When a small animal patient presents with repeatable lymphocytosis, the differential list suggested by clinicians and clinical pathologists usually includes antigenic stimulation from infectious disease, antigenic stimulation, or lymphocyte activation from autoimmune disease, hypoadrenocorticism, thymoma, and lymphoproliferative disorders. In rare cases, congenital immunodeficiency disorders might also be considered. When the lymphocytes are described as small and mature or reactive and clinical signs and other laboratory changes are nonspecific, the clinician is faced with a diagnostic dilemma: is this a neoplastic process (chronic lymphocytic leukemia [CLL] or lymphoma) or a nonneoplastic reactive process? Here, the authors have tried to create a narrower and more informative differential list for such patients. They have specifically not included excitement-induced lymphocytosis because this would be considered a transient and generally not repeatable cause of lymphocytosis. The focus in this review is on the primary literature, together with emerging data from the Clinical Immunopathology Service at Colorado State University.

First, the authors provide a review of current knowledge of lymphocytosis in nonneoplastic conditions. They conclude that the list of major differentials for persistent nonneoplastic lymphocyte expansion in dogs and cats is short and that most of these conditions are relatively uncommon. Persistent lymphocytosis of small, mature, or reactive lymphocytes is most commonly the result of CLL or lymphoma. The first step in distinguishing nonneoplastic from neoplastic lymphocytosis is immunophenotyping by flow cytometry to determine the phenotypic diversity of the circulating cells. Clonality testing using the polymerase chain reaction [PCR] for antigen receptor rearrangements (PARR) assay is a useful second step in cases in which the phenotype data are equivocal.
Once the diagnosis of malignancy has been established, the immunophenotype also provides prognostic information in dogs.

LYMPHOCYTOSIS IN NONNEOPLASTIC CONDITIONS
Canine Infectious Disease

Chronic infectious disease is often listed as a differential for lymphocytosis in dogs. Although studies that systematically analyze lymphocytosis as a primary presenting complaint are lacking, a review of the literature suggests that with the exception of *Ehrlichia canis* infection, lymphocytosis is not a common feature of canine chronic infectious disease. In reviewing these studies, the authors assumed that if hematologic abnormalities (eg, neutrophilia) were noted, the lack of comment on lymphocytosis meant that the lymphocyte counts were not elevated. Lymphocytosis has not been reported in case series for several protozoal infections. These diseases include *Trypanosoma cruzi* [1,2], *Babesia gibsoni* [3,4], *Babesia canis* [5] infections; hepatozoonosis [6]; and experimental infection with *Leishmania infantum* [7]. Lymphocytosis was reported in 8 of 23 foxhounds naturally infected with *L infantum* (the highest value was 15,000 cells/μL), but some of these dogs also had serologic evidence of *E canis* infection [8]. The nematode infection *Spirocerca lupi* was associated with lymphocytosis as high as 8000 cells/μL (8 of 32 cases [9]). *Dirofilaria immitis* was associated with a high lymphocyte percentage, but absolute counts were not reported [10].

The chronic bacterial infections that cause Lyme disease and Rocky Mountain spotted fever do not seem to be associated with lymphocytosis. The authors could find no reports describing lymphocytosis associated with naturally occurring or experimental disease. Although monocytosis was found in 4 of 5 dogs with Rocky Mountain spotted fever [11], no dogs were reported to have lymphocytosis, and lymphocytosis was also not reported in experimental Rocky Mountain spotted fever infection [12]. Naturally occurring granulocytic ehrlichiosis in 14 dogs was not associated with lymphocytosis [13], but granulocytic ehrlichial infection in the experimental setting was associated with mild lymphocytosis (4500 cells/μL) during the recovery phase [14]. These lymphocytes were characterized as being blasts, with some characterized as having granules.

