Hypocobalaminemia

Leonard E. Jordan, DVM
M. Katherine Tolbert, DVM, PhD, DACVIM (SAIM)
University of Tennessee

Background & Pathophysiology

Cobalamin (ie, vitamin B_{12}) is a water-soluble vitamin that plays an important role in DNA and RNA synthesis, amino acid (eg, cysteine, homocysteine) metabolism, and energy production. Following ingestion of cobalamin-rich nutrients (eg, fish, poultry, eggs, red meat, dairy products), cobalamin first binds to haptocorrin, which is produced in both the salivary gland and the stomach. In the duodenum, cobalamin is bound to intrinsic factor—a protein produced primarily in the pancreas of dogs and cats—and is later absorbed in the distal small intestine.

Any disease that affects the production of intrinsic factor or interferes with the intestinal absorption of cobalamin can cause cobalamin deficiency (***Table***, next page). Dogs and cats with exocrine pancreatic insufficiency (EPI) may have decreased production of intrinsic factor. Intestinal diseases (eg, inflammatory bowel disease, food-responsive enteropathy, intestinal lymphoma, dysbiosis, lymphangiectasia) can result in compromised ileal function and inadequate absorption of cobalamin.[1,2] Familial cobalamin deficiency resulting from a loss-of-function mutation in the receptor responsible for intestinal cobalamin absorption is an uncommon cause of hypocobalaminemia but should be considered in young patients presented with GI and neurologic signs, especially in predisposed breeds such as giant schnauzers, Australian shepherd dogs, border collies, beagles, shar-peis, and Komondors.[3,4]

EPI = exocrine pancreatic insufficiency

History & Clinical Signs

Common signs of cobalamin deficiency in dogs and cats include GI signs (eg, anorexia, weight loss), which often mimic those observed in animals with chronic GI disease; thus, the clinician may not immediately consider cobalamin deficiency as a contributing factor. Additional clinical signs of hypocobalaminemia can include failure to thrive, immunodeficiency, and neuropathies. These clinical signs may be more commonly observed in dogs with familial cobalamin deficiency. Unlike those occurring with pancreatic and GI disease, clinical signs induced by familial hypocobalaminemia are responsive to cobalamin supplementation alone.[5] In one case report, a border collie with selective cobalamin malabsorption was presented with hepatic encephalopathy secondary to hypocobalaminemia, which resolved following cobalamin supplementation.[6] In another report, a Yorkshire terrier with selective cobalamin malabsorption was presented with seizures that also resolved with parenteral cobalamin supplementation.[7] Thus, cobalamin deficiency should be considered in any animal presented with chronic GI signs, especially when in combination with neurologic signs.

TABLE

DISEASES ASSOCIATED WITH LOW COBALAMIN

Disease	Diagnostic Test(s)
Exocrine pancreatic insufficiency	Trypsinogen-like immunoreactivity
Pancreatitis	Pancreatic lipase immunoreactivity, abdominal ultrasonography
Inflammatory bowel disease	Intestinal biopsy and histopathologic examination
Intestinal lymphoma	Intestinal biopsy and histopathologic examination ± immunophenotyping, PCR for antigen receptor rearrangements (PARR)
Lymphangiectasia	Abdominal imaging, intestinal biopsy and histopathologic examination
Selective cobalamin malabsorption	Genetic testing for some patients (eg, evaluation for cubilin [*CUBN*] gene mutation), urine MMA testing

Diagnosis

Hypocobalaminemic cats often do not respond as readily as normocobalaminemic cats to treatment of the primary disease unless supplemented with cobalamin; this is unproven but, in the authors' clinical experience, is also suspected in hypocobalaminemic dogs. Thus, cobalamin deficiency is an important clinical consideration in any patient presented with signs of chronic enteropathy or pancreatic disease. Diagnosis of hypocobalaminemia requires measurement of serum cobalamin concentrations. However, patients may have serum cobalamin levels that are low-normal (250-350 ng/L) and still have critically low tissue cobalamin concentrations. In these cases, evaluating biomarkers of tissue cobalamin deficiency (eg, methylmalonic acid [MMA], homocysteine) may provide more insight, as these biomarkers often increase with tissue cobalamin deficiency in dogs.[4,8-10] In cats, MMA may be a better indicator of tissue cobalamin deficiency as compared with homocysteine.[6]

Treatment & Management

Cobalamin therapy (see ***Suggested Reading***, page 51, for dose, frequency, and administration information) should be instituted when serum concentrations fall below 250 ng/L. Additional consideration for supplementation is recommended in patients with a low-normal serum cobalamin (250-350 ng/L) and/or signs of intestinal or pancreatic disease. Hypocobalaminemia secondary to GI disease has anecdotally been thought to require parenteral supplementation of cobalamin until the intestinal or pancreatic disease was appropriately treated because of the inability to absorb cobalamin or produce intrinsic factor, respectively. However, recent research has suggested that oral administration of cobalamin in dogs and cats with chronic enteropathies[11,12] and dogs with EPI[13] is effective in restoring normal cobalamin concentrations. This may be secondary to enhanced passive absorption of cobalamin along the length of the small intestine.

