Lymphoma is the most common hematopoietic tumor in dogs and cats, and it has been recognized in both species for decades. New information has recently come to light that expands our knowledge regarding how to diagnose and manage this disease.

**DIAGNOSTIC TESTS**

**Fine-Needle Aspiration**
Cytologic examination of fine-needle aspirate samples is often sufficient to determine a diagnosis of large-cell lymphoma (Figure 1, page 18), which is the most common form in dogs. Recently, a small-cell form of lymphoma has been identified in both cats and dogs. Because the neoplastic cells in this type of lymphoma are similar in appearance to normal lymphocytes, it can be difficult to distinguish between lymphoid hyperplasia and small-cell lymphoma on cytology (Figure 2A, page 19).

**Biopsy**
As such, biopsy samples are often needed to diagnose small-cell lymphoma (Figures 2B–2D, page 19). Most dogs with lymphoma present with generalized peripheral lymphadenopathy. Although performing a lymph node excisional biopsy in a dog is certainly more invasive than fine-needle aspiration, it is considered a minor surgical procedure for most patients.

In contrast, the gastrointestinal tract is currently the most common anatomic site for feline lymphoma. Surgically obtained full-thickness biopsy samples are more likely to yield accurate histopathologic results compared to samples obtained via endoscopy; therefore, obtaining biopsy samples in cats is more invasive than in dogs (Figure 3, page 20).

Although a recent paper indicated that the risk for complications related to full-thickness intestinal biopsy in cats with lymphoma is low, owners may still hesitate to consent to this procedure due to its invasiveness and cost. In addition, the distinction between reactive and neoplastic lymphocytes can be challenging to make even on histopathologic samples.

**PCR for Antigen Receptor Rearrangement**
PARR (PCR for antigen receptor rearrangement) is an additional diagnostic test that can aid in diagnosing lymphoma using either cytologic or histopathologic samples. PARR determines if the cell population is clonal or not, and since neoplastic cell populations are often descended from one malignant transformed cell, a PARR result indicating a clonal population supports a diagnosis of lymphoid neoplasia.

In dogs, the sensitivity of this test is between 75% and 85%, with a specificity of 92% to 94%; in cats, a sensitivity of 60% to 78% has been reported. These values indicate that, similar to other diagnostic tests, PARR testing results must be interpreted in light of other clinical data.

PARR may be a reasonable diagnostic test to consider in the face of equivocal cytology findings when obtaining histopathology samples is not feasible or declined by owners; in addition, it may also be used when both cytology and histopathology results do not result in a definitive diagnosis of lymphoma, but lymphoma is still suspected based on other clinical findings.
Diagnostic Tests
• **PARR (PCR for Antigen Receptor Rearrangement):** Using cytologic or histopathologic samples, PARR determines if the cell population is clonal or not. A result indicating a clonal population supports a diagnosis of lymphoid neoplasia, but PARR results must be interpreted in light of other clinical data.

Prognostic Factors
• **Immunophenotype:** Immunophenotype is a well-known prognostic factor for canine lymphoma; however, despite several studies, more research is needed to determine if immunophenotype should be used to select one chemotherapy protocol over another.
• **Cell Type & Size:** In cats, small-cell lymphoma is characterized by an indolent course and significantly longer survival time compared to large-cell lymphoma; recent reports describing small-cell lymphoma in dogs suggest a similar indolent clinical course.
• **Body Weight & Condition Score:** Cats with weight loss prior to diagnosis of and during treatment for lymphoma had shorter survival times than cats that gained weight early in the treatment course. Body condition score was also a significant predictor of survival.

Treatment & Toxicity Management
• **Dose Intensity:** While increasing dose intensity is one strategy to improve chemotherapy outcome for canine lymphoma, dose intensity must be adjusted based on an individual patient’s tolerance.
• **Risk Factors for Chemotherapy-Induced Sepsis:** Risk factors for sepsis were recently identified and include dogs with lymphoma rather than solid tumors, smaller dogs, dogs with lymphoma in the induction phase of chemotherapy, and those receiving doxorubicin and vincristine.
• **Antibiotic Prophylaxis:** Use of prophylactic antimicrobial therapy (trimethoprim-sulfadiazine) following administration of doxorubicin to dogs with lymphoma decreases the risk of hospitalization and nonhematologic toxicity.
• **Drug Substitution:** Substituting vinblastine for vincristine in cats with lymphoma was evaluated to compare outcome and toxicity. While outcome did not differ significantly, cats that received vinblastine had less GI toxicity than those that received vincristine.
• **Rescue Therapy:** The response rate of relapsed feline lymphoma to doxorubicin is 22%; lomustine, 37%; and radiation therapy resulted in a clinical response in 10/11 cats.
**PROGNOSTIC FACTORS**

**Immunophenotype**

Immunophenotype is a well-known prognostic factor for canine lymphoma. Several reports have concluded that dogs with large-cell, T-cell lymphoma have lower response rates, shorter remission durations, and shorter survival times compared to dogs with B-cell lymphoma. Immunophenotype can be determined using PARR or immunohistochemical staining for T- and B-cell markers. Recent studies have attempted to expand on this information by evaluating response to specific chemotherapy protocols in dogs with B-versus T-cell lymphoma.