By contrast, lymphocytosis is a notable feature of chronic *E canis* infection. Numerous studies have shown that naturally occurring *E canis* infection can result in lymphocytosis with values up to 17,000 lymphocytes/μL [15–19], although not all case series describe lymphocytosis [20]. Anecdotal reports and the experience of some clinicians and clinical pathologists suggest that lymphocyte counts up to 30,000 cells/μL are possible in *E canis* infection. The lymphocyte response consists of cells with a large granular lymphocyte (LGL) phenotype [16,17,21], which were shown to be CD8+ T cells. Experimental *E canis* infection does not seem to have the same effect on lymphocyte count, but mild CD8+ T-cell expansion has been found [22]. Therefore, an important differential for lymphocytosis in dogs is *E canis* infection, and the frequency with which lymphocytosis is associated with *E canis* seems to be unique to this disease.
Feline Infectious Disease

There is less information about the development of lymphocytosis in feline infectious disease. It was not described in association with *Cytauxzoon felis* (34 cases [23]), natural *Toxoplasma gondii* infection (2 cases [24]), natural *Anaplasma phagocytophilum* infection (5 cases [25]), feline heartworm infection (50 cases [26]), or experimental *Mycoplasma felis* infection (18 cats [27]). Experimental *T. gondii* infection did result in mild lymphocytosis (9000 cells/μL [28]), and 3 of 21 cases of naturally acquired *M. felis* developed lymphocytosis with counts between 7000 and 9000 cells/μL [29]. Three cats infected with an *E. canis*-like organism developed anemia, thrombocytopenia and, in 1 case, pancytopenia similar to the canine infection, but none had lymphocytosis [30]. There are reports of feline immunodeficiency virus (FIV)–associated lymphocytosis (1 of 5 cats with a lymphocyte count of 13,000 cells/μL [31]), and lymphocytosis was present in 8 of 46 FIV-positive cats in a study by Hopper and colleagues [32]. At least 2 of the cats in this series had a lymphoid malignancy, and given the known association between FIV and B-cell lymphoma, it is important to establish that cases of lymphocytosis in FIV infection are not the result of malignancy. It is important to note that in a large study of 30 cats experimentally infected with several different FIV isolates and followed for 15 years, no cat developed lymphocytosis at any time during the study (Mathiason C and Hoover E, unpublished data, 1999). Taken together, the available primary literature indicates that mild lymphocytosis can occasionally be associated with several feline infectious diseases, but this finding is uncommon.

Autoimmune Disease

A finding of lymphocytosis in cases of canine autoimmune disease also seems to be rare. Immune-mediated hemolytic anemia (IMHA) is probably the best-studied canine autoimmune disease, yet lymphocytosis was not reported in any study series [33–35]. In contrast, however, two reports that examined presumptive cases of IMHA in a total of 22 cats found that 9 had lymphocytosis, with one case as high as 20,000 cells/μL [36,37]. Lymphocytosis was not reported in other canine systemic autoimmune diseases, and presumptive autoimmune diseases include systemic lupus erythematosus (in which lymphopenia was a dominant feature [38]), rheumatoid arthritis, and nonseptic and nonerosive polyarthritis [39].

Other Causes

Lymphocytosis has been associated with hypoadrenocorticism in dogs and cats. Studies vary on the incidence of lymphocytosis in dogs with Addison’s disease, ranging from 5% to 10% of patients, with the highest lymphocyte count recorded being 13,000 cells/μL [40–42], although in a report focusing on patients with glucocorticoid deficiency only, no cases of lymphocytosis were found [43]. Cats with hypoadrenocorticism can also present with lymphocytosis (20% of cases in the single case series that has been reported [44]). Therefore, although only a few animals with Addison’s disease have lymphocytosis, it should be considered a differential for unexplained mild persistent lymphocytosis.
Another endocrine disease that can be associated with lymphocytosis in cats is hyperthyroidism. In a comprehensive study of clinical data from cats with hyperthyroidism, Thoday and Mooney [45] found that 7% of 57 cats studied had lymphocytosis, with the highest lymphocyte count being 9000 cells/μL. Treatment of hyperthyroidism with methimazole can also cause lymphocytosis [46].