Prognosis & Prevention

The prognosis for hypocobalaminemic patients depends largely on the underlying disease process and how the patient responds to treatment of the primary disease. Low cobalamin concentration is associated with shorter survival with some diseases, including EPI and multicentric lymphoma.[13,14] Lack of recovery for dogs with chronic diarrhea due to inflammatory idiopathic or neoplastic disease may also be more likely when severe hypocobalaminemia (<200 ng/L) is present.[15] The benefit of supplementation in these disease states has not been definitively proven; however, it is recommended to evaluate the patient's serum cobalamin concentration and provide supplementation when hypocobalaminemia is identified. Prognosis for familial cobalamin deficiency is good with long-term supplementation.

Clinical Follow-Up & Monitoring

Daily oral cobalamin supplementation or a 6-week course of weekly parenteral supplementation followed by a single injection 30 days later and retesting after 30 days is recommended.[1,16] Some patients, especially those with EPI or ongoing intestinal disease, may require continued monthly cobalamin supplementation. If resolution of the primary disease cannot be achieved, more frequent cobalamin administration may be required. If remission of the underlying disease (eg, food-responsive enteropathy) is achieved, long-term supplementation may not be necessary; however, re-evaluation of the patient's serum cobalamin concentration is recommended if disease relapse occurs.

EPI = exocrine pancreatic insufficiency
MMA = methylmalonic acid

See page 51 for references.

References

1. Ruaux CG. Cobalamin in companion animals: diagnostic marker, deficiency states and therapeutic implications. *Vet J*. 2013;196(2):145-152.
2. Marks S. Diarrhea. In: Washabau RJ, Day MJ, eds. *Canine and Feline Gastroenterology*. St. Louis, MO: Elsevier Saunders; 2013:103-104.
3. Giger U, Smith J. Immunodeficiencies and infectious diseases. In: Greene CE, ed. *Infectious Diseases of the Dog and Cat*. 4th ed. St. Louis, MO: Elsevier Saunders; 2012:1108.
4. Bishop MA, Xenoulis PG, Berghoff N, Grützner N, Suchodolski JS, Steiner JM. Partial characterization of cobalamin deficiency in Chinese Shar Peis. *Vet J*. 2012;191(1):41-45.
5. Fyfe JC, Giger U, Hall CA, et al. Inherited selective intestinal cobalamin malabsorption and cobalamin deficiency in dogs. *Pediatr Res*. 1991;29(1):24-31.
6. Battersby IA, Giger U, Hall EJ. Hyperammonaemic encephalopathy secondary to selective cobalamin deficiency in a juvenile Border collie. *J Small Anim Pract*. 2005;46(7):339-344.
7. McLauchlan G, McLaughlin A, Sewell AC, Bell R. Methylmalonic aciduria secondary to selective cobalamin malabsorption in a Yorkshire terrier. *J Am Anim Hosp Assoc*. 2015;51(4):285-288.
8. Ruaux CG, Steiner JM, Williams DA. Early biochemical and clinical responses to cobalamin supplementation in cats with signs of gastrointestinal disease and severe hypocobalaminemia. *J Vet Intern Med*. 2005;19(2):155-160.
9. Berghoff N, Suchodolski JS, Steiner JM. Association between serum cobalamin and methylmalonic acid concentrations in dogs. *Vet J*. 2012;191(3):306-311.
10. Rossi G, Breda S, Giordano A, et al. Association between hypocobalaminaemia and hyperhomocysteinaemia in dogs. *Vet Rec*. 2013;172(14):365.
11. Torresson L, Steiner JM, Olmedal G, Larsen M, Suchodolski JS, Spillmann T. Oral cobalamin supplementation in cats with hypocobalaminaemia: a retrospective study. *J Feline Med Surg*. 2017;19(12):1302-1306.
12. Toresson L, Steiner JM, Suchodolski JS, Spillmann T. Oral cobalamin supplementation in dogs with chronic enteropathies and hypocobalaminemia. *J Vet Intern Med*. 2016;30(1):101-107.
13. Toresson L, Steiner JM, Suchodolski JS, Spillmann T. Oral cobalamin supplementation in dogs with exocrine pancreatic insufficiency (abstract). *J Vet Intern Med*. 2017;31(4):1283.
14. Batchelor DJ, Noble PJ, Taylor RH, Cripps PJ, German AJ. Prognostic factors in canine exocrine pancreatic insufficiency: prolonged survival is likely if clinical remission is achieved. *J Vet Intern Med*. 2007;21(1):54-60.
15. Cook AK, Wright ZM, Suchodolski JS, Brown MR, Steiner JM. Prevalence and prognostic impact of hypocobalaminemia in dogs with lymphoma. *J Am Vet Med Assoc*. 2009;235(12):1437-1441.
16. Texas A&M Gastrointestinal Laboratory. Cobalamin: diagnostic use and therapeutic considerations. Gastrointestinal Library website. http://vetmed.tamu.edu/gilab/research/cobalamin-information. Accessed October 4, 2017.

Suggested Reading

Texas A&M Gastrointestinal Laboratory. Cobalamin: diagnostic use and therapeutic considerations. Gastrointestinal Library website. http://vetmed.tamu.edu/gilab/research/cobalamin-information. Accessed October 4, 2017.

