



Abstract

Protein-losing diseases are common in dogs and cats. They are generally categorized as 2 different syndromes: protein-losing enteropathy (PLE) and protein-losing nephropathy (PLN). These diseases have multiple effects, including gastrointestinal tract and kidney dysfunction, decreased serum proteins, cachexia, increased blood pressure, and coagulopathies. Proper diagnosis of PLE and PLN requires patients to undergo anesthesia for advanced diagnostics such as biopsy and endoscopy; however, the comorbidities these patients present with can make anesthesia challenging. This article describes how protein-losing diseases affect the patient, common comorbidities and how to address them, and how to prepare and create an anesthetic plan for these patients.



CONTINUING EDUCATION

ANESTHESIOLOGY

Protein-Losing Diseases and Anesthesia

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Protein-losing diseases are common in dogs and cats. They primarily affect 2 body systems: the gastrointestinal (GI) tract (protein-losing enteropathy [PLE]) or the renal system (protein-losing nephropathy [PLN]). These disease processes affect the body in different ways, and both require advanced diagnostics for diagnosis. Anesthetizing these patients for diagnostic procedures can be challenging and requires certain considerations to be taken.

OVERVIEW OF PROTEIN-LOSING ENTEROPATHY

PLE is an umbrella term for protein loss caused by a plethora of diseases—inflammatory, infectious, or neoplastic—that affect the GI tract. Technically speaking, any disease that prevents the GI tract from properly absorbing nutrients and proteins can cause PLE. Most patients present with

vomiting, diarrhea, and weight loss; however, they may lack one or all of these clinical signs.

In PLE, protein is not absorbed from the GI tract, resulting in the loss of the serum proteins albumin and globulin. Albumin is responsible for keeping fluid within the blood vessels and contributing to intravascular oncotic pressure. If loss of serum albumin is significant (albumin < 2 g/dL), patients can present with ascites, ventrum and limb edema, and pleural effusion (with or without respiratory distress). Globulins, which are larger molecules than albumin, are made up of antibody molecules, clotting factors, and carrier proteins. High globulin levels usually indicate inflammation or infection. However, because patients with PLE can present with high, low, or normal globulin levels, albumin is typically the protein of interest when a diagnosis of PLE is being considered. Patients with PLE also lose antithrombin and clotting factors from the

Take-Home Points

- Patients with protein-losing enteropathy (PLE) or protein-losing nephropathy (PLN) can be challenging to anesthetize due to low serum protein levels, hypercoagulability, pleural and/or peritoneal effusion, and low body condition score.
- Albumin, the serum protein responsible for maintaining oncotic pressure and for drug binding and metabolism, is the serum protein most commonly lost in PLE and PLN.
- Patients with serum albumin lower than 2 g/dL are likely to have edema, ascites, and/or pleural effusion.
- With a custom-tailored anesthesia protocol, a PLE or PLN patient can be safely anesthetized.



intestines and can be prone to hypercoagulation and pulmonary thromboembolism.^{1,2} Patients with PLE often must undergo anesthesia for upper and lower GI endoscopy with biopsy, laparoscopic GI biopsy, or abdominal laparotomy for GI biopsies.

OVERVIEW OF PROTEIN-LOSING NEPHROPATHY

PLN is a disease that affects the renal glomeruli and, as a result, the kidneys' ability to properly filter proteins. Like PLE, it can be caused by inflammatory, infectious, or neoplastic disease processes. Soft-coated wheaten terriers and cocker spaniels have a genetic predisposition to PLN.³ PLN does not require azotemia for diagnosis, and patients present with inappetence, lethargy, and, in extreme cases, edema and pleural/peritoneal effusion.^{1,2}

Patients with PLN have proteinuria (urine protein: creatine ratio > 1). These patients can also be hypercoagulable from loss of antithrombin III in the urine and because platelets become hyperresponsive in the face of hypoproteinemia.¹⁻⁴ Hypertension is a common effect of PLN and requires angiotensin-converting enzyme (ACE) inhibitor treatment. ACE inhibitors work by decreasing renal blood flow and blood pressure, which can pose problems during anesthesia.^{4,5} Patients with PLN often need anesthesia (general and multimodal) for renal biopsy, whether via ultrasonography-guided needle-core biopsy (Tru-Cut; Merit Medical Systems, [merit.com](https://www.merit.com)), abdominal laparotomy, or laparoscopy.

ANESTHETIZING PATIENTS WITH PROTEIN-LOSING ENTEROPATHY

Patients with suspected PLE do not have a “one size fits all” disease process; therefore, the anesthetist must consider several factors in designing a customized anesthetic protocol for these patients.

