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Population analyses of anemia in Pets

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Anemia is a clinical syndrome that results from many etiologies. Laboratory results alone can't definitively identify the specific cause for a particular Pet. Rather, the laboratory test results, along with a comprehensive history and thorough physical examination of the Pet are all essential parts of the diagnostic process. In generating their rule-out list, clinicians should consider diagnoses that are most likely or common based on the clinical signs at hand. In this article, we ask the following questions. What is the profile of the average anemic Pet? What are the most common diagnoses for cats and dogs with anemia?

From the analysis reported in this issue, DataSavant presents population results on anemia, gathered from Banfield hospitals, that will not only help veterinarians better understand which Pets are at risk for anemia, but will also support owner communication and understanding of the disease. For Pet owners, gaining such knowledge can be empowering. And for veterinarians, providing such knowledge can strengthen their bond with the Pet owner.

Evidence-Based Medicine Toolkit

Statistical versus clinical significance: Research studies are designed and analyzed to **statistically** test a hypothesis. However, statistical significance is not always the same thing as **clinical significance.** Clinical significance refers to information that has relevance and impact for the care of patients in the clinical setting. Besides quantifying population estimates, statistical differences also reflect the size of the population sampled. A large sample has less variability in estimation and thus can find smaller differences in effect. And, conversely, a small sample has larger variability around estimates of effect and has less statistical power to detect differences, even if those differences are clinically relevant.

Odds ratio: A measure of the degree of association (also known as a cross-product ratio or relative odds); for example, the odds of exposure among the cases compared with the odds of exposure among the controls. Both the odds ratio and the relative risk compare the relative likelihood of an event occurring between two distinct groups. Some study designs, however, prevent the calculation of the relative risk and the odds ratio is used instead to estimate risk.

Confidence interval: A confidence interval helps describe the reliability of an estimate of association. The smaller the width of the interval, the more likely a similar result would be generated in repeated sampling. A wide confidence interval represents the fact that the true measure of association falls at a point somewhere within the range estimated. The larger the sample size, the more reliable the results as the estimate is representative of a larger portion of the population studies.

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DataSavant's mission is to:
- Explore the health and well-being of Pet populations
- Evaluate new clinical treatments
- Monitor Pets as sentinels of zoonotic disease in family environments
- Transform Pet medical data into knowledge, *i.e.*, open new windows into Pet health care using the Banfield medical caseload and database.

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Table 1: Prevalence and Disease Risk for Dogs with Anemia

	Prevalence in anemic dogs (n=30,946)	Prevalence in dogs with a normal Hct (n=251,601)	Relative risk*	Confidence interval**
Flea infestation	10.4%	7.2%	1.5	1.4, 1.6
Hookworm infection	3.7%	1.2%	3.2	3.0, 3.4
Hear murmur	2.2%	1.9%	1.2	1.1, 1.3
Renal failure, chronic	1.4%	0.2%	6.1	5.3, 6.9
Hemolytic autoimmune anemia	0.6%	0.03%	21.4	16.3, 28.0
Nutritional anemia	0.5%	0.01%	39.2	26.4, 58.1
Anemia, blood loss	0.4%	0.01%	33.2	22.0, 50.2
Anemia, chronic infection	0.3%	0.01%	38.6	24.3, 61.1
Vehicular trauma	0.3%	0.2%	1.8	1.4, 2.2
Anemia, chronic renal failure	0.05%	0.0%	43.4	12.6, 148.9
Aplastic anemia	0.04%	0.01%	8.1	3.8, 17.5
Heinz body anemia	0.02%	0.0%	20.3	3.9, 104.8
Babesiosis	0.02%	0.0%	24.4	4.9, 120.9
Anemia, macrocytic	0.01%	0.0%	16.3	1.5, 179.3
Anemia, pancytopenia, *Ehrlichia* infection	0.01%	0.0%	73.2	3.9, 1,359.3
Anemia, endogenous estrogen	0.01%	0.0%	40.7	2.0, 846.8

*Estimated by the odds ratio; **95% confidence interval

Methods of analysis

For our population analyses, we selected a series of canine and feline inpatients (cases) that were any age, breed or gender and had hematocrits determined in 2005. Results from the first hematocrit performed as part of a hospital visit in 2005 were used. Anemic cats were defined as having a hematocrit of less than 25 percent (normal range 25 percent to 45 percent[1]), and anemic dogs were defined as having a hematocrit of less than 37 percent (normal range 37 percent to 55 percent[1]). Using these parameters to define our case group, we compared the anemic patient population to the population of Pets that had hematocrit results in the normal range.