9. Weese JS, Dick H, Willey BM, et al. Suspected transmission of methicillin-resistant *Staphylococcus aureus* between domestic pets and humans in veterinary clinics and in the household. *Vet Microbiol*. 2006;115(1-3):148-155.
10. Lefebvre SL, Reid-Smith RJ, Waltner-Toews D, Weese JS. Incidence of acquisition of methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, and other health-care-associated pathogens by dogs that participate in animal-assisted interventions. *J Am Vet Med Assoc*. 2009;234(11):1404-1417.
11. Lefebvre SL, Weese JS. Contamination of pet therapy dogs with MRSA and *Clostridium difficile*. *J Hosp Infect*. 2009;72(3):268-269.
12. Borriello SP, Honour P, Turner T, Barclay F. Household pets as a potential reservoir for *Clostridium difficile* infection. *J Clin Pathol*. 1983;36(1):84-87.
13. Struble AL, Tang YJ, Kass PH, Gumerlock PH, Madewell BR, Silva J Jr. Fecal shedding of *Clostridium difficile* in dogs: a period prevalence survey in a veterinary medical teaching hospital. *J Vet Diagn Invest*. 1994;6(3):342-347.
14. Weese J, Finley R, Reid-Smith RR, Janecko N, Rousseau J. Evaluation of *Clostridium difficile* in dogs and the household environment. *Epidemiol Infect*. 2010;138(8):1100-1104.
15. Galdys AL, Nelson JS, Shutt KA, et al. Prevalence and duration of asymptomatic *Clostridium difficile* carriage among healthy subjects in Pittsburgh, Pennsylvania. *J Clin Microbiol*. 2014;52(7):2406-2409.
16. Arroyo LG, Kruth SA, Willey BM, Staempfli HR, Low DE, Weese JS. PCR ribotyping of *Clostridium difficile* isolates originating from human and animal sources. *J Med Microbiol*. 2005;54(Pt 2):163-166.
17. Lefebvre SL, Arroyo LG, Weese JS. Epidemic *Clostridium difficile* strain in hospital visitation dog. *Emerg Infect Dis*. 2006;12(6):1036-1037.
18. Rupnik M. Is *Clostridium difficile*-associated infection a potentially zoonotic and foodborne disease? *Clin Microbiol Infect*. 2007;13(5):457-459.
19. Carvalho AC, Barbosa AV, Arais LR, Ribeiro PF, Carneiro VC, Cerqueira AM. Resistance patterns, ESBL genes, and genetic relatedness of *Escherichia coli* from dogs and owners. *Braz J Microbiol*. 2016;47(1):150-158.
20. Damborg P, Morsing MK, Petersen T, Bortolaia V, Guardabassi L. CTX-M-1 and CTX-M-15-producing *Escherichia coli* in dog faeces from public gardens. *Acta Vet Scand*. 2015;57(1):83.
21. Cui L, Lei L, Lv Y, et al. blaNDM-1-producing multidrug-resistant *Escherichia coli* isolated from a companion dog in China. *J Glob Antimicrob Resist*. 2017;13:24-27.
22. González-Torralba A, Oteo J, Asenjo A, Bautista V, Fuentes E, Alós JI. Survey of carbapenemase-producing Enterobacteriaceae in companion dogs in Madrid, Spain. *Antimicrob Agents Chemother*. 2016;60(4):2499-2501.
23. Belas A, Salazar AS, Gama LT, Couto N, Pomba C. Risk factors for faecal colonisation with *Escherichia coli* producing extended-spectrum and plasmid-mediated AmpC β-lactamases in dogs. *Vet Rec*. 2014;175(8):202.
24. Wedley AL, Dawson S, Maddox TW, et al. Carriage of antimicrobial resistant *Escherichia coli* in dogs: prevalence, associated risk factors and molecular characteristics. *Vet Microbiol*. 2017;199:23-30.
25. Joffe DJ, Schlesinger DP. Preliminary assessment of the risk of *Salmonella* infection in dogs fed raw chicken diets. *Can Vet J*. 2002;43(6):441-442.
26. Lefebvre SL, Reid-Smith R, Boerlin P, Weese JS. Evaluation of the risks of shedding Salmonellae and other potential pathogens by therapy dogs fed raw diets in Ontario and Alberta. *Zoonoses Public Health*. 2008;55(8-10):470-480.
27. Leonard EK, Pearl DL, Janecko N, et al. Risk factors for carriage of antimicrobial-resistant *Salmonella* spp and *Escherichia coli* in pet dogs from volunteer households in Ontario, Canada, in 2005 and 2006. *Am J Vet Res*. 2015;76(11):959-968.
28. Lefebvre SL. *Animal-Assisted Therapy Programs and Zoonoses* [thesis]. Guelph, Ontario, Canada: University of Guelph; 2013.
29. Oehler RL, Velez AP, Mizrachi M, Lamarche J, Gompf S. Bite-related and septic syndromes caused by cats and dogs. *Lancet Infect Dis*. 2009;9(7):439-447.