Bovine leukemia virus: the silent thief

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Abstract
Bovine Leukemia Virus (BLV) is the causative agent of enzootic bovine leukosis. Prevalence of BLV for dairy herds in North America is about 35 to 45% of cows, and slightly lower for beef (cow-calf) operations. The virus primarily targets B-lymphocytes, causing disruptions in host cells that lead to altered leukograms, immune dysfunction, and in a small minority of cases, lymphosarcoma. Depending on the stage of infection, affected dairy cattle may have decreased milk production and longevity, and the prevalence of infection within herds is associated with decreased productivity. This paper will offer a brief review the current understanding of this disease, and practical measures to monitor BLV prevalence in herds, as well as control measures that are pragmatic and economical.

Key Words: Bovine Leukosis Virus, Diagnosis, Herd Control

Epidemiology and pathogenesis
Enzootic bovine leukosis is a contagious disease of cattle induced by a retrovirus, bovine leukemia virus (BLV). The disease complex is characterized by a persistent lymphocytosis which can culminate in B cell lymphoma.[24] The National Animal Health Monitoring System (NAHMS) 1996 study indicated that BLV is widely distributed in U.S. dairy operations with herd prevalence of 89% and an average within-herd prevalence of 45%.18 More recently, a study of 103 herds from 11 states found 94% of herds to have BLV and an average within-herd prevalence of nearly 47%.9 Similar herd- and cow-level prevalence has been described among herds in Canada. The overall trend over time has increased because, 1) rapid expansion of dairy herds has occurred, with increased inter-herd sale of animals 2) changes in management practices in many dairies that result in higher risk of exposure, such as increased injections, palpations, movement of animals among pens, and increased confinement, and 3) lack of monitoring and BLV control programs on most dairies.

Most BLV-infected cows never show outward signs of disease, and these animals are referred to as asymptomatic or aleukemic. Approximately 30-50% of BLV-infected cattle will eventually develop a persistent lymphocytosis while fewer than 5% of infected cows will ever develop malignant lymphosarcoma.[24] Since BLV seldom causes outward clinical signs of leukemia, the effects of BLV infection on overall bovine health and productivity are minor when only malignant lymphosarcoma is considered.

The progression of BLV is now known to significantly affect both humoral and cell-mediated immunity in cattle.6 There is a dramatic increase in B lymphocyte populations with significant decreases in the percentages of both CD4+ and CD8+ T lymphocyte populations. Certain type 1 cytokines from CD4+ T lymphocytes, including interleukin-2 (IL2), IL12, and interferon gamma (IFN-γ), are reduced during persistent lymphocytotic BLV infections and this altered cytokine production was suggested to suppress mitogen-induced B- and T -lymphocyte proliferation and function.[11,15,21]

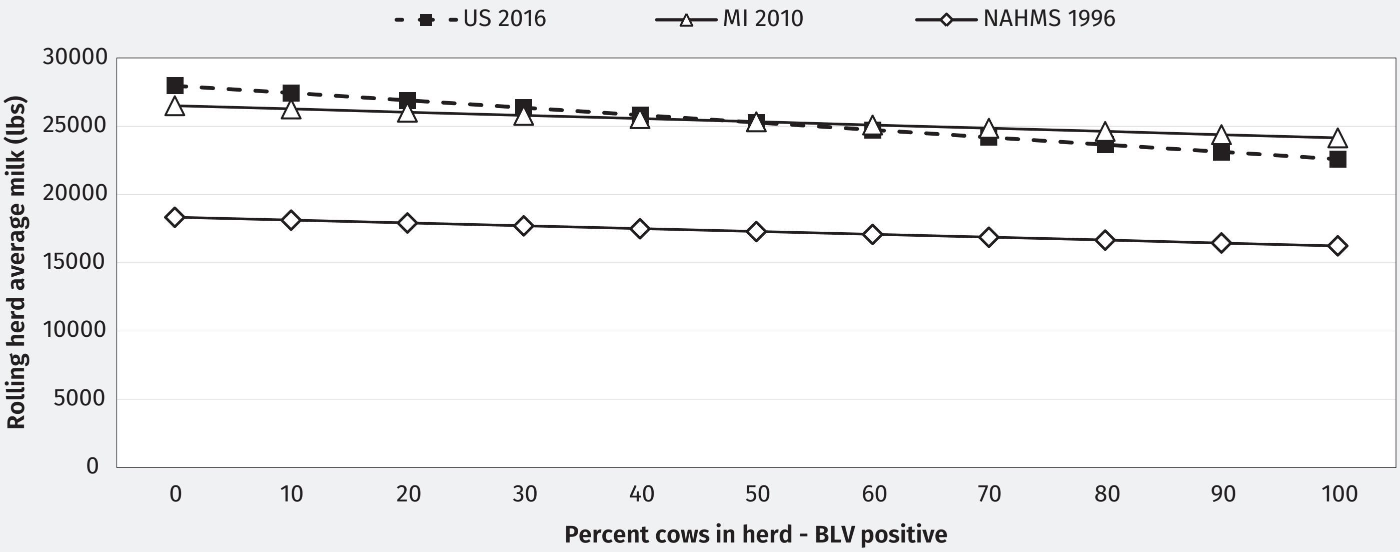
Practically, the immune dysfunction caused by BLV can impair host immune responses to both infections from other pathogens and immunization. Impairment of rotaviral immune responses in BLV-positive animals were documented in dry cows following vaccination.[1] Additionally, serum-neutralization titers for BVD Type I, and ELISA titers for anti-J5 Escherichia coli IgG2 antibodies, were lower in BLV-positive as compared to BLV-negative animals.7 Negative immune responses among BLV-infected cows to both BHV-1 and Leptospiral immunization and the clinical outcome of concurrent Johne's disease have also been reported.[5,12] Thus, BLV-induced immune dysfunction may have a greater impact on cattle health than previously believed; and economic losses from this disease are likely underestimated.

