prednisolone sodium succinate (10 mg/kg, q 12 h). To maintain hydration during rejection therapy, cats received IV fluid treatment (saline solution, 3 to 4 mL/kg/h).

Statistical analyses—For each variable assessed, data obtained after surgery were compared with preoperative values. Age, serum TIBC, and time to resolution of anemia were expressed as mean ± SD. A paired *t* test was used for comparison of parametric data. Because of the data distribution, all other variables were expressed as median values. The Wilcoxon signed rank test was used for comparison of nonparametric data. Values of $P < 0.05$ were considered significant.

Results

Laboratory findings prior to transplantation—Fourteen cats were enrolled in the study. Before surgery (day 0), serum creatinine concentration in these cats ranged from 2.7 to 13.7 mg/dL (median, 5.7 mg/dL; reference range, 1 to 2 mg/dL). For the purposes of this study, cats with values of Hct < 28% were considered to be anemic. Among the 14 cats, Hct ranged from 14 to 32% (median, 20%; reference range, 31.7 to 48%); all but 1 cat were classified as anemic. In the study cats, anemia was poorly regenerative or nonregenerative. Aggregate reticulocyte percentage ranged from 0 to 0.7% (median, 0%); values < 0.4% were considered representative of nonregenerative anemia. The anemia was normocytic (median MCV, 46 fL; reference range, 37 to 54 fL) and normochromic (median MCHC, 34 g/dL; reference range, 30 to 36 g/dL). In 7 of 14 cats, anemia was severe (Hct, < 20%). Serum erythropoietin concentrations ranged from 1 to 6 mU/mL (median, 4 mU/mL; reference range, 1 to 10 mU/mL), which were inappropriately low for the degree of anemia.

Transfusions—Transfusions were given at the time of induction of anesthesia and during the surgical procedure as needed. All cats had type A blood and received transfusions of compatible stored whole blood (typed and crossmatched). Eight cats received 2 units of blood each, and the other 6 cats received 1 unit of blood each. The blood volume administered to each cat ranged from 10 to 26 mL/kg; no excessive blood loss was observed during surgery. In 2 cats, during episodes of acute rejection after surgery, compatible stored whole blood transfusions (typed and crossmatched) were administered (2 transfusions in 1 cat and 1 transfusion in the other).

Laboratory findings after transplantation—Grafted kidneys recovered function in all cats within 1 to 6 days after renal transplantation. Median serum creatinine concentration on days 1 and 6 after surgery was 2.3 and 1.8 mg/dL, respectively. The serum creatinine concentration remained within reference range throughout the observation period in 12 cats. Two cats had acute rejection episodes on days 25 and 29, respectively. In the first cat, the serum creatinine concentration increased from 1.6 to 3.4 mg/dL (days 14 and 25, respectively), and in the second cat, the serum creatinine concentration increased from 1.3 to 2.6 mg/dL (days 14 and 29, respectively). After treatment for rejection, the duration of azotemia was 96 hours in the first cat and 48 hours in the second cat before serum biochemical values returned to within reference limits.

Although the anemia was not expected to resolve during the first week after transplantation, the median Hct increased from 20 to 24% on day 1 after surgery. This was probably associated with transfusions given during the perioperative period (**Fig 1**).

Serum erythropoietin concentration was measured before surgery in 11 study cats. Between days 1 and 4 after transplantation, an increase in serum erythropoietin concentration was detected; compared with concentrations before surgery, the increase ranged from 49 to 13,257%. In 7 of 11 cats, the increase in serum erythropoietin concentration occurred during the first 24 hours after surgery. In these 7 cats, median serum erythropoietin concentration increased from 4 mU/mL

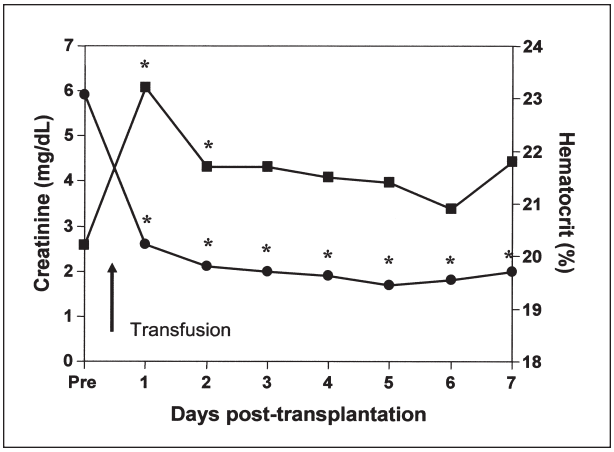

Figure 1—Median serum creatinine concentration (circle) and hematocrit values (square) before (Pre) and during the first 7 days after renal transplant surgery in 14 cats with chronic renal failure. *Value significantly ($P < 0.05$) different from values obtained before surgery (day 0).

