Development of anemia, phlebotomy practices, and blood transfusion requirements in 45 critically ill cats (2009–2011)

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Abstract

Objective – To describe the incidence of the development of anemia, the number of phlebotomies performed daily, the approximate volume of blood withdrawn, the transfusion requirements and their association with duration of hospitalization and survival to discharge in critically ill cats.
Design – Retrospective study from January 2009 to January 2011.
Setting – University teaching hospital.
Animals – Cats hospitalized in the intensive care unit (ICU) for >48 hours.
Interventions – None.
Measurements and Main Results – Medical records of cats hospitalized for >48 hours in the ICU were examined. Of the 45 cats included, 60% (27/45) were not anemic upon admission to the ICU. Of these, 74.1% (20/27) developed anemia during their ICU stay. Development of anemia was associated with a longer duration of hospitalization ($P = 0.002$) but not with survival ($P = 0.46$). Fourteen cats (31.1%; 14/45) received one or more packed red blood cell transfusions and had significantly longer ICU stays ($P < 0.001$). Transfusion requirements were not associated with survival ($P = 0.66$). The median number of phlebotomies per day for all cats in the ICU was 3 (range 1–6). This was significantly associated with the development of anemia ($P = 0.0011$) and higher transfusion requirements ($P = 0.16$) in the 14 cats that received a transfusion. The estimated volume phlebotomized was significantly ($P < 0.001$) greater in cats that required a transfusion (median volume 3.32 mL/kg/ICU stay) compared to cats that did not require a transfusion (median volume 1.11 mL/kg/ICU stay) but was not associated with survival to discharge ($P = 0.84$).
Conclusions – Development of anemia necessitating blood transfusions is common in critically ill cats and leads to significantly longer duration of ICU hospitalization. Iatrogenic anemia from frequent phlebotomies is an important cause for increased transfusion requirement. Fewer phlebotomies and other blood conserving strategies in these patients may help reduce the incidence of anemia and decrease transfusion requirements, as well as result in shorter hospital stays.

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Keywords: blood conservation, feline anemia, ICU, pRBC

Introduction

Anemia in critically ill patients is a common clinical finding and can be due to multiple causes, including a blunted erythropoietic response, alterations in iron metabolism and bone marrow suppression during criti-

Abbreviations

CBC	complete blood count
ER	emergency services
ICU	intensive care unit
pRBC	packed red blood cells

cal illness, shortened red blood cell lifespan, and blood loss.[1] The blunted erythropoietic response may be secondary to high levels of proinflammatory cytokines such as IL-1β and TNF-α, which have been shown in experimental studies to suppress erythropoietin secretion and increase iron storage by the reticuloendothelial system limiting the availability of iron for erythropoiesis. A

shortened red blood cell lifespan may occur through oxidative damage or hemolysis, while blood loss can occur from trauma, surgical procedures, occult loss through gastrointestinal bleeding, and secondary to coagulopathies. Repeated phlebotomies and blood removal for diagnostic sampling are also cited as contributing factors for the development of anemia during critical illness.[1–6]

Critically ill patients, both people and animals, are more likely to have multiple diagnostic phlebotomies and more frequent blood sampling than other categories of hospitalized patients. Diagnostic testing in these patients typically includes complete blood counts (CBCs), blood gas, electrolyte and acid-base analysis, evaluation of renal and hepatic function, and evaluation of coagulation parameters among other tests. Although this testing is important in the management of these patients and helps guide therapeutic decisions, significant volumes of blood can be withdrawn. The cumulative effect of the diagnostic tests has been shown to be a significant factor in the development of anemia of critical illness in people, particularly in children who have a smaller blood volume and anecdotally is thought to also contribute to anemia in small animal patients.[7–10]

Similar to critically ill people, anemia in critically ill cats is common and it tends to be nonregenerative. This has been documented in various diseases such as sepsis, diabetic ketoacidosis, and systemic inflammatory response syndromes.[11–14] However, to the authors' knowledge, there is limited information regarding whether anemia is present on hospital admission or whether it develops during the course of hospitalization. Regardless of when the anemia develops, the underlying cause of anemia in cats is likely multifactorial similar to what is seen in critically ill people. Critically ill cats that develop significant anemia are often treated with blood transfusions. Red blood cell transfusions can help improve oxygen carrying capacity and may improve survival. However, at least in people, blood transfusions are associated with an increased expense, longer hospital stays, and carry the risk of several potentially life threatening medical complications such as immunological transfusion reactions, infectious diseases, transfusion associated circulatory overload, and transfusion related acute lung injury.[15–17]