Thymomas in people have occasionally been associated with lymphocytosis consisting of CD4 and CD8+ T cells [47]. These cells are likely present because of increased production of nonneoplastic T cells, whose growth and differentiation are stimulated by the neoplastic thymic epithelium. Thymomas in dogs and cats can also present with concurrent lymphocytosis, although this is not described in all case series [48]. Of two cases reported in one study [49], one dog had a lymphocyte count of 19,000 cells/μL and the lymphocyte count of the other dog was within normal limits. The authors have evaluated nine cases of canine thymoma through the Clinical Immunopathology Service at Colorado State University (five of these are reported in the article by Lana and colleagues [50]) for the purpose of immunophenotyping aspirates from the tumor. In the complete blood cell counts (CBCs) available from these nine cases, two dogs had lymphocytosis. One cat with thymoma and lymphocytosis was reported in the article by Weiss [37], and a single cat had a high lymphocyte count (7000 cell/μL). Thus, thymoma should be included as a differential for lymphocytosis, although it is seen in only a few cases.

Postvaccination lymphocytosis is listed as a differential for an increased lymphocyte count in some references. The literature does not support this as a routine finding. In a study of 92 mixed-breed dogs, four commercially available polyvalent vaccines caused an actual decrease in circulating lymphocytes on days 3, 5 and 7 after vaccination [51]. Miyamoto and colleagues [52] demonstrated a similar decrease in lymphocyte count in puppies and adult dogs at day 7 after vaccination. A study examining the response of racing Greyhounds to a traditional or intense vaccination schedule failed to demonstrate any increase in circulating lymphocytes in samples taken biweekly during the 6-month study [53].

Summary of Nonneoplastic Lymphocytosis
Overall, review of the literature suggests that when presented with a case of persistent lymphocytosis, there is a relatively small list of nonneoplastic conditions to consider. In terms of infectious disease, *E canis* infection in dogs can result in significant lymphocytosis. Increased lymphocyte counts have been reported in canine *S lepi* and *L infantum* infections. Some reports of cats infected with *T gondii* and *M felis* have documented lymphocytosis, and a subset of cats with FIV infection may have lymphocytosis, but an underlying malignancy would also be a consideration in this disease. Lymphocytosis has been reported in some cats with IMHA, but this has not been reported in dogs. In a few cases, metabolic diseases, such as hypoadrenocorticism and feline hyperthyroidism, have been associated with persistent lymphocytosis. Finally, thymoma has
been associated with benign expansion of peripheral lymphocytes in a small number of feline and canine cases.

**NEOPLASTIC LYMPHOCYTOSIS**

Lymphoproliferative disorders often present with peripheral lymphocytosis. CLL, acute lymphoblastic leukemia (ALL), and lymphoma with circulating neoplastic cells (stage V lymphoma) are the three forms of lymphoid malignancy in which lymphocytosis is a primary feature.

**Chronic Lymphocytic Leukemia**

CLL in people and animals involves the transformation and expansion of mature-appearing lymphocytes. The diagnosis of CLL in people requires lymphocytosis of greater than 5000 cells/μL of mature-appearing lymphocytes that express specific surface markers. CLL in people is primarily an expansion of immunophenotypically atypical B lymphocytes, and the disease usually has a prolonged clinical course. In people, it is thought that these cells arise from the bone marrow.

In veterinary medicine, there is no consensus on the criteria for making the diagnosis of CLL, partly because the immunophenotype of the cells is usually normal and B- and T-cell forms occur. Furthermore, it is likely that one or more subtypes of CLL arise in the spleen rather than in the bone marrow [21], making marrow involvement potentially unhelpful in establishing a diagnosis. Canine and feline CLL patients are often asymptomatic at presentation, with lymphocytosis ranging from 6000 to greater than 200,000 cells/μL [54,55]. Peripheral cytopenias tend to occur in a relatively small subset of cases and are generally mild (reviewed in the article by Workman and Vernau [56]). Canine CLL has been described as an indolent disease, although survival times can vary greatly [55]. Less is known about survival in feline CLL. Workman and colleagues [57] presented survival data for 17 cats with CLL and showed that treated cats (8 of 17 cats) had a mean survival of 28 months, whereas untreated cats (which were generally not treated because they tended to have severe disease and a poorer prognosis) survived 1 to 6 months.

**Lymphoma**

Lymphoma can also present as lymphocytosis. Published studies have reported a range of estimates of lymphocytosis associated with canine lymphoma of 7% [58], 28% [59], 37% [60], and 65% [61]. Fewer studies are available for cats; in one report, 5% of 97 cats with lymphoma had absolute lymphocytosis, with values reaching 80,000 cells/μL [62].