In the analysis, we determined differences between the case and control groups for age, gender and breed to assess the risk for anemia. Statistical differences between the case and control groups for other hematologic measures were estimated. Overall prevalence rates for selected diagnoses were also generated for anemic versus nonanemic Pets from the U.S. Banfield inpatient population seen in 2005. Reticulocyte counts, however, were not included in the analysis. Although this measure is important in the diagnostic plan for anemic patients, reticulocyte counts are performed by reference laboratories for Banfield hospitals. And as such, acquiring the population data for this lab result requires more intensive data retrieval than was feasible for this analysis.

Chi-square analyses with Mantel-

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Table 2: Prevalence and Disease Risk for Cats with Anemia

	Prevalence in anemic cats (n=2,889)	Prevalence in cats with a normal Hct (n=71,819)	Relative risk*	Confidence interval**
Flea infestation	20.0%	13.5%	1.6	1.5, 1.8
Renal failure, chronic	9.7%	1.9%	5.5	4.8, 6.3
Heart murmur	3.5%	1.8%	2.0	1.6, 2.4
FeLV infection	2.4%	0.3%	7.4	5.6, 9.7
Hemobartonellosis	1.6%	0.1%	15.6	10.8, 22.5
Anemia, blood loss	1.4%	0.01%	144.0	64.5, 321.8
Anemia, chronic infection	1.3%	0.04%	33.6	20.3, 55.3
Hemolytic autoimmune anemia	1.2%	0.02%	67.7	35.8, 128.2
FIV infection	0.9%	0.4%	2.1	1.4, 3.2
Anemia, chronic renal failure	0.7%	0.02%	40.4	20.2, 80.9
Anemia, FeLV infection	0.7%	0.0%	500.6	67.2, 3,731.7
Hookworm infection	0.6%	0.2%	2.9	1.8, 4.7
Nutritional anemia	0.4%	0.02%	17.2	8.0, 37.0
Aplastic anemia	0.4%	0.01%	49.9	17.0, 146.1
Vehicular trauma	0.3%	0.1%	3.3	1.6, 7.0
Anemia, FIV infection	0.1%	0.0%	33.2	7.4, 148.4
Anemia, macrocytic	0.07%	0.0%	49.8	4.5, 548.8
Anemia, congenital bone marrow hypoplasia	0.07%	0.0%	124.4	6.0, 2,591.0
Heinz body anemia	0.03%	0.0%	74.6	3.0, 1,831.4
Anemia, congenital hemolytic	0.03%	0.0%	24.9	1.6, 397.7
Anemia, porphyria	0.03%	0.0%	74.6	3.0, 1,831.4
Anemia, *Cytauxzoon felis* infection	0.03%	0.0%	74.6	3.0, 1,831.4
Anemia, endogenous estrogen	0.03%	0.0%	74.6	3.0, 1,831.4

*Estimated by the odds ratio; **95% confidence interval

Haenszel statistics[2] were used to determine the association and risk for disease by breed, gender and neuter status. A student's t-test was used to compare mean age and values for hematologic parameters from the complete blood count (CBC) and clinical chemistry between case and control groups. Canine breed risk was estimated for all breeds, from the total Banfield population that had at least 1,000 dogs of that breed seen in 2005.