Information in the veterinary medical literature regarding the development of anemia in hospitalized critically ill cats, phlebotomy practices, and documentation of blood transfusion practices in these patients is limited. One study evaluating red blood cell transfusions in hospitalized cats found an increased rate of death in cats that received transfusions than cats that did not; however this study included cats with both acute and chronic anemia, including cats with anemia secondary to chronic kidney disease.[18] The primary objectives of this study were to describe the incidence and development of anemia in critically ill cats, to document phlebotomy practices and transfusion requirements in these cats, as well as to evaluate the association between these factors on both duration of hospitalization and outcome.

Materials and Methods

The records of all cats that were admitted to the intensive care unit (ICU) at the authors' institution from 2009 to 2011 were examined. Inclusion criteria included hospitalization in the ICU for >48 hours. Only critically ill animals requiring advanced care and monitoring are admitted to the ICU. These animals often require oxygen support, advanced pain management, aggressive fluid therapy, advanced hemodynamic monitoring, serial bloodwork including lactate concentrations, frequent blood pressure (both invasive and noninvasive) measurements, central venous pressures, and respiratory support including mechanical ventilation. Cats were excluded if they were documented to have anemia secondary to underlying chronic kidney disease, or if they had incomplete medical records.

The data recorded included signalment, primary presenting complaint, and any comorbidities, final diagnosis, packed cell volume (PCV) and total plasma protein (TPP) upon admission to the hospital and upon admission to the ICU, the lowest PCV and TPP during the ICU stay, and the last PCV and TPP during the ICU stay. Anemia was defined as a PCV <30%. All instances where the PCV of a patient was <30% during the ICU stay were recorded. Other data recorded included total duration of hospitalization, average number of phlebotomies/day, bloodwork performed during ICU stay, CBC data at ICU admission including red blood cell indices and reticulocyte counts (if available), incidence of blood loss (if known), presence of a sampling catheter or a central venous catheter, any blood transfusions and outcome (defined as survival to discharge, death or euthanasia). Reticulocytosis was defined as a reticulocyte count $>>50.7 \times 10^9$/L [50.7×10^3/μL]. The approximate volume of blood drawn in milliliters (mL) was estimated using the minimum amount of blood required for any given diagnostic test by the Clinical Laboratory at the authors' institution.

The Shapiro–Wilks test was used to assess the distribution of continuous variables. Not normally distributed continuous variables are described using median (min, max) while mean (±SD) was used to describe continuous variables with normal distribution. Dichotomous variables are described using proportions (%) and the Fisher's exact test was used to compare these variables if the expected count in any cell was <5, otherwise the chi-square test was used. For all analyses a *P* value < 0.05

Table 1: Final clinical diagnoses for the 45 cats in this study

Final diagnosis	Number of cats (%)
Respiratory disease	8/45 (17.8%)
Congestive heart failure	6/45 (13.3%)
Neoplasia	6/45 (13.3%)
Sepsis	4/45 (8.9%)
Diabetic ketoacidosis	3/45 (6.7%)
Pancreatitis	3/45 (6.7%)
Urethral obstruction	2/45 (4.4%)
Neurologic disease	2/45 (4.4%)
GI disease	1/45 (2.2%)
Acute kidney injury	1/45 (2.2%)
Other	9/45 (20%)

was considered significant. All analyses were performed using a statistical software program.[a]