It is not clear whether some cases of lymphoma with lymphocytosis might be considered primary leukemia with lymph node involvement. In people, the nomenclature of human small lymphocytic lymphoma and leukemia has evolved to reflect the observation that lymph node infiltration is not uncommon in human CLL. Therefore, CLL and small B-cell lymphoma are considered together as one disease entity (CLL/small lymphocytic lymphoma). As discussed
elsewhere in this article, this grouping of two disease entities might be appropriate in canine CLL as well.

**Acute Lymphoblastic Leukemia**
ALL is a rapidly fatal disease [54] that generally does not pose a diagnostic dilemma. Typical canine ALL presents with large numbers of circulating lymphoblasts and commonly has coexisting peripheral cytopenias. Therefore, malignancy can often be diagnosed by morphology alone, although immunophenotyping may help to assign a lineage in cases in which morphology cannot determine if the leukemia is lymphoid or myeloid.

**Distinguishing Reactive from Neoplastic Expansions**
In the previous sections, the authors outlined the nonneoplastic and neoplastic causes of lymphocytosis in small animal patients. When presented with a patient with persistent lymphocytosis, the first decision a clinician must make is whether the lymphocytosis is neoplastic or not. Such a distinction can be difficult when using clinical signs and lymphocyte morphology alone. Clinical signs in many of the diseases described may be nonspecific, and lymphocyte morphology may reveal only small, mature, or reactive lymphocytes. Lymphocyte morphology has been shown to be of limited use in distinguishing cell phenotype in veterinary and human medicine [54,63].

Several assays can be used to aid in the distinction between reactive and neoplastic lymphocyte populations (reviewed in the article by Avery and Avery [64]): (1) demonstrating a phenotypically homogeneous expanded lymphocyte population with or without the presence of aberrant antigen expression, (2) establishing cellular clonality, (3) identifying chromosomal abnormalities, and (4) identifying the presence of an oncogene associated with the malignancy. The first two methods are now readily available in veterinary medicine. The latter two are less well developed; however, the full sequence of the canine genome [65,66] and work by Breen and colleagues [67] to develop molecular methods of examining chromosomal aberrations should facilitate the development of future diagnostic assays. For the remainder of this review, the authors discuss methods that are now routinely available to practitioners: immunophenotyping and clonality assessment.

**Immunophenotyping Using Flow Cytometry**
Flow cytometry is the method of choice for immunophenotypic analysis. The methodology has been thoroughly reviewed in a previous issue in this series [56]. The value of flow cytometry lies in its ability to detect the expression of multiple antigens on the surface of lymphocytes efficiently. A continually expanding number of species-specific and cross-reactive antibodies for labeling canine and feline hematopoietic cells makes more detailed multiparameter flow cytometry possible [54,68]. Commercially available directly conjugated antibodies recognizing canine CD3 and CD5 (all T cells), CD4 (T-cell subset), CD8 (T-cell subset), CD21 (B cells), CD34 (precursor cells), and CD45 (a panleukocyte antigen) are all useful to characterize circulating lymphocytes. The
commercially available repertoire of antibodies for feline immunophenotyping is more limited.

Lymphocytosis caused by leukemia or lymphoma is characterized by homogeneous expansion of cells with a single phenotype, whereas reactive lymphocyte expansions are likely to be heterogeneous, involving multiple lymphocyte subsets. Thus, the first immunophenotypic criterion suggesting malignancy is homogeneous expansion of lymphocytes, such as CD21+ cells (B cells) or CD8+ cells (T-cell subset). An important exception to this concept is the homogeneous expansion of CD8+ T cells in E canis infection. The authors know of no other disease in dogs or cats that causes a similar homogeneous reactive lymphocyte expansion.

Immunophenotyping by flow cytometry is a service that is now being provided by an increasing number of laboratories, most of which are in veterinary schools. There is no consensus as to the best combination of antibodies, the methods of cell preparation, how results are reported, or cost. Because of this diversity, it is probably best to find one laboratory and to use that service consistently so that the clinician can build familiarity with the interpretation of results.