Preanesthesia Patient Assessment

First, a thorough physical examination should be performed, noting respiratory rate and effort, heart rate, body condition (e.g., edema, ascites, body condition score, muscle wasting), and body temperature (these patients can be cachectic, resulting in hypothermia).

Second, blood analysis—including a complete blood count (CBC), serum biochemistry panel, and prothrombin time (PT)/activated partial thromboplastin time (aPTT)—should be done prior to anesthesia and evaluated by the anesthetist. Care should be taken to ensure that the CBC shows the patient to have adequate platelets. In the serum biochemistry results, it is especially important to look at the albumin levels. PT measures the extrinsic coagulation pathways, while aPTT measures the intrinsic coagulation pathways (both measure the time it takes for a fibrin clot to form when calcium and tissue activating factor are added to a whole blood sample); both should be assessed prior to any surgical incision and biopsy.

Third, the patient's disposition and anticipated level of pain related to the procedure to be performed should be considered when formulating an anesthetic plan. If the patient is highly stressed or agitated, it will require a higher gas inhalant concentration or dose of anesthetic medications to remain at the desired anesthetic plane (also known as the minimum alveolar concentration [MAC]), which could be detrimental to cardiac output, perfusion, and blood pressure during general anesthesia. Reducing the patient's stress/agitation prior to induction of anesthesia helps improve patient outcomes and decreases the anesthetic doses needed. Providing preemptive analgesia also reduces MACs of gas inhalants and decreases mortality and morbidity.⁶

Anesthetic Drug Metabolism and Choice

Although research into how anesthesia causes unconsciousness continues, it is believed that plasma proteins, particularly albumin, play a role.⁷ Many common anesthetic drugs—such as diazepam, propofol, and gas inhalants—bind to albumin, with only the unbound portion responsible for the anesthetic effect.⁷ Because patients with PLE generally have dangerously low albumin and protein levels, the anesthetist must consider that these patients may not have enough albumin to bind anesthetic drugs, which can result in overdose, as well as prolonged drug metabolism and recovery.^{8,9}

The ability to reverse a medication can be lifesaving in patients that have an unexpected negative reaction to an anesthetic drug. The author generally lowers the initial anesthetic doses for patients with PLE, knowing they can be increased if needed. If the patient's disposition allows it, intravenous catheter placement

without any premedication reduces the amount of long-acting or irreversible medications needed.

Multimodal Anesthesia/Analgesia

Multimodal anesthesia/analgesia is very important for patients with PLE/PLN. Multimodal anesthesia/analgesia blocks different parts of the pain pathway, which allows the anesthetist to reduce the doses of individual pain medications used, as well as gas inhalants. Gas inhalants are the most potent vasodilators and decrease cardiac output compared with other anesthetic medications; therefore, decreasing the amount of gas inhalant used generally reduces the likelihood of patient hypotension under anesthesia. Decreasing the dose of each pain medication used (e.g., ketamine plus an opioid) decreases the negative effects of each drug, such as myoclonus (ketamine) and constipation and regurgitation (opioids).

Sedatives

If sedation is needed, the author's sedative of choice is dexmedetomidine with an opioid to be given intramuscularly. Dexmedetomidine has a wide dose range, can be reversed with atipamezole, and provides additional analgesia. However, because it causes vasoconstriction and bradycardia, dexmedetomidine should only be used in patients that can tolerate such effects. It should be avoided in patients with mitral valve disease and dilated cardiomyopathy.¹⁰

Acepromazine is not recommended in patients with PLE due to its inability to be reversed and the risk of vasodilation leading to hypotension under general anesthesia. Hypotension during anesthesia is a particular risk in patients with PLE because they already have low oncotic pressure from hypoalbuminemia.^{8,11}

Opioids

The opioid of choice depends on the procedure. Opioids have effects on several different receptors in the dorsal horn of the spinal cord, but most used in veterinary medicine act on the μ and κ receptors.¹² They may be full receptor agonists, partial receptor agonists, or mixed antagonist-agonists. Each of these provides different levels of analgesia and/or sedation, depending on the receptors they engage with.¹³

If the patient is not undergoing surgery and is having upper/lower endoscopy, the author generally chooses



Acepromazine is not recommended in patients with PLE due to its inability to be reversed and the risk of vasodilation leading to hypotension under general anesthesia.

butorphanol. Butorphanol is a partial μ antagonist and κ agonist, meaning that it provides mild analgesia and good sedation.¹³ It is relatively short acting (1 to 2 h) and is reversible with naloxone. On the other hand, the author avoids buprenorphine prior to anesthetic events. Buprenorphine is a partial μ agonist that provides mild sedation and moderate analgesia. It has a high affinity for the μ receptors, and reversal can be near impossible.¹⁴

