# Bovine Lymphosarcoma

**Janice M. Miller,** *D.V.M., Ph.D.*
*Veterinary Medical Officer*
*U.S. Dept. of Agriculture*
*National Animal Disease Center*
*Ames, IA 50010*



Lymphosarcoma is the pathologic term that describes a fatal cancer of lymph glands or lymphoid tissue. Other terms that have been used to describe this condition in cattle are leukemia and leukosis. The designation of leukosis was given by European veterinarians who first recognized the disease in an area near the Baltic Sea in the latter part of the 19th century. During the next few decades it became clear that the disease was spreading westward across Europe and this epidemiologic observation suggested the tumor was due to an infectious agent. Although death losses from lymphosarcoma were not severe, many European countries already had eradicated the more lethal infectious diseases, or at least reduced them to a very low incidence, so they were interested in doing whatever they could to maintain their high standards of animal health.

Initial efforts to control the spread of bovine lymphosarcoma were based on evidence of clinical disease (tumor). Subsequently, however, investigators found that many healthy cattle in the affected herds had persistent lymphocytosis and this was quickly accepted as an indicator of subclinical infection with an unknown etiologic agent. Using this hematologic test and epidemiologic observations, European researchers determined that there were 4 clinical forms of lymphosarcoma, only 1 of which was infectious.

The 3 forms of lymphosarcoma that are not infectious are called Sporadic Leukosis. These are the calf, thymic, and skin forms. Characteristic features of these syndromes are as follows: calf—occurs in animals less than 6 months old and tumors are found in all lymph nodes and major body organs: thymic—occurs in animals 6 to 30 months of age and tumor involves thymus and sometimes adjacent tissues or regional lymph nodes; skin—occurs in young adults, tumors are usually restricted to the skin and frequently regress.

The remainder of this discussion will focus on the form of lymphosarcoma that European scientists recognized as an infectious disease and gave the designation Enzootic Bovine Leukosis. The condition is commonly referred to as the adult form because it is seen in animals over 2 years old, the incidence increasing with advancing age. Tumors can be present in any lymph node or in other tissues, especially heart, abomasum, kidney, and spleen.

The etiologic agent of Enzootic Bovine Leukosis, or adult type lymphosarcoma, was identified in 1969 and given the name bovine leukemia virus (BLV). It is now known that BLV is a member of the Retrovirus family. All retroviruses contain a unique enzyme known as reverse transcriptase that allows the RNA virus to make a DNA copy of itself which then can be integrated into chromosomal DNA. Once the viral genome becomes incorporated into host cell genome, BLV infection is persistent for life, replicating its protein coding capacity by the same processes that are normally used for cell division. There apparently is a continual production of viral proteins in infected animals because they maintain viral antibody for life. The antibody does not eliminate infection, however, as virus is present only in the form of specific nucleic acid sequences, and virion production is not necessary to perpetuate infection. Infectious virus is produced when infected cells are removed from the animal, and antibody is either washed away or diluted below the minimal level needed for neutralization. The virus then can be detected by infection of cell cultures *in vitro* or by injection into a susceptible animal and subsequent observations for viral seroconversion.

We now know that BLV infection resides in the B lymphocyte, a cell that is produced in lymphatic tissue and circulates in peripheral blood. All research evidence indicates the major mechanism of BLV transmission between animals involves a transfer of blood. The blood also contains antibody but apparently it is diluted out in the recipient's tissue and the infected B lymphocyte, freed from its immunologic constraint, and proceeds to produce mature virions that infect B lymphocytes of the new host. It is likely that the blood must reach subepithelial tissue so some kind of penetrating or abrasive injury to skin or mucous membrane must be a prerequisite for successful mechanical transmission to occur.

Several possibilities for fomite transmission of BLV by blood contamination have been suggested and some have been experimentally shown to result in BLV infection. Various types of human actions should be considered: the use of blood administration for therapy or prophylaxis; blood sampling with a common needle; dehorning, castration, ear tagging, and tatooing; use of nose leads; performing rectal palpations with a common sleeve. Even if all these medical and management practices were conducted with care, however, there would still be numerous opportunities for blood transmission between animals due to their own physical contacts. Other possible mechanical means for virus transmission that have been suggested include insects, vaccinations and drug administrations, and skin testing for hypersensitivity reactions. It seems unlikely that these activities should be a major source of concern, however, because the amount of blood transferred by such procedures normally would be relatively small.