**Doxorubicin versus CHOP Chemotherapy**

- Dogs with B-cell lymphoma are reported to have a higher likelihood of responding to doxorubicin compared to dogs with T-cell lymphoma.
- Dogs in that study received doxorubicin as the first chemotherapy for lymphoma, and response was evaluated 1 week after the first dose.
- In contrast, in another study no survival difference according to immunophenotype was found in dogs that received a CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) chemotherapy protocol, which included 5 doses of doxorubicin.
- Previous studies, however, have found that dogs with T-cell lymphoma have a worse outcome compared to those with B-cell lymphoma when treated with a CHOP chemotherapy protocol.

**MOPP versus CHOP Chemotherapy**

- One report found that dogs with T-cell lymphoma had a high response rate (98%) to MOPP (mechlorethamine/vincristine/procarbazine/prednisone) chemotherapy with a median progression-free survival of 189 days and median overall survival of 270 days.
- When CHOP chemotherapy was evaluated specifically for dogs with T-cell lymphoma, a similar response rate (96%) was noted, with a comparable median overall survival (235 days) and shorter progression-free survival (104 days).
- It is worth pointing out that neither of these studies had a control group, and dogs were included in the first study if they had confirmed T-cell lymphoma or were hypercalcemic, while all dogs in the second study were confirmed to have T-cell lymphoma. More research is needed to determine the value of immunophenotype for predicting differential response to chemotherapy protocols in canine lymphoma.

**Cell Type & Size**

Although immunophenotype has not been demonstrated as a prognostic factor for feline lymphoma, cell type/size is significantly associated with outcome. In cats, small-cell lymphoma is characterized by an indolent disease course and significantly longer survival time compared to large-cell lymphoma, and recent reports describing small-cell lymphoma in dogs suggest that it has a similar indolent clinical course.

**Body Weight & Condition**

Recent literature has also evaluated the relationship between body weight and body condition score (BCS) and outcome in cats with lymphoma, revealing new prognostic factors.

**Survival Based on Body Weight & Condition Score**

- A recent paper evaluating the effect on survival of body weight and BCS in cats with cancer found that, among all cats, lower body weight was associated with shorter survival.
- The association between lower body weight and shorter survival was not statistically significant in the subgroup of cats with lymphoma, but BCS was a significant predictor of survival for that group.
- Weight loss prior to the diagnosis of lymphoma is also associated with shorter survival, and lower body weight has been associated with shorter survival following rescue radiation therapy in cats with gastrointestinal lymphoma.

**Survival Based on Body Weight Changes During Treatment**

- A recent study performed at University of Pennsylvania found that body weight changes during treatment of feline lymphoma also affect survival.
• Cats that gained weight early in the treatment course had a longer survival compared to cats that lost weight or had stable weight.
• The majority of cats with lymphoma have moderate to severe loss of muscle or fat mass, which is in stark contrast to canine lymphoma patients, of which 29% are overweight and only 15% have decreased muscle mass.²²,²⁶

The high frequency of muscle and fat loss in cats with lymphoma coupled with the significance of body weight and BCS on prognosis indicates that further research into these aspects of feline lymphoma are needed. Potential areas for study include:
• Modifications in chemotherapy protocols to decrease the risk of treatment-related weight loss
• Examining treatment options in addition to chemo-

**Figure 2A.** Mandibular lymph node aspirate: A monomorphic population of small- to medium-sized lymphocytes with a single mitotic figure (red arrow). Small lymphocytes are 9 to 11 mc in diameter with round, eccentrically located nuclei containing mature, clumped chromatin, and no visible nucleoli. Cytoplasm is scant, deeply basophilic, and often has a single cytoplasmic projection (mirror-handle morphology, black arrows). (Wright-Giemsa; magnification, 100×)