If the patient is undergoing laparotomy for intestinal biopsy, then a full μ opioid is indicated. Full μ opioids are superior analgesics and should be administered prior to the start of a noxious stimulus. Hydromorphone, morphine, methadone, fentanyl, and remifentanyl can be safely administered to patients with suspected PLE. Hydromorphone and morphine cause vomiting after administration; therefore, the author recommends antiemetics be given prior to their administration. Methadone provides less sedation than hydromorphone, but it has multimodal effects—it antagonizes *N*-methyl-D-aspartate (NMDA) receptors and agonizes opioid receptors—making it a superior analgesic.¹⁵ Fentanyl is short acting and needs to be given as an intravenous bolus followed by a constant-rate infusion (CRI), which makes it titratable.

Induction Agents

For induction, the author generally chooses a benzodiazepine (e.g., midazolam, diazepam) with propofol. Diazepam requires protein binding for metabolism⁷; therefore, the author prefers midazolam as a coinduction agent. Midazolam potentiates the activity of γ -aminobutyric acid (GABA) receptors; it produces muscle relaxation with minimal cardiovascular side effects and is short acting.



Propofol is a sedative-hypnotic agent with rapid induction and recovery times that depresses the inhibitory neurotransmitter GABA; it causes myocardial depression and decreased contractility with transient hypotension and apnea. However, these effects are dose dependent. Using a benzodiazepine in conjunction with propofol reduces the amount of propofol needed, resulting in fewer undesirable side effects of propofol.¹⁶

Alfaxalone is also another option for induction. Alfaxalone is a neurosteroid that is a GABA agonist. It potentiates central nervous relaxation, resulting in minimal cardiopulmonary depression, muscle relaxation, rapid induction and recovery, and extrahepatic metabolism. If alfaxalone is given too fast intravenously, it can cause vasodilation and apnea; titrating it slowly is key to prevent these effects.¹⁷ Recovery can also be rough with tremors and noise/light sensitivity when alfaxalone is used, but when it is added with benzodiazepines and opioids, the tremors can be reduced.

Ketamine is not contraindicated in patients with PLE and is another good option for induction or analgesia due to its ability to provide analgesia when given at lower rates and as a CRI. Ketamine is a dissociative anesthetic that increases sympathetic tone, thus increasing heart rate, cardiac output, and blood pressure. Ketamine's analgesic effects come from its antagonistic effects on NMDA receptors, which are responsible for wind-up that contributes to neuropathic and chronic pain.

Fresh frozen plasma is generally chosen if the patient has coagulopathies due to PLE (e.g., increased clotting times, increased buccal mucosal bleeding time), whereas frozen plasma can be used in the face of albumin support.



Analgesic Drugs

For perioperative analgesia, it is recommended to add an opioid, ketamine, or lidocaine CRI. If the patient is undergoing upper/lower GI endoscopy, a CRI is generally not necessary other than to reduce gas inhalant requirements, especially if the patient is experiencing hypotension, tachycardia, bradycardia, or hypoventilation.

Fluid Therapy

Fluid therapy is an important consideration for patients with PLE because they can be dehydrated. IV fluids (typically crystalloids) are administered during anesthesia to help with perfusion and provide blood pressure support when the body is faced with vasodilation from gas inhalants and anesthesia medications.¹⁸ However, without albumin to provide oncotic pressure, crystalloids can cause further edema, including pulmonary edema and pleural effusion. A patient with PLE can easily become fluid overloaded with crystalloids. If serum albumin is less than 2 g/dL, the author considers colloid therapy.^{1,2} Three colloid options exist in veterinary medicine: fresh frozen plasma/frozen plasma, hetastarch, and albumin. The choice of colloid depends on the patient.¹⁹

Fresh frozen plasma is a natural colloid that has certain clotting factors and can help replenish what the patient has lost through the GI tract. Frozen plasma is a natural colloid that has minimal clotting factors but still contains albumin and antithrombin. Fresh frozen plasma is generally chosen if the patient has coagulopathies due to PLE (e.g., increased clotting times, increased buccal mucosal bleeding time), whereas frozen plasma can be used in the face of albumin support. It takes a large amount of fresh frozen plasma/frozen plasma to replenish albumin (about 22 mL/kg to raise the albumin 0.5 g/dL).²⁰

Hetastarch (VetStarch; Zoetis, [zoetisus.com](https://www.zoetisus.com)) is a synthetic colloid that mimics albumin and stays within the vasculature for 24 hours. It can be used to help provide oncotic pressure support for patients with PLE undergoing anesthesia.¹¹ Hetastarch has had some controversy with regard to causing coagulopathies and acute kidney injury. Giving less than 20 mL/kg/day and using the lowest amount possible seems to be the safest way to avoid those issues.²¹

Lyophilized canine-specific albumin has been developed for use in dogs and can be safely administered with

minimal side effects to patients with hypoalbuminemia. It can be reconstituted to the desired concentration based on patient needs.