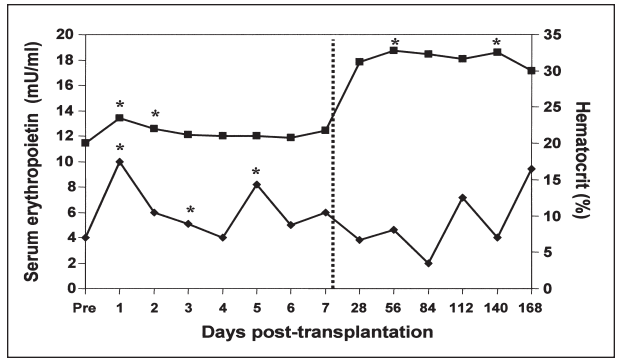

Figure 2—Median serum erythropoietin concentration (diamond) and hematocrit values (square) before (Pre) and after renal transplantation in 10 of 14 cats. *Value significantly ($P < 0.05$) different from values obtained before surgery (day 0).

(day 0) to 10 mU/mL (day 1 after surgery) and then returned to preoperative values by day 4; thus, the rise was generally transient and minor. In the remaining 4 cats, an increase in serum erythropoietin concentration was detected 72 (n = 3) and 96 (1) hours after surgery. In 9 of 11 cats, an increase in serum erythropoietin concentration was again detected between days 5 and 58 after surgery, with a 111 to 4,500% increase from preoperative values. The timing of the second peak varied between cats, and when all of the cats that displayed a second peak were evaluated as a group, only the median serum erythropoietin concentration on day 5 was significantly increased from the median concentration before surgery. After the second increase (> 58 days), serum erythropoietin concentrations were extremely variable in all cats. Only a mild regenerative reticulocyte response was seen by day 4 (median aggregate reticulocyte percentage, 0.45%). The greatest reticulocyte response among the cats was detected on day 21 (aggregate reticulocyte percentage, 3.9%; median, 0.2%). The peak median aggregate reticulocyte percentage was detected on day 14 after surgery (1.1%).

In 10 of 14 cats, Hct values increased to > 28% at 3 to 49 days after surgery (mean time to Hct > 28%, 21.8 ± 15.8 days; **Fig 2**). Hematocrit values > 28% were considered to indicate resolution of anemia. In 2 cats, resolution of the anemia occurred at 3 and 7 days following surgery. The resolution in both cats appeared to be associated with blood transfusions given during the perioperative period as well as the discontinuation of IV fluid therapy. In the other 8 cats, Hct was > 28% at 13 to 49 days after transplantation. Resolution of the anemia was delayed in 2 cats that experienced acute rejection episodes and could not be evaluated in 2 cats that died prematurely. One cat died as a result of traumatic avulsion of the allograft from the aorta on day 10. The other cat died 25 days after surgery as a result of reactivation of a latent toxoplasmosis infection.

Data for evaluation of MCV and MCHC after surgery were limited (n = 3 to 7 cats). Values of MCV remained in the reference range at all time points after surgery except in 2 cats that had mild microcytosis: 1 cat on day 21 and a second cat on day 56 (MCV, 35.4 and 35.9 fL, respectively). Compared with the median MCHC value before surgery (34 g/dL), there was a significant ($P = 0.01$) decline in median MCHC at day 14 (31.9 g/dL) and at day 28 (32.7 g/dL); however, these values remained within reference range.