Courtesy Dr. Reema Patel, University of Pennsylvania

**Figure 2B.** Mandibular lymph node biopsy: The paracortical region of the node is expanded by sheets of neoplastic intermediate-sized lymphocytes (nuclei are approximately 1.5× diameter of a red blood cell). The cells have round to oval nuclei, with occasional nuclear indentations and a moderate amount of lightly eosinophilic cytoplasm. (H&E stain [hematoxylin & eosin stain]; magnification, 20×)

Courtesy Dr. Amy Durham, University of Pennsylvania

**Figure 2C.** Mandibular lymph node biopsy from 2B: The paracortex is expanded by sheets of neoplastic intermediate-sized T-cells (arrow), confirming the diagnosis of T-cell lymphoma. (Immunohistochemical staining for CD3; magnification, 4×)

Courtesy Dr. Amy Durham, University of Pennsylvania

**Figure 2D.** Mandibular lymph node biopsy from 2B: The neoplasm peripheralizes the B-cell follicles against the nodal capsule (fading follicles) (arrows). (Immunohistochemical staining for CD79a; magnification, 4×)

Courtesy Dr. Amy Durham, University of Pennsylvania
therapy that may reverse the cycle of weight loss and poor survival in cats at risk.
• It is currently not clear if low body weight/BCS is a prognostic factor in itself or an indication of the severity of disease.

NEW STRATEGIES FOR TREATMENT & TOXICITY MANAGEMENT
Combination chemotherapy is considered standard of care treatment for canine and feline lymphoma. Both COP- (cyclophosphamide, vincristine, and prednisone) and CHOP-based chemotherapy protocols are used commonly for feline lymphoma, while CHOP-based protocols are considered standard of care for canine lymphoma.

Newer reports on treatment of canine and feline lymphoma have investigated:
• The effect of increasing dose intensity of CHOP-based protocols and using protocols containing fewer drugs
• Risk factors for chemotherapy-induced sepsis in canine patients
• Additional induction and rescue treatment strategies for lymphoma in cats.

Increased Dose Intensity
One strategy to improve chemotherapy treatment outcome for lymphoma is to increase the dose intensity and/or dose density of a protocol. Increased dose intensity is achieved by increasing the doses of the individual chemotherapy drugs in a protocol; dose density is increased by decreasing the time interval between doses.
• A recent report of a dose-intense, CHOP-based protocol for canine lymphoma reported similar response and outcome but higher toxicity when compared to previously reported, less intense protocols.14
• Over half of the dogs required dose reductions, almost half had treatment delays, and over 10% were hospitalized for sepsis or gastrointestinal toxicity.
• Interestingly, dogs that had dose reductions and/or treatment delays had significantly longer time to progression and lymphoma specific survival compared to dogs that did not.
• The authors conclude that modifying dose intensity remains important in the treatment of canine lymphoma, but dose intensity must be adjusted based on an individual patient’s tolerance.

Chemotherapy-Induced Sepsis
As dose-intense chemotherapy protocols carry an increased risk of toxicity, it is helpful to have updated and accurate information about how to decrease this risk.

Neutropenic Sepsis
Neutropenic sepsis is a serious complication of chemotherapy in veterinary patients, and treatment generally involves intravenous fluids, antimicrobial therapy, and additional supportive care medications. Antibiotic prophylaxis is often used to prevent this condition, but until recently, the risk factors for sepsis (and thus knowledge of which patients would benefit the most from prophylactic antimicrobial therapy) were unknown.

Recent Studies
Several risk factors for sepsis were identified in a case control study that compared patients with chemotherapy-induced sepsis to patients undergoing chemotherapy that did not experience sepsis.27
• Specifically, dogs with lymphoma were more likely to become septic than dogs with solid tumors and smaller dogs had a higher risk than larger dogs.
• Among dogs with lymphoma, sepsis occurred more
often during the induction phase of chemotherapy, and doxorubicin and vincristine were the drugs most commonly associated with neutropenic sepsis. Results from a placebo-controlled clinical trial showed that trimethoprim-sulfadiazine prophylaxis decreased the incidence of hospitalization and nonhematologic toxicity following doxorubicin chemotherapy in dogs with lymphoma as well as osteosarcoma. These two studies provide evidence supporting the use of prophylactic antimicrobial therapy following administration of doxorubicin and vincristine to dogs with lymphoma.

Protocols Requiring Fewer Visits
Dose-intense CHOP chemotherapy protocols require financial and time commitments from owners, which may not be feasible for all clients, prompting evaluation of protocols that may require fewer clinic visits. The combination of doxorubicin and cyclophosphamide versus single-agent doxorubicin has been evaluated in a randomized, placebo-controlled clinical trial.