To quantify risk, we estimated the relative risk (RR) using the odds ratio (OR)[3] for the association between breed, gender and neuter status and the disease. A relative risk greater than 1 suggests a positive association

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Table 3: Canine Risk for Anemia by Breed (Most Common Breeds)

Breed	Breed distribution in anemic group	Breed distribution in control group	Relative risk*	Confidence interval**
Rottweiler (n=5,978)	3.9%	1.9%	2.1	1.9, 2.2
Pit Bull (n=7,413)	4.5%	2.4%	1.9	1.8, 2.0
Akita (n=1,066)	0.6%	0.4%	1.8	1.5, 2.1
English Bulldog (n=1,835)	1.1%	0.6%	1.8	1.6, 2.1
Boxer (n=7,260)	3.5%	2.5%	1.5	1.4, 1.6
Golden Retriever (n=9,810)	4.9%	3.3%	1.5	1.4, 4.6
Pug (n=5,465)	2.7%	1.8%	1.5	1.4, 4.6
Shar Pei (n=1,334)	0.7%	0.5%	1.5	1.3, 1.8
Siberian Husky (n=1,243)	0.6%	0.4%	1.5	1.3, 1.8

*Estimated by the odds ratio; **95% confidence interval

between an outcome and a factor, whereas a relative risk less than 1 suggests an inverse relationship between a factor under study and a disease outcome. A relative risk equal to 1 reflects no association.

For our analysis, we used a P-value of ≤0.05 to establish statistical significance. The P-value represents the probability that the association between the outcome (anemia) and a risk factor under consideration (*e.g.*, concurrent diagnosis) is at least as extreme as the relative risk calculated by the analysis, assuming the result happened by chance alone. Confidence intervals (95 percent) were estimated for each odds ratio (relative risk). The confidence interval represents the range in the risk estimate variability if the population were sampled numerous times. A 95 percent confidence interval for an odds ratio/relative risk that includes 1 (no association) reflects the lack of statistical significance.

Results

We identified 1,036,052 canine inpatients from the records from U.S. Banfield hospitals during 2005; 282,547 of these dogs had hematocrit results. We identified 278,372 feline inpatients from the records from U.S. Banfield hospitals during 2005; 74,708 of these cats had hematocrit results in 2005. Of the dogs that had hematocrit performed in 2005, 11 percent (n=30,946) had a hematocrit less than 37 percent; 4 percent of the cats (n=2,889) had a hematocrit less than 25 percent. Canine and feline prevalence of anemia in the general population (including Pets in the denominator *without* hematocrit results) was 3 percent and 1 percent, respectively.

We found statistically significant differences between the mean age of anemic Pets and Pets with normal hematocrit levels. The mean age of dogs with anemia was 3.1 years versus 4.2 years in dogs with normal hematocrits; the mean age of cats with anemia was 6.6 years versus 4.8 years in cats with normal hematocrits.

Canine and feline results for the comparison of hematologic parameters related to assessment of anemia were also statistically significant. Mean hemoglobin was 7.2 for anemic cats and 12.8 for the controls (normal range 8.0 to 15.0 g/dL[1]); mean