**Immunophenotype of Canine Chronic Lymphocytic Leukemia**

Canine CLL is primarily a CD8+ T-cell disease. Vernau and Moore [54] examined 73 cases of canine CLL and determined that 73% were of T-cell origin, whereas only 26% expressed B-cell markers. Most T-cell leukemias were of the CD8+ subset, and many of these had an LGL morphology. Similarly, Ruslander and colleagues [69] found that 68% of canine CLLs were CD8+. A smaller subset of CLLs are composed of B cells (CD21+), and CD4+ T-cell CLLs seem to be rare. Immunophenotyping of CLLs by the authors’ laboratory produced similar results [70].

**Immunophenotype of Feline Chronic Lymphocytic Leukemia**

There is little information about feline CLL in the literature. Workman and colleagues [57] presented a series of 20 cases of feline CLL whose lymphocyte counts ranged from 22,000 to 575,000 cells/µL. In that series, the predominant phenotype was CD4+ T cell. The authors’ laboratory has phenotyped 60 cases of homogeneous lymphocyte expansion in cats with lymphocyte counts greater than 8000 cells/µL. Forty-two percent of these were CD4+; these cases had lymphocyte counts that ranged from 8000 to 125,000 cells/µL. Eleven percent of the 60 cases had homogeneous expansion of B cells (as determined by the expression of CD21). These cases tended to have a lower lymphocyte count, with the highest being 37,000 cells/µL. The remainder were a mixture of CD8+, CD4+8+, CD4−CD8−CD5+, and null cell. The authors do not have survival data for these cats yet; however, such studies are clearly a high priority to aid veterinarians and owners in making informed choices. A broader range of antibodies for feline studies is also an important goal.
Aberrant Antigen Expression

Aberrant antigen expression can further support the diagnosis of malignancy [71,72], because reactive lymphocytes retain expression of their normal constellation of antigens. Human T-cell leukemias are characterized by their tendency to lose expression of normal T-cell antigens or to express aberrant combinations of antigens [73]. In one study of 87 human malignant T-cell disorders, Gorczyca and colleagues [74] found that complete loss of any T-cell antigen (CD2, CD5, or CD7) or the panleukocyte antigen CD45 was diagnostic for malignancy. Aberrant antigen expression (failure to express CD4 or CD8 or coexpression of these two markers) was reported by Vernau and Moore [54] on 10 of 73 canine cases of CLL. Nevertheless, one of the drawbacks of older studies is that directly conjugated antibodies, which facilitate multicolor fluorescence, were not available, making aberrant antigen expression difficult to detect. In the authors’ experience, almost half of T-cell leukemias (11 of 26 cases) during a 1-year period exhibited aberrant antigen expression (no expression of CD4 or CD8, loss of the panleukocyte antigen CD45, and occasional loss of the T-cell antigen CD5). Loss of expression of CD4 and CD8 or loss of CD5 expression has been associated with more rapid disease progression in human cases of adult T-cell leukemia [75]. Precursor T-cell ALL that lacks CD5 or CD4 expression has an increased risk of treatment failure and shorter event-free survival [76,77]. The authors’ analysis of 89 cases of canine leukemia has not shown any significant survival difference in dogs with T-cell leukemias that lack CD4 and CD8 or CD45 expression as compared with phenotypically normal T-cell leukemias [78]. Thus, although aberrant antigen expression can be used to help make the diagnosis of neoplastic lymphocytosis, the more common variants do not seem to have prognostic significance in dogs. Too few cases of feline leukemia with aberrant antigen expression have been documented to reach similar conclusions in cats.