- Thirty-two dogs received either doxorubicin and placebo or doxorubicin and cyclophosphamide.
- Response rate and toxicity were similar between the groups, and although there appeared to be a clinically significant longer progression-free interval in the doxorubicin and cyclophosphamide group compared to the placebo group (246 versus 169 days). However, the difference was not statistically significant.

A protocol consisting of lomustine and prednisone has been reported in an even smaller group of dogs (N = 17), with a response rate of 53% and remission duration of less than 2 months, which does not compare favorably to other first-line chemotherapy protocols for canine lymphoma.

Strategies for Feline Lymphoma
Combination chemotherapy is also considered standard of care treatment for feline lymphoma, and common toxicities include decreased appetite and weight loss. Because of the association between body weight/BCS and survival in cats with lymphoma, treatment strategies that minimize such toxicity may be beneficial to those patients.

Drug Substitution to Decrease Toxicity
One potential modification is the use of chemotherapy drugs that have the same efficacy with less toxicity. The substitution of vinblastine for vincristine is one such example.

- A recently completed randomized clinical trial performed at University of Pennsylvania compared outcome and toxicity between cats that received either vincristine or vinblastine as part of a COP-based chemotherapy protocol.
- Outcome did not differ significantly according to treatment group, but vinblastine was associated with less GI toxicity compared to vincristine.

Drugs for the Rescue Setting
Additional studies have evaluated new treatment strategies for cats with relapsed lymphoma.

### Table. What’s New: Chemotherapy Protocols

<table>
<thead>
<tr>
<th>Chemotherapy Protocol</th>
<th>Species Discussed</th>
<th>Notes</th>
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<tr>
<td>CHOP</td>
<td>Canine Feline</td>
<td>• CHOP is a commonly used chemotherapy protocol for canine and feline lymphoma.</td>
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<td>• Increased dose intensity can improve treatment outcome for canine lymphoma, but intensity must be adjusted based on an individual patient’s tolerance.</td>
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<td>COP</td>
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<td>• When vincristine was replaced with vinblastine in a COP-based chemotherapy protocol, feline patients experienced less GI toxicity.</td>
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<tr>
<td>Doxorubicin</td>
<td>Canine Feline</td>
<td>• Dogs with B-cell lymphoma reportedly have a higher likelihood of responding to doxorubicin than those with T-cell lymphoma.</td>
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<td></td>
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<td>• Doxorubicin (along with vincristine) is most commonly associated with neutropenic sepsis in dogs; however, use of prophylactic antimicrobial therapy decreased hospitalization and nonhematologic toxicity.</td>
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<td>• The response of relapsed feline lymphoma to doxorubicin is 22%.</td>
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<td>Lomustine</td>
<td>Feline</td>
<td>• The response of relapsed feline lymphoma to lomustine (specifically cats with relapsed GI lymphoma) is approximately 37%.</td>
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<tr>
<td>MOPP</td>
<td>Canine</td>
<td>• Dogs with T-cell lymphoma had a high response rate (98%) to MOPP chemotherapy, with median overall survival of 270 days.</td>
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CHOP = cyclophosphamide/doxorubicin/vincristine/prednisone; COP = cyclophosphamide/vincristine/prednisone; GI = gastrointestinal; MOPP = mechlorethamine/vincristine/procarbazine/prednisone
Until recently, only the effectiveness of doxorubicin in the rescue setting was reported. The response rate of relapsed feline lymphoma to doxorubicin is 22%, with a 0% response rate in cats with large-cell lymphoma.

Lomustine has been evaluated more recently, specifically in cats with relapsed GI lymphoma. The results seem more promising, with a response rate of approximately 37%, but response duration data was not reported.

A recent retrospective study on the efficacy and toxicity of radiation therapy to the abdomen as a rescue treatment for intestinal lymphoma reported a clinical response in 10/11 cats and median survival time of 214 days after radiation therapy.

CONCLUSION

New information continues to emerge regarding the diagnosis and treatment of lymphoma in both cats and dogs. This new information allows us to continue to ask and answer more specific questions, ultimately leading to advances in our ability to accurately diagnose, classify, and treat canine and feline lymphoma.

BCS = body condition score; CHOP = cyclophosphamide/doxorubicin/vincristine/prednisone; COP = cyclophosphamide/vincristine/prednisone; MOPP = mechlorethamine/vincristine/procarbazine/prednisone; PARR = PCR for antigen receptor rearrangement

References
27. Soremo KJ, Harwood LP, King LG, Drobatz KJ. Case-control study to evaluate risk factors for the development of sepsis (neutropenia and fever) in dogs receiving chemotherapy. JAVMA 2010; 236:650-656.