Blood Pressure Support

Because patients with PLE lack plasma proteins to help with oncotic pressure and generally have decreased perfusion because of edema, hypotension can be a concern. Besides providing a colloid for fluid therapy during anesthesia, the anesthetist should have a backup plan should the patient be persistently hypotensive and not responsive to colloid therapy.

Vasopressors and positive inotropes are the 2 options available in veterinary medicine for blood pressure support. The 2 most common vasopressors are norepinephrine and phenylephrine. Norepinephrine is an α_1 agonist with moderate β_1 effects that increases blood pressure via vasoconstriction and increased cardiac contractility. Phenylephrine is a true α agonist and causes vasoconstriction, thus increasing blood pressure; however, it decreases heart rate and cardiac output.²²

The 2 positive inotropes available in veterinary medicine are dopamine and dobutamine. Dopamine is an α_1 , β_1 , and β_2 agonist that increases cardiac output by increasing contractility and heart rate and can cause vasoconstriction at higher doses. Dobutamine works only on β receptors, increasing cardiac contractility and heart rate while causing vasodilation. The patient's comorbidities determine which agent should be chosen.

Temperature Support

Hypothermia is a particular concern for patients with PLE. Because they are often cachectic and have low body condition scores, they quickly become hypothermic under anesthesia due to lack of insulation, as well as from heat loss through convection (open body cavities), radiation (vasodilation), conduction (lying on a cold table), and evaporation (dry air). Patients that experience hypothermia under anesthesia are at risk for decreased cardiac output, decreased drug metabolism, longer recovery times, and delayed wound healing.²³

Procedural tables and gurneys should be properly padded and active warming measures taken during anesthesia. After the patient has received its physical examination and its temperature has been measured, it

should be placed on a warm water blanket or a warm air circulating device on a low/medium setting during the premedication phase and through induction and preoperative preparation. To avoid anesthesia-induced hypothermia caused by inhalation of cold, dry anesthetic gases, a low-flow oxygen rate (6 to 10 mL/kg/min) can be used to replace only the oxygen required by the patient (i.e., no excess oxygen consumption) and warm water bags placed around the breathing circuit to warm the air the patient is breathing. Placing blankets and padding between patients and the operating table is essential.²⁴

Ventilation

Patients with PLE may not need ventilation if there is no pleural effusion. All patients should be preoxygenated prior to induction, and if pleural effusion is present, a thoracocentesis should be performed prior to anesthesia. Ventilation will be required if the patient is undergoing a laparoscopic GI biopsy as the abdomen will be filled with carbon dioxide, which decreases the functional residual capacity of the lungs and increases pressure on the diaphragm. Carbon dioxide will also diffuse from the abdomen into the bloodstream and out of the body via the lungs. Ventilating during laparoscopic procedures is imperative to help the patient breathe off the excess carbon dioxide and to prevent respiratory acidosis.

ANESTHETIZING PATIENTS WITH PROTEIN-LOSING NEPHROPATHY

Patients with PLN presenting for an anesthetic event generally have the same anesthetic considerations as patients with PLE, such as the need for a thorough physical examination, blood analysis, and assessment of patient disposition. For patients with PLN, it is important to include blood pressure as part of the physical examination as these patients are often hypertensive. Knowing what is "normal" for these patients is vital, as their body cannot adjust to a lower heart rate, blood pressure, or respiratory rate.

As for patients with PLE, blood analysis for patients with PLN should include a complete blood count, serum biochemistry panel, and clotting times. Albumin and protein levels are especially important, as are liver/kidney function measures. Urinalysis and abdominal ultrasonography should also be performed in these patients to assess kidney function. Using large



volumes of fluids during an anesthetic event can be detrimental in these patients; therefore, lower isotonic fluid resuscitation rates or a plasma or hydroxyethyl starch CRI should be used instead of regular IV fluid therapy (e.g., lactated Ringer's, Normasol-R, Plasma-Lyte).^{4,11,25}

Preanesthesia Patient Assessment

Patients with PLN generally have systemic hypertension. Although the reason is unknown, kidney disease may play a role, as kidney disease causes hypertension through sodium retention, activation of the renin-angiotensin system, and sympathetic nervous system stimulation. Patients with PLN are often prescribed ACE inhibitors for hypertension. The ACE inhibitor of choice is generally enalapril because it not only decreases proteinuria but also delays the onset of kidney failure.