Results

Records of 118 cats were examined, of which 59 cats had ICU stays longer than 48 hours. Fourteen of these cats were excluded due to a known history of chronic kidney disease, leaving 45 cats in the final analysis. The mean age was 8.4 ± 4.5 years. Breeds included domestic shorthairs (38 cats; 84.44%), domestic longhairs (2 cats; 4.44%), Himalayan, Oriental shorthair, Persian, Ragdoll, and Siamese (1 cat each, 2.22% each). There were 17 female cats (2 intact, 15 ovariohysterectomized; 4.44% and 33.33%, respectively) and 28 male cats (4 intact, 24 castrated; 8.89% and 53.33%, respectively). The mean weight was 4.8 ± 1.6 kg. All cats were admitted to the hospital initially through the emergency service (ER). Presenting complaints for these cats included respiratory distress (11/45, 24.4%), lethargy (9/45, 20.0%), trauma (4/45, 8.9%), decreased appetite (3/45, 6.7%), neurologic signs other than seizures (3/45, 6.7%), seizures (2/45, 4.4%), inability to urinate (2/45, 4.4%), inappropriate urination (2/45, 4.4%), and weight loss (2/45, 4.4%). The remaining 7 cats (7/45; 15.6%) presented for a variety of conditions including: collapse, vomiting, hypersalivation, perineal hernia, neuter incision dehiscence, cough, and diarrhea. Cats spent variable amounts of time in the ER prior to ICU transfer, with a majority of them spending <12 hours (30/45, 66.7%) and 15 cats (15/45, 33.3%) spending between 12 and 24 hours in the ER. Twelve cats underwent one or more surgical procedures, with 4 (33.3%) of these having moderate to significant intraoperative bleeding as recorded in the surgical reports in the medical records. There were a variety of final diagnoses (see Table 1).

Ten cats (10/45, 22.2%) were anemic upon admission to the hospital, and an additional 8 cats (18/45; 40.0%) developed anemia prior to admission to the ICU. Of the 27 cats that were not anemic upon ICU admission, 20 (20/27; 74.1%) developed anemia during ICU hospitalization. Cats that developed anemia after admission to the ICU had a significantly ($P = 0.0015$) longer duration of hospitalization (median 5 days, range 3–24 days) than cats that did not develop anemia while in the ICU (median 4 days, range 3–13 days). However, the development of anemia in the ICU was not statistically associated with outcome ($P = 0.459$; see Table 2).

CBC data showed that 13 cats (13/45; 31.1%) had Heinz bodies evident on peripheral blood smear examination. Only 4 cats (4/45; 8.9%) had a regenerative anemia based on the presence of reticulocytosis. Fifteen cats (15/45, 33.3%) were thrombocytopenic in addition to being anemic, with platelet counts $<175 \times 10^9/\text{L}$ [175 $\times 10^3/\mu\text{L}$] (range 30–$150 \times 10^9/\text{L}$ [30–$150 \times 10^3/\mu\text{L}$]).

Fourteen cats (14/45; 31.1%) required a transfusion of packed red blood cells (pRBC) during their ICU stay. Eleven of these cats received 1 unit of pRBC each while 3 cats received 2 units each. The median volume of blood transfused was 5.7 mL/kg (range 2.6–13.1 mL/kg). The PCV at which these cats were transfused ranged from 12 to 21% with a median pre–transfusion PCV of 16%. All 4 cats that experienced significant intraoperative bleeding prior to their admission to the ICU received a transfusion postoperatively in the ICU except for 1 cat that received a transfusion prior to surgery. Cats that required a blood transfusion were found to have a significantly ($P < 0.001$) longer duration of hospitalization (median 7.5 days, range 4–24 days) than cats that did not require a blood transfusion (median 4 days, range 3–12 days). However, a blood transfusion requirement was not statistically associated with outcome ($P = 0.66$; see Table 3). No significant transfusion reactions were observed in any of the cats in this study. Thirty-seven cats (37/45, 82.2%) had either a sampling catheter or a central venous catheter. None of the 6 cats (6/45, 13.3%) without a sampling or central venous catheter required a blood transfusion while 14 cats that had a central or sampling catheter received a transfusion (14/37, 37.8%).

The median number of phlebotomies per day for all cats in the ICU was 3 (range 1–6). The 20 cats that developed anemia during their ICU stay had a significantly ($P = 0.0011$) greater number of phlebotomies per day (median 3, range 1–5) than the 7 cats that did not develop anemia (median 1, range 1–2). Cats that required a pRBC transfusion had a significantly ($P = 0.016$) greater number of daily phlebotomies (median 3, range 1–6) than cats that did not require a transfusion (median 2, range 1–4). Cats that had a sampling or central venous catheter had a significantly ($P = 0.001$) greater number of phlebotomies (median 3, range 1–6) than cats without either of these catheters (median 1, range 1–2). The most common diagnostic tests for which blood was phlebotomized

Table 2: Relationship between development of anemia in the ICU and outcome

Outcome	Developed anemia in the ICU	Did not develop anemia in the ICU	Total number of cats
Survived to discharge	19/20 (95%)	6 /7 (85.7%)	25
Euthanized	1/20 (5%)	1/7 (14.3%)	2
Total number of cats	20	7	27

Fisher's exact test: $P = 0.46$.