Impact of BLV on herd productivity
There is growing evidence that BLV infection negatively impacts milk production, and in particular, longevity.[2,8,20,22] It is probable that the negative effects of BLV on milk production is related to early culling of poor performing infected cows, and therefore the major effect of BLV in many herds may be realized by reduced cow longevity. As part of the USDA-NAHMS 1996 dairy study, it was estimated that the average reduction in productivity was approximately $59 per cow for BLV test-positive herds, with losses to the entire dairy industry of $285 million to producers and $240 million for consumers.[18] Additionally, a 2016 national study[16] and a 2010 Michigan study[9] found a 220 to 250 lb milk loss from the Rolling Herd Average for each 10% of cows that were infected within a herd (Figure 1).

In our 2010 Michigan study, we found that herds with higher BLV prevalence had a significantly lower proportion of older cows.[9] A follow-up study of 3,849 dairy cattle demonstrated a decreased ($P < 0.0001$) survival of cattle with BLV infection as compared to their uninfected herd mates.[2] Compared with age-matched herd mates, infected cattle were 23% more likely to be culled over the 19-month monitoring period, and cattle with the highest ELISA OD values (> 0.5) were over 40% more likely to be culled. A large Canadian study corroborated our findings in reporting that BLV positive cattle had a greater probability of being culled or dying when compared to BLV-negative cows.[19]

Controlling within-herd transmission with management
Transmission of BLV occurs through the transfer of lymphocytes harboring the infectious BLV provirus. Thua, management methods to reduce BLV transmission involve employing single-use hypodermic needles and reproductive sleeves, control of biting flies, freezing or pasteurizing colostrum, avoiding natural breeding, and avoiding blood transfer during tattoos, tail docking, extra teat removal, hoof trims, etc.[3] However, the relative importance of each route is unknown and may be different for each farm. Many of these proposed interventions were identified as statistically significant risk factors in observational surveys.[10] Direct transmission from the exchange of body fluids (nasal secretions, milk, saliva, feces, etc.) can realistically only be controlled by segregation of the infected animals from the rest of the herd.

Figure 1: Association between herd prevalence of bovine leukemia virus and rolling herd average milk production (NAHMS USDA, 1999; Erskine, 2012a; Ott, 2003; LaDronka, 2018)



Switching to single- use needles and obstetric sleeves is probably the most frequently attempted method of control. Anecdotal reports from several herds that switched to single-use needles and/or reproductive sleeves often indicate no measurable decrease in their BLV prevalence. However, there certainly are other reasons for improvement in medical hygiene in that veterinarians need to be 100% sure that they are not in any way causing any disease transmission. A three-herd intervention trial to reduce BLV transmission found that the rate of new BLV infections in cattle receiving single-use hypodermic needles and rectal examination sleeves did not differ from herd mate controls.[23] We speculate that specific management interventions by themselves showed little effect due to their inability to control all of the multiple routes of direct and indirect transmission.