Figure 1: Gender Distribution in Dogs

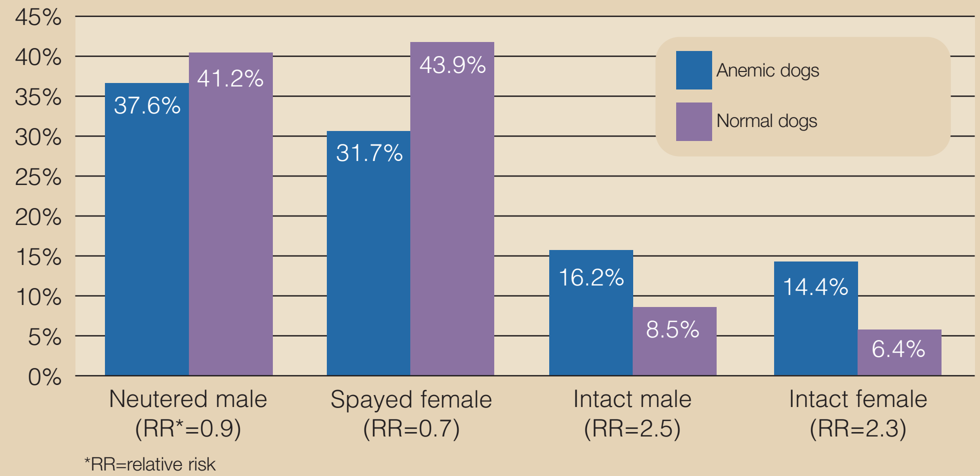
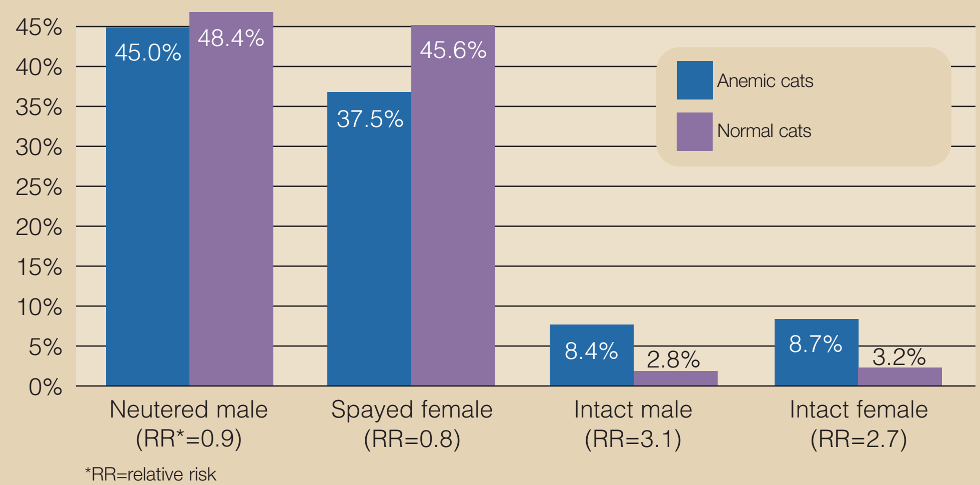


Figure 2: Gender Distribution in Cats



hemoglobin was 11.3 for anemic dogs and 16.2 for controls (normal range 12.0 to 18.0 g/dL[1]). Mean red blood cell (RBC) count was 5.0 for anemic cats and 8.6 for controls (normal range 5.0 to 11.0 x 10^6/µL[1]); mean RBC count was 5.1 for anemic dogs and 7.0 for controls (normal range 5.5 to 8.5 x 10^6/µL[1]).

There were statistically significant differences observed in anemic and control Pets for other hematologic parameters, but mean values for these parameters in both cases and controls fell within the normal laboratory ranges (*e.g.*, mean total bilirubin was 0.8 mg/dL for anemic cats and 0.4 mg/dL for normal cats; however, both fall within the normal range of 0.0 to 0.9 mg/dL[4]).

Tables 1 and *2* (pages 17, 18) detail the relative risk for the association between anemia and selected canine and feline diseases from the population studied. Disease diagnoses include specific diagnoses of anemia as well as diseases known to be associated with anemia. As the relative risk values in these tables are reviewed, it is important to keep in mind that the impact of a disease association in a population is a function of not only the relative risk but also disease prevalence. Diseases of lower relative risk, but with higher prevalence, can have greater consequences for a population than those of higher relative risk and lower population prevalence. In our study, this contrast is exemplified by flea infestation and blood-loss anemia (or other specific causes of anemia).

Table 3 (page 20) depicts the canine breeds that have a statistically significant increased risk for anemia with an odds ratio of 1.5 or greater. However, there is little evidence to support a strong feline breed predilection for anemia. The only statistically significant association between anemia and breed was for Domestic Longhair cats. They were slightly overrepresented in the anemic group: 11.3 percent of the anemic group consisted of Domestic Longhair cats, while only 9.9 percent of the control group were Domestic Longhair cats.