Table 3: Relationship between transfusion requirements and outcome

Outcome	Required a pRBC transfusion	Did not require a pRBC transfusion	Total number of cats
Survived to discharge	27/31 (87.1%)	11/14 (78.6%)	38
Euthanized	4/31 (12.9%)	3/14 (21.4%)	7
Total number of cats	31	14	45

Fisher's exact test: $P = 0.66$.

included venous blood gases (median 12, range 2–60 per cat during ICU stay), CBCs (median 1, range 0–7 per cat during ICU stay), chemistry panels (median 3, range 0–10 per cat during ICU stay), coagulation panels (median 1, range 0–6 per cat during ICU stay), and other miscellaneous bloodwork (median 2, range 0–10 per cat during ICU stay). The estimated volume phlebotomized over the ICU stay was significantly ($P = 0.001$) greater in cats that required a blood transfusion (median volume 3.3 mL/kg, range 0.7–8.5 mL/kg) compared to cats that did not require a blood transfusion (median volume 1.1 mL/kg, range 0.4–5.1 mL/kg). However, the volume of blood phlebotomized was not statistically associated with outcome ($P = 0.84$). The median blood volume phlebotomized in the 6 cats that did not have a sampling or central venous catheter was 0.52 mL/kg (range 0.4–1.1 mL/kg), while the median volume phlebotomized in the remaining 37 cats was 1.9 mL/kg (range 0.4–8.5 mL/kg), and this difference was statistically significant ($P < 0.001$)

Thirty cats (84.4%) survived to discharge. All 7 (15.6%) cats that did not survive were euthanized. The relationships between development of anemia, transfusion requirements, and outcome are outlined in Tables 2 and 3.

Discussion

This retrospective study documents the incidence and development of anemia during hospitalization in a population of critically ill cats. Only cats that were hospitalized in the ICU for >48 hours were included in this study. This inclusion criterion ensured the exclusion of 2 patient subpopulations: (1) the population of stable postoperative patients that were hospitalized in the ICU during their initial recovery from surgery and (2) the subpopulation of ICU patients that either died or were euthanized very early in the course of their ICU stay due

to either owner financial constraints or due to the illness severity and prognosis.

Overall, of the 45 cats included in this study, 38 (84%) were anemic at some point during hospitalization. Eighteen (47%) of these cats were anemic on hospital presentation or developed anemia during the emergency stay, whereas 20 cats (52%) developed anemia after ICU admission. Of the 8 cats that developed anemia after hospital admission but prior to ICU admission, hemodilution from fluid resuscitation may be one possible reason for the development of anemia. The development of anemia during the course of ICU stay in the remaining cats is most likely multifactorial, including anemia secondary to hemodilution from fluid therapy, frequent phlebotomies, oxidative damage (31% of cats in this study had evidence of oxidative damage with Heinz bodies noted on the CBC), blood loss from other causes and a poor regenerative response. Cats may be more likely to develop anemia from blood loss due to their small size and overall smaller blood volume (40–60 mL/kg) compared to other species.[18] Additionally, cats tend to have a particularly poor erythropoietic response in the face of critical illness.[19] Finally, Heinz body associated anemia is hypothesized to occur more commonly in cats because their erythrocytes are extremely sensitive to oxidative denaturation due to the presence of extra sulfhydryl groups on the feline hemoglobin molecule.[13]

Blood transfusions are commonly used to treat anemia of critical illness, and 31% of the cats in this study required a blood transfusion during their ICU stay. The PCV at which a blood transfusion is administered can be variable (12%–21% in this study) and may be dependent on the degree and chronicity of anemia, the presence of clinical signs of anemia, and is often influenced by financial considerations and clinician discretion. In this study, neither the development of anemia in the ICU,

nor the requirement for a blood transfusion was found to be statistically associated with outcome. This is in contrast to several human studies that have found that the development of anemia in the ICU and increased need for blood transfusions to be independently associated with worse clinical outcomes.[1,7,10] The lack of association with outcome found in this study could be due to a small sample size and increased risk of a type II statistical error, in addition to death secondary to euthanasia. Although not associated with outcome, the development of anemia, as well as the requirement of pRBC transfusions was found to be significantly associated with a longer duration of hospitalization and number of daily phlebotomies. While illness severity scores (ie, APPLE scores) were not calculated in this study due to the difficulty in obtaining all of the required information retrospectively, these findings are likely reflective of greater severity of illness requiring a longer ICU stay, with the more severely ill patients having more frequent diagnostic testing performed.