One cat had sustained high serum erythropoietin concentration values for the duration of the study period (range, 25.9 to ≥ 400 mU/mL), but unfortunately, the value before transplantation in this cat was not known. Before the cat underwent surgery, Hct was 26%. It received 1 transfusion during the perioperative period. A mild regenerative reticulocyte response was detected on day 2 after surgery (aggregate reticulocyte percentage, 0.4%); maximum aggregate reticulocyte percentage (2.1%) was detected on day 6. After transplantation (day 3), Hct had decreased to 19% in this cat; however, this cat had been administered fluids IV (nutritional supplement solution, 2 to 3 mL/kg/h) for 3 days beginning the day of surgery. After discontinuation of fluid treatment on day 4, the cat's Hct was 25%; on day 7, Hct was 28%. During the study period, Hct did not exceed 35% in this cat.

An acute graft rejection episode was observed in 2 cats at 25 and 29 days (1 episode/cat). In both cats, rejection was diagnosed on the basis of sudden onset of polyuria, polydipsia, and vomiting; detection of an enlarged, hyperechoic renal graft ultrasonographically; and increased serum creatinine concentration. In both cats, a decrease in the Hct was observed in association with the rejection episode. Prior to the rejection episode on day 25, Hct in that cat was 20% (measured on day 14); prior to the rejection episode on day 29, Hct in that cat was 25% (measured on day 28). At the time of rejection (days 25 and 29), values of Hct were 14 and 15%, respectively, and there was no evidence of blood loss in either cat. Additionally, the cat with the rejection episode on day 29 had an increase in serum erythropoietin concentration detected in conjunction with the rejection episode; the value was 10 mU/mL on day 14, but was 18 mU/mL on day 28. Treatment for rejection was initiated on days 25 and 29. Both cats were treated for 2 days with IV administrations of cyclosporine diluted in physiologic saline solution (6.6 mg/kg administered during 6 hours, q 24 h) and prednisolone sodium succinate (10 mg/kg, q 12 h). To

maintain hydration, cats received IV fluid treatment (saline solution, 3 to 4 mL/kg/h). One cat was administered 1 unit of whole blood, and the other received a transfusion of 2 units. Azotemia resolved in 4 days in the first (serum creatinine concentration, 1.7 mg/dL) and 2 days in the second cat (serum creatinine concentration, 1.5 mg/dL), and they were subsequently administered cyclosporine and prednisone orally. After successful treatment for rejection of the renal graft, the cats continued to have Hct values < 28%, but they did not require any more transfusions of whole blood. In the cat with the rejection episode on day 25, Hct was 30.1% on day 112; in the cat with the rejection episode on day 29, Hct was 33% on day 140. In the cat with the rejection episode on day 25, no increase in serum erythropoietin concentration was detected in conjunction with the rejection episode.

Serum iron concentration and TIBC values were obtained before and 14 days after surgery in 10 cats. Serum ferritin concentration was obtained before and 14 days after surgery in 7 cats. Prior to transplantation, median serum iron concentration was 69 µg/dL (reference range, 60 to 134 µg/dL); 8 cats had low to low-normal serum iron concentration, whereas 2 cats had slightly high values (169 and 261 µg/dL, respectively). Five cats had serum iron concentrations below the reference range prior to transplantation. Despite transfusions and prompt increase in Hct to values > 28% in 6 cats, serum iron concentrations decreased further by day 14 in 6 cats; at day 14, none of the 10 cats had high serum iron concentration (median, 59.5 µg/dL). Before surgery, mean serum TIBC value was 217.6 ± 80.5 µg/dL (reference range, 169 to 325 µg/dL). In 8 cats, serum TIBC before surgery was within reference range; of the 2 other cats, 1 cat had a slightly low value (47 µg/dL), and the other had a slightly high value (342 µg/dL). The serum TIBC values increased after surgery; at day 14, mean TIBC was 285.9 ± 51.8 µg/dL. At day 14, none of the 10 cats had low TIBC values, and 3 had slightly high TIBC values (ie, 333, 329, and 359 µg/dL). Prior to transplantation, serum ferritin concentration was high in the 7 cats for which data were collected (median, 195 ng/mL; reference range, 31 to 144 ng/mL); 2 of the 7 cats had serum ferritin concentration within reference range (ie, 103 and 130 ng/mL). At day 14, serum ferritin concentration increased in 2 cats and decreased in 5 cats; in the 2 cats with normal serum ferritin concentration before surgery, values decreased after surgery. Differences in serum iron variables between values before and 14 days after transplantation were not significant.