Determination of Lymphocyte Clonality

In cases in which the lymphocyte count is not markedly elevated and the lymphocytes do not exhibit aberrant antigen expression, additional support for the diagnosis of malignancy can be obtained from clonality testing by the PARR assay [79]. In human medicine, determination of clonality by detecting rearranged antigen receptor genes is the test of choice if routine cytology, histology, and immunophenotyping are not able to provide a definitive diagnosis of malignancy [80]. The principle behind this assay has been described by Avery and Avery [64] and Workman and Vernau [56]. Briefly, DNA is extracted from lymphocytes, and the size of the antigen receptor hypervariable region is determined by PCR. In B cells, the antigen receptor is immunoglobulin, and in T cells, it is the T-cell receptor. Because the size of the hypervariable region differs slightly in each lymphocyte, the finding of a single-sized hypervariable region indicates that all the lymphocytes are derived from a single clone and are most likely neoplastic. Reactive lymphocytes are derived from multiple different clones. Thus, the finding of a clonal population of lymphocytes by means of
the PARR assay, coupled with homogeneous expansion of lymphocytes based on immunophenotyping, is strong evidence of neoplasia. To date, the authors know of only a single exception to this theory. *E canis* infection in dogs can cause not only homogeneous expansion of CD8 T cells but, in rare cases, clonal expansion \[54,79\]. Thus, in dogs positive for *E canis*, the response to treatment for *E canis* infection may be the best diagnostic tool for determining if lymphocytosis is attributable to infection or to an underlying malignancy.

Clonality testing in dogs and cats is presently established at two institutions (Colorado State University and the University of California, Davis), but it is likely that it will be available through other laboratories in the future. It is important that as laboratories develop this assay, they provide sensitivity and specificity numbers for their assay; published results from one laboratory do not translate to another because of the wide variation in the way the assay is performed. The sensitivity of the Colorado State University assay in dogs is 80%, and the specificity is 92%, but other laboratories may have different results. The authors estimate that the primers used in their laboratory at the present time can detect approximately 60% of confirmed feline lymphomas and leukemias, and they are working toward developing better reagents for cats.

Phenotypic homogeneity, aberrant antigen expression, and clonality can together distinguish reactive from neoplastic lymphocytosis. Immunophenotyping by flow cytometry is valuable not only for establishing a diagnosis but for predicting prognosis in cases of canine neoplastic lymphocytosis. In the following section, the authors summarize data from their study of a series of dogs with neoplastic lymphocytosis in which they correlated immunophenotype and other parameters with outcome.

**Immunophenotyping Predicts Prognosis in Canine Lymphocytosis**

Peripheral blood from 208 dogs with lymphocytosis was submitted to the Clinical Immunology Service at Colorado State University for immunophenotyping. A total of 202 of the 208 cases had homogeneous expansion (>80% of the lymphocytes) of one lymphocyte phenotype or aberrant antigen expression. Of these, clinical information and follow-up data were available for 89 cases. Thirty-one percent of these dogs had homogeneous expansion of B cells, 24% had homogeneous expansion of CD8+ T cells, 20% had expansion of CD34+ progenitor cells, 14% had CD5+ T cells that lacked CD4 or CD8 expression, 6% expressed other aberrant antigens, and 5% had homogeneous expansion of CD4+ T cells. The authors chose the B-cell and CD8+ T-cell groups for further analysis. They purposely included all cases with homogeneous expansion of circulating lymphocytes, knowing that the cases would encompass stage V lymphomas and primary leukemias. The authors are commonly asked to distinguish between these two entities; however, specific phenotypic markers to make this distinction are lacking. They were hopeful that more objective prognostic indicators would emerge to help distinguish between neoplastic T-cell and B-cell expansions as well as within phenotypes.
Canine B-Cell Lymphocytosis: Cell Size Matters
The distinction between human CLL/small lymphocytic lymphoma and other B-cell lymphomas with circulating atypical cells is made primarily based on cellular phenotype, because CLL/small lymphocytic lymphoma consists of B cells that express the T-cell marker CD5 [81]. Canine B-cell leukemia does not express CD5 [54] and is immunophenotypically indistinguishable from canine B-cell lymphoma (the most common form [82,83]) using commercially available antibodies. Therefore, the authors examined all cases of B-cell lymphocytosis, as defined by greater than 5000 lymphocytes/µL and greater than 80% CD21⁺ cells, and segregated them by size [78]. Dogs whose circulating lymphocytes were large (presumed stage V lymphoma or prolymphocytic/lymphoblastic leukemia) had a significantly shorter median survival time (115 days) than those with small circulating lymphocytes (CLL/small lymphocytic lymphoma, median survival not reached; \( P = .035 \)). In the authors’ cases series, all the dogs with circulating small CD21⁺ lymphocytes had corroborating evidence of neoplastic transformation, including (1) a lymphocyte count greater than 30,000 cells/µL or (2) cytologic evidence supporting a diagnosis of leukemia or lymphoma in bone marrow or lymph nodes. It is important to note that more than half of the dogs with circulating, small, mature-appearing CD21⁺ lymphocytes had detectable peripheral lymphadenopathy, suggesting that the designation of small lymphocytic lymphoma/CLL may be appropriate in dogs as well.