The number of daily phlebotomies in this population of cats was large with most cats having a median of 3 phlebotomies per day with a median blood volume of 3.3 mL/kg sampled. The presence of a sampling catheter or central venous catheter was associated with significantly higher volumes of blood phlebotomized, and a greater number of daily phlebotomies. Increased ease of sampling through these catheters may be a contributing factor for this. Blood volumes as high as approximately 8.5 mL/kg were sampled from some of the cats in this study. This would represent approximately 15%–18% of a cat's total blood volume of 45–60 mL/kg. In an average cat weighing 4 kg, this would translate into a total volume of blood phlebotomized of nearly 34 mL, which is substantial when one considers that this is equivalent to nearly one and a half feline pRBC units (the average size of a unit of feline pRBC at this institution is approximately 20 mL). In addition, the volume of blood that was phlebotomized was an approximation at best. It was estimated based on the minimal amount of blood required for a diagnostic test, and did not include any presamples that were obtained from catheters or blood that may have been drawn and discarded. Therefore, it likely underestimates the actual volume of blood phlebotomized in these cats. A previous study in research cats evaluated critical levels of blood volume for the onset of hypotension and found that when between 8 and 27 mL/kg of blood was phlebotomized, hypotension ensued.[20] In the present study, critically ill cats that likely had a blunted cardiovascular response to blood loss had as much as 8.5 mL/kg of blood phlebotomized, albeit over the course of multiple phlebotomies.

A major limitation of this study is the small sample size. This is likely a consequence of our inclusion criteria, and could have resulted in a selection bias toward the sickest cases. Calculation of illness severity scores was not performed in this study, given the difficulty in obtaining the required data retrospectively. All 7 cats that did not survive to discharge were euthanized, and it is unclear from the medical records whether euthanasia was prompted by owner financial constraints, progressive disease with a poor prognosis, or both. It is possible that had these animals not been euthanized and continued to receive treatment, an association may have been found between development of anemia, transfusion requirements, and outcome.

In light of our study findings, adoption of blood conservation strategies should be considered. Blood conservation strategies are widely advocated in human intensive care medicine, particularly in critically ill children and include minimizing daily routine diagnostic phlebotomies, use of small volume or pediatric phlebotomy tubes, point of care and bedside microanalysis, minimization of blood sample wastage, lowering transfusion thresholds and transfusing only in response to physiologic need and removing central venous and arterial catheters when no longer needed for patient monitoring purposes.[21–25] Special in-line blood gas monitoring devices are available for commercial use in human medicine, which can also greatly reduce phlebotomy blood loss.[26,27] There are several veterinary studies that have evaluated the use of microsample blood collection tubes for routine diagnostic testing in dogs and cats, which have found results to be comparable to results obtained from standard sized blood collection tubes.[28–31] Adoption of some of these strategies, particularly minimizing daily routine diagnostic testing unless absolutely necessary and using pediatric phlebotomy tubes wherever possible, is easily achievable in small animal ICUs, especially when dealing with cats and other small patients such as puppies or exotic animals. Clinician education about blood conservation strategies in the ICU may also help reduce the incidence of anemia in critically ill cats, and subsequently reduce the significant expense associated with blood transfusions and longer durations of hospitalization in ICUs.

Conclusion

In conclusion, this study describes the incidence and development of anemia, phlebotomy and transfusion practices in a population of critically ill cats. Development of anemia necessitating blood transfusions is common during critical illness in cats and results in significantly longer duration of hospitalization in the ICU. Fewer phlebotomies and other blood conserving strategies in these patients may help reduce the incidence of anemia and decrease transfusion requirements, as well as result

in shorter hospital stays. Although the development of anemia is likely multifactorial (ie, some of these cats had surgical blood loss and evidence of oxidative damage), to the authors' knowledge, this is the first study to document the effect of daily phlebotomies on the development of anemia during critical illness in cats. Iatrogenic anemia from frequent phlebotomies is common in these cats and is an important cause for increased transfusion requirement. Future studies aimed at prospectively evaluating the impact of blood sampling on a daily basis in cats hospitalized in the ICU, as well as evaluating the functionality and lifespan of red blood cells drawn from catheters as presamples and returned to the patient, would be valuable.

Footnote

^a   Stata 12.1 for Mac, Stata Corporation, College Station, TX.

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