Discussion

From our analyses, we found that the overall prevalence of anemia in the general population of dogs and cats seen at U.S. Banfield hospitals in 2005 was 3 percent and 1 percent, respectively. When the prevalence of anemia was estimated for only the population of dogs and cats that had hematocrit results in 2005, the prevalence was 11 percent and 4 percent, respectively. The true population prevalence for anemia likely rests between these two sets of estimates because of misclassification, a concept described below.

The average anemic dog seen in a Banfield hospital was 3.1 years old and was more likely to be an intact male or female from the following breeds: Rottweiler, Pit Bull, Akita, English Bulldog, Boxer, Golden Retriever, Pug, Shar Pei and Siberian Husky. Diseases most frequently (greater than 1 percent) reported for anemic dogs in this population include flea infestation (10.4 percent), hookworm infection (3.7 percent), heart murmur (2.2 percent) and chronic renal failure (1.4 percent). The average anemic cat seen in a Banfield hospital was 6.6 years old and was more likely to be an intact male or female from any breed. Diseases most frequently reported (greater than 1 percent) for anemic cats in this population include flea infestation (20.0 percent), chronic renal failure (9.7 percent), heart murmur (3.5 percent), feline leukemia virus infection (2.4 percent), hemobartonellosis (1.6 percent), anemia with blood loss (1.4 percent), anemia with chronic infection (1.3 percent) and hemolytic autoimmune anemia (1.2 percent).

Anemic cats are older, on average, than the feline population that has blood drawn for a CBC. By contrast, anemic dogs are younger on average than the canine population that has blood drawn for a CBC. Intact reproductive status puts both dogs and cats at increased risk for anemia compared with neutered and spayed Pets (*Figures 1* and *2*, page 21). However, while intact reproductive status may be associated with an increased risk of anemia, this does not establish failure to neuter or spay a Pet as a *cause* of anemia. Rather, it is likely a reflection of other factors that are associated with both anemia and being intact, such as decreased level of veterinary care. The same potential for confounding could be true for the canine breeds associated with an increased risk of anemia.

Is risk related to environment or lifestyle most commonly associated with these breeds? Or, alternatively, is breed a marker for genetic susceptibility for immune-mediated disease? It would be important for future studies to determine whether the risk associated with intact neuter status reflects a difference in lifestyle and environment or a physiologic difference. In these future studies, it would also be important to determine whether these associations are confounded by age, neuter status or breed.

Not surprisingly, RBC counts and hemoglobin concentrations were significantly decreased in both dogs and cats classified as anemic in this study. In addition, many other results from patient CBCs and clinical chemistries were also found to be significantly different in anemic Pets versus controls. However, mean values for both groups nonetheless fell within the normal ranges for these parameters, meaning that while these results were *statistically* significant, they were nonetheless not *clinically* significant (see *Evidence-Based Toolkit*, page 16). Because the Banfield database contains so many records, analyses often generate statistically significant results that must also be assessed for clinical significance before they can be applied.

Potential misclassification of cases is another aspect of this study design that illustrates an important concept in epidemiology. Misclassification refers to the error introduced when a research subject is placed into the wrong category based on study design or measurement error. In this study, we defined anemia in Pets based on a *single* hematocrit result found to be less than the lower bound of the normal range. A particular Pet, therefore, may be misclassified as anemic in this population analysis because this single assessment didn't take into account the variation for an individual over time or potential laboratory error. However, our large sample size helps reduce the effects of these potential misclassifications.

To generate our prevalence estimates, we used hematocrit results to define our cases. There are likely to be Pets with undetected anemia in the population because they have not had a CBC performed. This makes it more challenging in this study to generate a true estimate of anemia in the general population.

More research is needed to further understand the associations found in this analysis and to understand the risks specific to different etiologies of anemia. Additional research should include methods that help control for potential confounding by age, breed and neuter status. For veterinarians, the information provided from this analysis is a reminder that "common diseases occur commonly" and that they shouldn't overlook the common and important causes of anemia, such as parasitism and renal disease.

References

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