Discussion

Prior to surgery, all but 1 of the cats included in the study reported here had mild to severe anemia (ie, Hct, < 28%), secondary to CRF. The anemia was characterized as normocytic, normochromic, and nonregenerative. Serum erythropoietin concentration in the cats was inappropriately low in the presence of mild to severe anemia; this supported the finding in humans that an inadequate production of erythropoietin is the principle cause of the anemia of CRF.[1-11] Despite the rapid resolution of the azotemia within the first week after transplantation and extremely variable pattern of erythropoietin production, the return of Hct values to within reference limits took approximately 1 month, unless complications arose.

Results of human studies[2,8,15,17,22] of renal transplantation indicate that patterns of erythropoietin production are also variable and appear to be associated with the source of the transplanted kidney (ie, whether the kidney was obtained from a living donor or from a cadaver). In humans who receive a kidney from a living donor, the most common pattern of erythropoietin production is a small increase in serum erythropoietin concentration within the first 4 days after surgery (approx 100% increase in serum concentration, compared with the preoperative value). This increase is associated with the resolution of azotemia and is maintained for up to 1 month after surgery.[2] In 1 study, 4 of 5 recipients that received a kidney from a living donor had another peak of erythropoietin production between 14 and 28 days after transplantation.[17]

The data obtained from the cats in the study reported here were similar to those obtained from humans who received a kidney from a living donor. All cats in our study had an initial increase in serum erythropoietin concentration (an increase of 150% of the median preoperative value). The magnitude and duration of this peak in serum erythropoietin concentration were similar to that detected in humans who receive a kidney from a living donor. Because azotemia resolved within 6 days after transplantation and living donors are used in renal transplantation in cats (which minimizes the warm ischemia time to < 1 hour), the increase in serum erythropoietin concentration detected in the cats of the study reported here may represent erythropoietin production by a functioning graft. However, erythropoietin may accumulate in an ischemic graft secondary to hypoxic conditions and may be released after reperfusion, which could contribute to an increase in serum erythropoietin concentration. Conceivably, the increase in serum erythropoietin concentration in the cats in our study could have resulted from a combination of both mechanisms. In 9 of 12 cats that survived to the completion of our study, another increase in serum erythropoietin concentration was detected between 5 and 58 days after surgery. It seems likely that this corresponded to erythropoietin synthesis from the functional graft. After this second increase, serum erythropoietin concentrations in the study cats were extremely variable, but the small sample sizes at 3, 4, 5, and 6 months postoperatively do not allow any further conclusions.

In contrast, humans who receive a kidney from a cadaver have early and late peaks of serum erythropoietin concentrations after transplantation.[8,15,17,22] In these recipients, the early peak in serum erythropoietin concentrations (a 9-fold increase from preoperative values) is detected at 2 days after transplantation, and its duration is ≤ 4 days. This peak is not associated with resolution of azotemia, anemia, or reticulocytosis. The mechanism by which the early peak in serum erythropoietin concentration develops is unclear; it has been suggested that erythropoietin accumulates in the graft as a result of hypoxic conditions in the ischemic kid-

ney until adequate perfusion of the transplanted kidney is reestablished during surgery. During reperfusion of the graft, erythropoietin is released into the plasma. Because renal function is delayed in some humans that have an early peak in serum erythropoietin concentration, the early peak after transplantation may develop secondary to acute tubular necrosis with subsequent damage to the renal tubular cells.[2] Other investigators have suggested that the early peak is associated with acute graft rejection.[17] In humans, no correlation has been found between the initial peak of serum erythropoietin concentration, and a decrease in Hct has been noted in some recipients during the period immediately after transplantation.[15] In 1 study,[14] an early peak in serum erythropoietin concentration was found mainly in humans with severe anemia after transplantation; the peak was considered to be the result of a positive erythropoietin feedback response. In the cats of the study reported here, Hct increased from values before transplantation in the early postoperative period (day 1); however, this increase was transient and appeared to be associated with transfusions given during the perioperative period.