Detecting super-shedders for culling or segregation

Proviral load (PVL) is the number of viral copies per cell or volume of blood, nasal secretions, saliva, milk or other fluids.[13,25] PVL differs vastly among ELISA-positive cattle. The first herd we tested 2 years ago had 12 ELISA-positive cattle, with PVL ranging from 30 to 48,826 (x 104 copies per µl of blood). This means that the cow with the highest PVL had 1,648 times more provirus per unit of blood than did the cow with the lowest PVL. Hence, the term "Super-Shedder" is used for high-PVL cattle. The standard BLV antibody ELISA test cannot distinguish low PVL from high PVL cattle.[4] Also, the correlation between ELISA antibodies and PVL is generally weak, but there is a strong correlation between BLV PVL and blood lymphocyte counts.[4]

Field data supports the idea that most natural BLV transmission is from high PVL cattle; there was no transmission in the subsequent 20 months after 20 low PVL cows were introduced into a herd of 105 BLV ELISA-negative cattle.[14] The same paper also noted that the minimum BLV infective dose from low PVL cattle would require the transfer of such a large volume of blood between animals that this would rarely happen. Cattle infected with less than 3 copies /100 cells (i.e., low PVL) did not transmit BLV to other cattle for more than 30 months.[17] All transmission was from cattle with higher PVL. This laboratory and field evidence strongly supports our working hypothesis that PVL is positively associated with infectivity. The many routes of BLV direct and indirect transmission appear to be largely dependent upon transmission from this subset of highly infectious cattle, making their removal from the herd (via culling or segregation) the obvious critical control point. Further studies have shown a low BLV proviral load in milk, saliva, nasal secretions, smegma and semen, especially when blood PVL values are high.[13,25] Focusing on transmission from so many infectious fluids could prove very difficult compared to removing the high PVL cows whose presence in the herd is the common factor and the weakest link in the various chains of transmission.

The term "Super-shedder" is relative to the distribution of PVL values within each herd. Therefore, in application, the term "super-shedders" is defined as the highest PVL cow, relative to herd mates.

First steps: The BLV herd profile

The first step for a dairy client interested in BLV control is the BLV herd profile (Erskine, et al., 2012c; Figures 2 and 3), which can be done via ELISA testing of either blood or milk samples. Milk samples submitted through the local DHI organization is usually the easiest, and can be done whether or not the herd uses routine DHI testing. The 10 most recently calved cows in the 1st, 2nd, 3rd and 4th+ lactations are tested. Don't let the producer "'pick and choose'" which cattle to test. The prevalence in each lactation group is simply the percentage of tested animals which were positive. The 1st lactation prevalence is particularly useful because it reflects transmission that occurred in the young stock. An estimate of overall prevalence in the herd is determined by taking the simple average of the 4 lactation-specific measures of prevalence. This average is independent of the herd age breakdown so it can be used to compare among herds and with historical records from the same herd. Herds with a low estimated prevalence may choose to do a whole herd test and cull positive cows to be free of the disease, providing they maintain a closed herd and make sure their young stock are also negative.

The herd profile can also help identify age groups where management should be targeted. For example, the herd profile in Figure 2 shows the typical pattern of first lactation cows entering the milking herd at a low prevalence, but then increasing prevalence in later lactations. For a herd with this pattern, management changes should be targeted to reduce transmission within the milking herd. The herd profile in Figure 3 is less common, and demonstrates a pattern where cows are entering the herd already having a high BLV prevalence, which is maintained relatively constant in later lactations. Such a herd should focus their efforts on eliminating risk factors for calves and growing heifers.

Summary

The prevalence of BLV in our U.S. dairy cows has increased from about 10% in the 1970s to almost 50%. Along with this increase in prevalence has been a new recognition of the hidden economic impact of this disease on milk production and cow longevity. Successful eradication programs in other countries have relied on culling antibody-positive cattle, sometimes preceded by temporary segregation. Management interventions to reduce intra-herd transmission may be unsuccessful if monitoring of herd prevalence and PVL cows ("super-shedders") is not done concurrently. New diagnostic and disease control approaches are under development to help dairy producers control BLV transmission.

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Figure 2: Results of a BLV herd profile from a herd in which cows enter the milking herd with low prevalence but then become positive in subsequent lactations. This pattern suggests that most transmission is in the milking herd.