As any body secretion can contain blood, or at least blood lymphocytes, the materials could be a potential source of BLV infectivity. Nevertheless, research indicates that in healthy animals there are rarely enough lymphocytes in urine, nasal secretion, saliva, or semen to effect a virus transmission. This is not true for mammary secretion because cows with no evidence of clinical mastitis can produce colostrum or milk that contains significant numbers of infected lymphocytes. However, epidemiologic studies indicate that BLV infection of calves by this route is not an important mechanism of infection, probably because the antibody levels in colostrum usually are high enough to afford protection from this source. The calves at greatest risk are those from noninfected dams that receive milk from infected cows at an early age. After the first week of life calves become relatively resistant to oral infection by BLV.

Although it is accepted that the great majority of BLV infections result from some type of blood transfer after birth, a small number of calves are infected *in utero* due to virus transmission across the placenta. Epidemiologic and experimental studies have led to estimates that 3-18% of the calves born to infected dams carry the virus at birth. Our observations suggest the smaller percentage is more typical.

As indicated previously, BLV infections are life-long and most infected cattle produce relatively antibody levels for life. Therefore, serological tests afford a simple and accurate means to diagnose *infection.* It is important to recognize, however, that very few infected animals develop lymphosarcoma. Studies done in France and Canada suggest that only 0.2% to 0.3% of BLV-infected cattle develop tumors annually. If we assume an animal's productive lifetime averages 7 years, we can estimate that no more than 2% of all infected animals would be expected to die of lymphosarcoma. It is important to remember, however, that these figures were generated by observations on a large number of cattle from a large number of herds. We know there can be considerable variation of lymphosarcoma incidence from one herd to another, even when the prevalence of BLV infection is similar, so it is impossible to accurately predict the tumor loss in an individual herd. Nevertheless, it is safe to assume that tumor rates usually will be higher in herds that have a higher prevalence of infection as compared to those with only a few infected cattle.

Because the number of infected cattle directly influences the number of lymphosarcoma cases, it is important to have some knowledge of BLV prevalence in various cattle populations. We know that in the United States and Canada the virus is more prevalent in dairy herds than in beef cattle and there is some evidence that suggests the infection rate varies greatly from one geographic region to another, being generally higher in warmer climates. The surveys that have been done are limited in scope and selective in many ways, but it is obvious that BLV is a very common infection in U.S. cattle, especially in the dairy breeds. Estimates of virus prevalence in dairy cattle have ranged from 10% to 48% and in beef cattle from 1.5% to 19% depending on the survey cited. Even within a particular geographic area, however, there can be vast differences of virus prevalence between various populations, ranging from 0% in some herds to virtually 100% of all adults being infected in other herds.

After it became obvious that the mortality of BLV infection was very low compared to the morbidity, many people began to question why the virus was of much interest. The primary reason for concern can be traced back to the early recognition in Europe that leukosis was a contagious disease and the efforts made by several European countries to control or eradicate the condition. Their programs were begun long before the identification of BLV, so the regulatory policies were based on diagnosis of lymphosarcoma or persistent lymphocytosis. Denmark followed a protocol that required slaugher or quarantine of affected herds whereas other countries only restricted movement of affected cattle. Both types of program were effective in reducing the incidence of lymphosarcoma cases, but neither approach was successful in totally eradicating the disease. After BLV was discovered and researchers observed that only about 1/3 of the infected cattle develop persistent lymphocytosis, it was apparent that the European programs had been failing to identify many virus carriers. Once the serologic tests for BLV became available, however, the improvement in diagnostic sensitivity and specificity allowed the established programs to become fully successful and consequently several other countries decided to initiate control measures. The most commonly used serological test is an agar gel immunodiffusion (AGID) test which was developed in the U.S. and is commercially available here for sale to diagnostic laboratories that are certified by U.S.D.A. as having demonstrated a satisfactory proficiency in conducting the test.

It is important to recognize the dedication and financial resources that were required to achieve the BLV-free (or nearly free) status that many European countries now can legitimately claim. Some people believe that many of the health certification requirements for importation of cattle, semen, and embryos are unreasonable and designed only to present trade barriers for political reasons. Undoubtedly this may be the case in some instances. Nevertheless, we can not ignore the historical facts that illustrate the long-standing interest many Europeans have shown in controlling bovine lymphosarcoma and the efforts they have expended toward this goal. If their primary motivation for eradicating the disease was to create another standard of excellence for breeding stock, then perhaps the current situation with international trade restrictions justifies the foresight of individuals and governments that initiated such programs.