A late peak in serum erythropoietin concentration is also detected in humans who are recipients of a kidney obtained from a cadaver. This increase is detected 5 to 60 days after transplantation; it appears to be associated with recovery of graft function and is accompanied by erythropoiesis.[14] Compared with the magnitude and duration of the early peak, this late peak is of lesser magnitude (ie, 2- to 3-fold increase compared with preoperative serum erythropoietin concentration) and is sustained for a longer period.[2,8,14,15,17] Serum erythropoietin concentration in humans has been reported to return to normal as Hct reaches 32%, which is expected to occur 1 to 6 months after transplantation.[8]

In humans, an increase in serum erythropoietin concentration typically precedes the increase in numbers of reticulocytes and the subsequent increase in Hct.[3,6,14] The onset of reticulocytosis after transplantation is variable and appears to be associated with whether the transplanted kidney is obtained from a cadaver or a living donor. In a study[1] of 10 humans who received a cadaveric kidney, median time after surgery to detection of reticulocytosis was 3 weeks. In a study[2] in which recipients of kidneys from living donors were evaluated, the reticulocyte percentage increased significantly from preoperative day 1 (0.5 ± 0.3%) to postoperative day 5 (1.7 ± 1.1%) after surgery and remained increased throughout the remainder of the study period (28 days).

In the cats of the study reported here, the reticulocyte response after surgery was mild in 7 cats (detected between day 3 and 28 after surgery; median time to detection of reticulocytosis, 4 days); the response may have been undetected in 5 cats. In 1 cat that had an acute rejection episode, reticulocytosis occurred 134 days after surgery. The time to detection of reticulocytosis after transplantation in 7 of the 14 study cats was similar to that observed in humans who receive a kidney from living donors; this finding supports the suggestion that the early peak in serum erythropoietin concentration may be the result of erythropoietin production from a functioning graft. After the early peak in serum erythropoietin concentration, an interval of 4 days before reticulocytosis is detected is not unexpected because maturation of RBCs in the bone marrow normally takes approximately 4 to 7 days. The damage to the bone marrow caused by uremic toxins may further delay or blunt the marrow response.[2] Additionally, it is possible that reticulocyte response in the cats of our study was mild (and perhaps undetected) because cats have an ability to adapt to low Hct values, or the technique used to evaluate reticulocytes was inadequate. In the study reported here, aggregated reticulocytes were assessed via manual enumeration after supravital staining, but evaluation via flow cytometry might have been more sensitive.[23]

Regardless of the reticulocyte response, anemia resolved in 10 of 14 cats between 3 and 49 days after transplantation (mean time to resolution, 21.8 ± 15.8 days). In 2 cats, resolution of anemia occurred within 7 days after surgery and was likely associated with perioperative administration of blood transfusions and subsequent discontinuation of IV fluid treatment. In the remaining 8 cats, resolution of anemia was likely the result of erythropoiesis stimulated by the production of erythropoietin from a functioning allograft.

In humans, there does not appear to be a direct correlation between detection of peak serum erythropoietin concentrations and resolution of anemia, but good graft function has been described as a prerequisite for correction of anemia.[1,3,7,10,14,15] In humans, resolution of anemia is detected 1 to 6 months after transplantation.[7,8,11,14,17] The range of time required to attain Hct values within reference limits may be attributed to iron availability, presence of mild inflammation, drug toxicoses (including adverse effects associated with cyclosporine administration), or possibly rate of removal of toxins associated with uremia that affect the bone marrow.[7,15] However, on the basis of the findings of our limited study in cats, the resolution of anemia after transplantation appears to occur more rapidly in cats than it does in humans.

Interestingly, 1 cat had sustained high serum erythropoietin values for the duration of the study period (range, 25.9 to ≥ 400 mU/mL). Although serum erythropoietin concentration reached ≥ 400 mU/mL, the reticulocyte response was mild, and anemia did not resolve more rapidly than it did in the other study cats. High serum erythropoietin concentration was sustained over the entire observation period of 6 months without any evidence of erythrocytosis. This extreme erythropoietin response following transplantation has not been reported in any human papers. This cat may have had a poorly responsive bone marrow or produced erythropoietin that was dysfunctional.