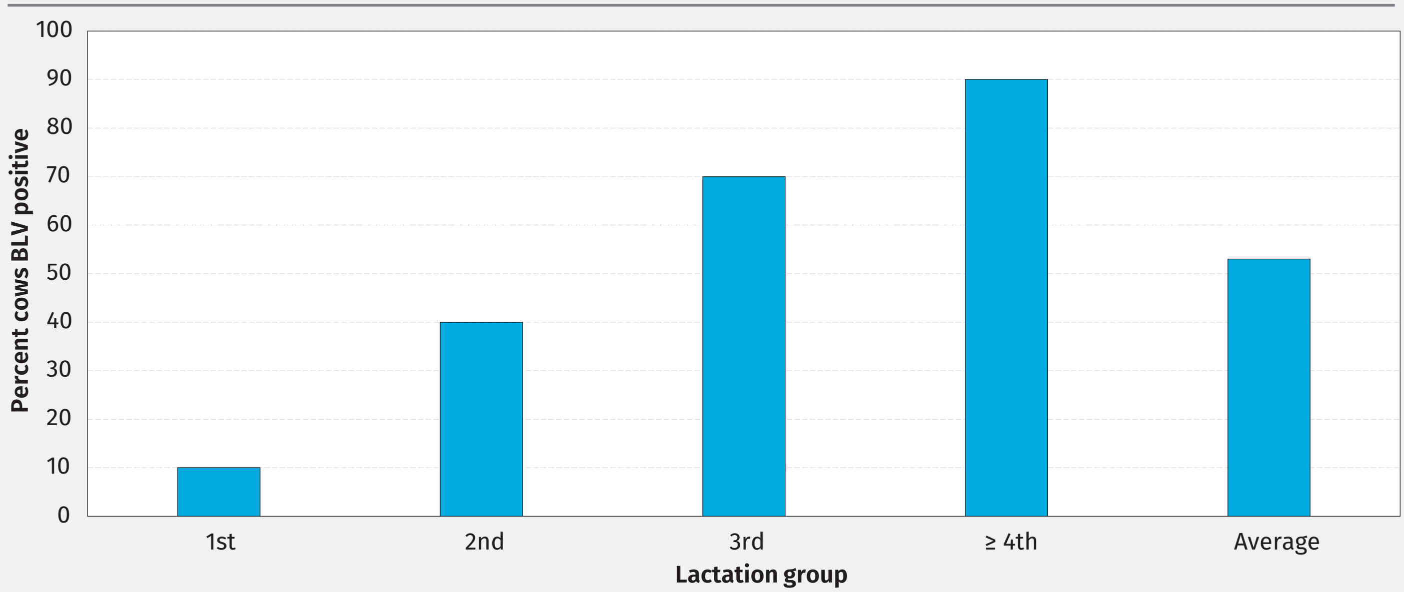
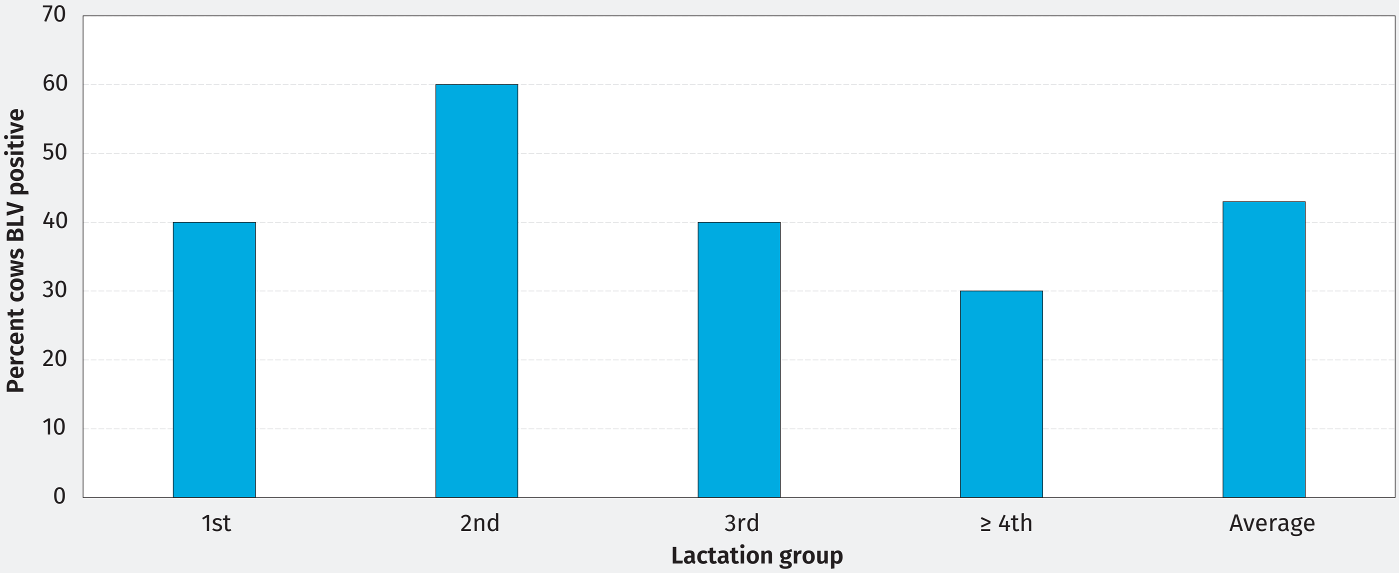


Figure 3: An example of a BLV herd profile from a herd in which a high percentage of young stock enter the milking herd already infected with BLV.



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