Canine T-Cell Lymphocytosis: Cell Numbers Matters
The two most commonly used clinical staging systems to predict prognosis in human B-cell CLL do not take into account initial lymphocyte count [84], and when initial lymphocyte counts have been specifically studied, they have not provided prognostic information [85]. The authors have found this to be true in dogs with small cell B-cell leukemias as well. When the more common CD8⁺ T-cell variant of canine CLL was examined, however, the initial lymphocyte count had a significant impact on survival. Dogs that presented with fewer than 30,000 lymphocytes/µL had a median survival time of 1098 days (indolent form), whereas those dogs with an initial lymphocyte count greater than 30,000 lymphocytes/µL had a median survival time of 131 days (aggressive form; \( P < .008 \)) [78]. The dogs with fewer than 30,000 CD8⁺ lymphocytes/µL had additional evidence supporting a diagnosis of neoplasia, including (1) PCR positivity for a clonal T-cell receptor rearrangement, (2) aberrant antigen expression (loss of CD45), (3) atypical appearance of the circulating lymphocytes, or (4) persistence of the lymphocytosis with negative serology for *E canis*. Because longitudinal data were not available for most cases, the authors could not determine if indolent and aggressive forms represent ends of a single disease spectrum or if they are two discrete entities. As described previously, the authors also found that cases of canine neoplastic lymphocytosis with aberrant antigen expression did not have a significantly different length of survival than those expressing a normal constellation of antigens.
**Prognosis in Feline Neoplastic Lymphocytosis**

There are no studies correlating the immunophenotype with outcome in feline neoplastic lymphocytosis, although two recent reports may help with prognostication in some cases. Workman and colleagues [57] found a wide range of survival in cats with CD4⁺ CLL, with a mean of 28 months in treated cases. By contrast, LGL malignancy in cats, which is most commonly CD8⁺, can...
present as lymphocytosis associated with intestinal lymphoma \[86,87\]. These cases have a poor survival time (mean of 84 days). Thus, LGL phenotype is one feature that seems to provide prognostic information.

**SUMMARY: PROPOSED DIAGNOSTIC APPROACH TO PERSISTENT LYMPHOCYTOSIS**

Based on data from the literature and the authors’ clinical experience, they propose the following algorithm for the workup of cases of persistent lymphocytosis (Fig. 1A). Dogs with absolute lymphocytosis on two occasions should be immunophenotyped. Those animals with a mixed population of lymphocytes (defined by an expansion of more than one subset) should be evaluated for nonneoplastic causes of lymphocytosis. These patients should be in the minority. Most dogs have a homogeneous population (in the authors’ experience, the expanded population of lymphocytes consistently comprises greater than 80% of the lymphocytes) and are likely to have neoplasia. The presence of an aberrant phenotype or a positive test result by PARR can help to confirm this. If these cells are CD8\(^+\) T cells, the lymphocyte count at presentation is highly prognostic. If these cells are B cells, the size of the lymphocytes by light scatter is highly prognostic. Information about survival in other subsets (CD4\(^+\), CD4\(^-\)CD8\(^-\)CD5\(^+\) ) is not yet available.

Cats with repeatable absolute lymphocytosis should be immunophenotyped. If their lymphocytes are heterogeneous, they should be evaluated for nonneoplastic causes of lymphocytosis (see Fig. 1B). If there is homogeneous expansion of lymphocytes, leukemia or lymphoma with circulating lymphocytes should be considered likely. The immunophenotype of neoplastic lymphocytes is not yet prognostically useful in cats, but the cells should be carefully examined to determine if the lymphocytes have an LGL morphology. These cases seem to have a poor outcome.

**References**


SIGNIFICANCE OF PERSISTENT LYMPHOCYTOSIS


[76] Uckun FM, Gaynon PS, Sensel MG, et al. Clinical features and treatment outcome of childhood T-lineage acute lymphoblastic leukemia according to the apparent maturational stage