Acute renal rejection occurred in 2 of 14 cats in the study reported here. This proportion (14%) is comparable to that in a study[18] of 66 renal transplants in cats, in which presumptive episodes of acute renal rejection occurred in 18% of transplantations. In humans, the onset of acute rejection within the first month after transplantation can cause recurrence of anemia and abrogate the hematopoietic response until the rejection is fully reversed.[10,16] In the 2 cats of the

study reported here, there was a precipitous decrease in Hct after acute renal rejection; the cause of this decrease is not known but is likely multifactorial. Factors that may have contributed to the decrease in Hct include concurrent IV fluid treatment that was administered to these cats to maintain adequate hydration status and IV administration of cyclosporine at a high dosage for treatment of the graft rejection. Although signs of hemolysis were not noted in either cat, cyclosporine administration has been associated with acute hemolysis in both humans and cats.[24,25]

Furthermore, after the rejection episodes were successfully overcome, resolution of anemia was not achieved for months. Similarly, some humans remain anemic after transplantation despite normal graft function, and a relative erythropoietin deficiency or erythropoietin resistance has been suggested as the cause.[16] In the 2 cats of our study, an erythropoietin deficiency was not suspected because serum erythropoietin concentrations during and after the rejection episodes were similar to values in other study cats that had prompt resolution of anemia. Because anemia eventually resolved in both cats, a relative erythropoietin resistance was also less likely. Other causes of a blunted erythropoietic response in humans may include an iron or cobalamin deficiency, gastrointestinal blood loss, fluctuations in erythropoietin production coincident with alterations in the function of the allograft, and bone marrow suppression caused by chronic infections or inflammation or administration of immunosuppressive agents.[1,16,26] In humans, iron deficiency has been reported to be the most common cause of bone marrow hyporesponsiveness after renal transplantation. In the 2 cats of the study reported here, it is also possible that subclinical inflammation associated with the rejection episode or direct effect of the cyclosporine treatment may have impaired the erythropoietic response. There were no signs of gastrointestinal bleeding in either cat. Vitamin B deficiency was not investigated in either cat.

Additionally, in 1 cat, a slight increase in erythropoietin secretion was detected in association with acute rejection. In humans, both increases and decreases of erythropoietin production have been observed during episodes of acute rejection.[6,8,10,11,14,17,21,27] As acute rejection is characterized by graft hypoperfusion, erythropoietin production may be stimulated by renal hypoxia. Low serum erythropoietin concentration detected in some humans during acute renal graft rejection may be associated with the release of cytokines that interfere with erythropoietin production.[17]

Although there was no significant difference in serum iron and ferritin concentrations and TIBC before and after transplantation, serum iron concentrations in the study cats were in the low to low-normal range, which may indicate limited bioavailability of iron that may have blunted the erythroid response. Iron deficiency occurs commonly in humans with CRF.[28] Treatment with recombinant erythropoietin may require the inclusion of an iron supplement for an adequate erythropoietic response to occur.[12] The use of transfusions during the perioperative period and the establishment of normal food intake within a week after surgery in the cats described in this report did not appear to facilitate return of serum iron concentrations to normal. In humans, a rapid depletion of iron stores (manifested as a decrease in serum iron and ferritin concentrations) often follows successful renal transplantation that is accompanied by an appropriate rise in serum erythropoietin concentration. The administration of supplemental iron and vitamins to cats that undergo transplantation may be considered; such supplementation might have hastened the time to resolution of anemia in the 2 cats of our study. In humans, treatment with supplemental iron is a critical factor for support of erythropoiesis and prevention of iron deficiency after transplantation.[28]

In contrast to the low to normal serum iron concentration, serum ferritin concentrations before surgery were high in all cats of this study, which may have been an indication of an inflammatory condition. Similarly, human renal transplant patients also have high serum ferritin concentrations preoperatively.[29] After transplantations performed in our study, serum ferritin concentration increased in 2 and decreased in 5 cats. After transplantation in humans, a decrease in serum ferritin concentration is typically observed and is associated with an increase in hemoglobin concentration.[29]

After renal transplantation in cats, anemia associated with CRF typically resolved within 1 month despite a highly variable erythropoietic response. In cats, delay in the resolution of anemia in a renal transplant recipient may indicate poor graft function, concurrent illness, limited iron availability, or persistent bone marrow damage caused by uremia-associated toxins and suggests the necessity for further evaluation.

[a]Liberty Research, Waverly, NY.
[b]York County SPCA, York, Pa.
[c]Neoral, Novartis, East Hanover, NJ.
[d]Normosol-R, Abbott Laboratories, North Chicago, Ill.
[e]Pediatric 2-lumen central venous catheter, Arrow International Inc, Reading, Pa.
[f]Medac GmbH-GE Diagnostica, Hamburg, Germany.
[g]Analyses performed at the Hematology Laboratory of the School of Veterinary Medicine, Kansas State University, Manhattan, Kan.

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