In addition to the consideration of BLV as a bovine pathogen, there is also the question as to whether the virus poses any possible risk to human health. There have been a number of epidemiologic, serologic, and biochemical studies that address this problem. The virus can be grown in human cells *in vitro,* it has been shown to infect chimpanzees and macaque monkeys experimentally, and infectivity has been demonstrated in unpasteurized milk from infected cows.

These observations illustrate that there is a potential for exposure of people to BLV and evidence that suggests humans might be susceptible to infection; however, all scientific studies that have been designed to detect human infection have been negative. These include numerous reports of work that was done with the most sophisticated serological, virological and biochemical technologies currently available. In addition to the negative findings of these laboratory studies, epidemiologic surveys have failed to show any link between BLV infections of cattle and any type of human cancer. Thus, the opinion of the majority of scientists who have examined the data favors a view that BLV should not be considered a zoonotic disease.

Even though the scientific community might not see any reason for concern about BLV as a human health risk, the reactions of news media personnel and the general public are unpredictable. Therefore, this issue must always be considered when making decisions regarding the need for action to control or eliminate the virus from a cattle population. Nevertheless, the primary consideration usually will be the financial impact of BLV on an individual herd. The incidence of lymphosarcoma cases may be high enough to justify some kind of control effort; however, this is rather unusual. More commonly, the interest in BLV is generated from impingement on export or domestic sales of infected cattle or of products derived from them (semen and embryos).

If there is a desire to control or eradicate BLV in a herd, what approaches are available? Control may be initiated by serologic testing of the adult herd followed by segregation of the positive cattle. Calves from the positive dams also must be kept isolated until colostral antibody has disappeared (about 6 months of age), and then tested to detect those animals that were infected *in utero*. Another alternative is to feed such calves negative (frozen) colostrum or a colostrum substitute; then they can be tested earlier, at 1-2 months of age. It must be recognized that this type of program will only be useful in controlling the spread of BLV within a herd and that extremely careful management will be needed to prevent human-borne transmission by blood contamination of fomites.

The establishment of programs that require removal or slaughter of all serological reactors to BLV has led to eradication of the virus in many herds and in several countries. In herds where the prevalence of infection is very high this may not be possible immediately so a control type program is used until the numbers of infected cattle are sufficiently low to permit culling of all reactors. There are many different recommendations for the frequency of testing that is desirable, but in general, the shorter the interval the better. Most programs require testing at 2-3 month intervals with 3 consecutive negative herd tests being accepted as an indication the population is BLV free. Of course any purchased replacement stock must either come from BLV free herds or they should be tested before arrival, then segregated on the premise and retested 3 months later.

Another method that has been proposed for obtaining a BLV-free population is to employ the embryo transfer technology on seropositive dams, thus assuring that there will be no spread of virus via *in utero* infections (assuming that recipient dams are seronegative). There is considerable evidence that this is a scientifically valid approach and the only consideration here is an economic one. The guarantee that offspring will be free of BLV may warrant the cost of the transfer procedure, especially in genetically superior cows.

When discussing BLV, it is important to know that another bovine retrovirus currently is of considerable interest to the scientific community and especially to the news media. This agent is being called the bovine immunodeficiency-like virus (BIV) because it is structurally and biochemically similar to the human immunodeficiency virus (HIV) that causes AIDS. I prefer to refer to the cattle virus as bovine lentivirus because there is no evidence, as yet, that it produces any disease in cattle. The term lentivirus refers to the retrovirus subfamily in which this agent is classified (BLV is in the oncovirus subfamily). The bovine lentivirus was isolated in 1972 (Van Der Maaten, *et al*) but very little research has been done on it so there is no information on its epidemiology or possible pathologic effects. However, because of current interest in the AIDS syndrome and in animal models for this type of virus infection, it is likely that more effort will be made in the future to initiate investigations on the bovine lentivirus. **Veterinarians, especially bovine practitioners, need to understand the differences between this agent and BLV so they can provide accurate information to their clients, the news media, and the public.**

#### References

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