When preparing for a patient with PLN to be anesthetized, the anesthetist should obtain a blood pressure measurement prior to any anesthetic medications being administered to the patient. These animals are used to perfusing vital organs at higher blood pressures; therefore, during an anesthetic event, in which hypotension is common, all measures should be taken to keep the patient's blood pressure as close to their norm as possible. The anesthetist should also ensure that the patient does not receive its ACE inhibitor the morning of the anesthetic event. If the patient is anesthetized while an ACE inhibitor is active, it can experience hypotension that is hard to correct. The author often postpones an anesthetic event if the patient has received an ACE inhibitor that day.⁵

Anesthetic Drug Metabolism and Choice

Patients with PLN usually have some form of kidney damage unless PLN is caught very early. As the kidneys are mainly responsible for filtering drugs—including anesthetic drugs—out of the body, decreased kidney function from any cause (e.g., age, glomeruli damage, sepsis) can decrease drug filtration.

If PLN is caught early, then the likelihood of kidney disease is low. However, PLN is usually not diagnosed until signs of kidney disease are present. If kidney disease is present, drug filtration will be decreased, which can increase recovery times and negative drug effects. For patients with PLN, the author likes to use

lower drug doses and short-acting, reversible anesthetic drugs. This allows for more control of the anesthetic drugs in case of any detrimental effects due to the patient's inability to properly excrete the drugs.

SUMMARY

Patients with PLE and PLN can be challenging for the veterinary anesthesia team. However, with preparation and as much diagnostic information as possible, these patients can be safely anesthetized. **TVN**

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CONTINUING EDUCATION

Protein-Losing Diseases and Anesthesia

TOPIC OVERVIEW

This article describes how protein-losing diseases affect dogs and cats, common comorbidities and how to address them, and how to prepare and create an anesthetic plan for these patients.

LEARNING OBJECTIVES

After reading this article, veterinary nurses will be able to describe how protein-losing enteropathy and protein-losing nephropathy influence the anesthetic plan for affected patients and the precautions that need to be taken when preparing to anesthetize these patients.

This article has been submitted for **RACE approval for 1 hour of continuing education credit** and will be opened for enrollment upon approval. To receive credit, take the test at **vetfolio.com** by searching the name of the article or scanning the QR code below. Free registration is required. Questions and answers online may differ from those below. Tests are valid for 2 years from the date of approval.



- Protein-losing enteropathy (PLE) and protein-losing nephropathy (PLN) are syndromes, not singular diseases.**
 - True
 - False
- Albumin is a blood serum protein responsible for which of the following?**
 - Keeping fluid within the blood vessels and contributing to intravascular oncotic pressure
 - Keeping fluid outside of the blood vessels and contributing to edema
 - Keeping proteins within the blood vessels and preventing edema
 - None of the above
- What are the 2 serum proteins?**
 - Albumin and globulin
 - Blood urea nitrogen and creatine
 - White blood cells and red blood cells
 - Albumin and creatine
- PLN is characterized by:**
 - Breakdown of the kidney glomeruli that prevents them from retaining serum proteins during filtration
 - Protein loss in the gastrointestinal (GI) tract
 - Protein not being produced by the liver
 - A and B
- Why can patients with PLE be hypercoagulable?**
 - Loss of clotting factors and antithrombin through the GI tract
 - Failure of the GI tract to make proteins
 - Failure of the kidney to make proteins
 - All of the above
- Which option is a synthetic colloid that can be administered for fluid therapy during anesthesia?**
 - Hetastarch
 - Albumin
 - Fresh frozen plasma
 - Globulin
- Short-acting, reversible drugs are not necessary for patients with PLE/PLN undergoing anesthesia.**
 - True
 - False
- Hypothermia is a concern for patients with PLE due to which of the following?**
 - Cachexia and low body condition scores
 - Low serum albumin
 - Failure of the GI tract to absorb proteins
 - Hypotension
- Kidney disease causes hypertension through which 3 mechanisms?**
 - Sodium retention, activation of the renin-angiotensin system, and sympathetic nervous system stimulation
 - Chloride retention, circulating serum proteins, hypercoagulable platelets
 - Potassium retention, activation of the renin-angiotensin system, and sympathetic nervous system stimulation
 - Sodium retention, circulating serum proteins, and sympathetic nervous system stimulation
- Enalapril is a(n):**
 - Angiotensin-converting enzyme inhibitor
 - Positive inotrope
 - Pure μ opioid
 - Analgesic