Chronic diarrhea, vomiting, and weight loss are common clinical conditions in canine general practice. The underlying causes are numerous, including poorly understood syndromes (Table 1). This article reviews gastrointestinal (GI) mucosal immunity and the following syndromes, which we collectively refer to as chronic idiopathic enteropathies, in dogs: inflammatory bowel disease (IBD), lymphangiectasia, and antibiotic-responsive enteropathy and diarrhea (ARD).

The GI diseases discussed here are chronic but may occasionally manifest acutely. The initial diagnostic evaluation involves differentiation of small bowel from large bowel diarrhea, which is an important step in creating the differential diagnosis and formulating a diagnostic plan (Table 2). Histopathologic evaluation of intestinal biopsy specimens is required to diagnose most of the conditions discussed here; thus differentiating small from large bowel disease is crucial in determining where in the GI tract to perform a biopsy. It is imperative to exclude other causes of chronic diarrhea, such as parasitism, exocrine pancreatic insufficiency, and hypoadrenocorticism, before collecting intestinal biopsy specimens.

The genetic makeup of an individual, exposure to dietary antigens, and the components of GI flora are intimately related in the development of GI disease. Individual genetic makeup dictates how the immune system reacts to antigenic exposure. For example, the immunologic response could be inappropriate and/or overwhelming, as with immunoproliferative enteropathy in basenjis, or it may be inadequate, resulting in bacterial overgrowth or colonization by pathogenic species, as may occur with ARD. The response to dietary antigens could be inappropriate, as with gluten sensitivity in Irish setters and protein-losing enteropathy (PLE) or protein-losing nephropathy (PLN) in soft-coated wheaten terriers. Chronic, idiopathic enteropathies most likely

**ABSTRACT:** Gastrointestinal disorders, including chronic diarrhea, are common in canine general practice. Many of these diseases do not have a clearly defined underlying cause, despite thorough diagnostic investigation. This article reviews several syndromes with poorly understood causes that are associated with chronic diarrhea in dogs. Because the immune system plays a central role in the pathogenesis of many of these syndromes, gastrointestinal mucosal immunity is also reviewed. Therapeutic interventions discussed in this article, including diet, immunosuppressive agents, antibiotics, probiotics, and prebiotics, are mostly aimed at modulating the intestinal immune response.
represent a deviation from the normal immune response to bacterial, endogenous, and/or dietary antigens.

**ANATOMY, HISTOLOGY, AND MUCOSAL IMMUNITY**

**Basic Gastrointestinal Anatomy and Histology**

Mucosal epithelium is composed of enterocytes, goblet cells, endocrine cells, and M cells. Enterocytes comprise approximately 80% of mucosal epithelial cells. Immature enterocytes are located within the intestinal crypts. Migration from the crypt to the villus tip occurs over 3 to 5 days as the enterocyte matures and is finally sloughed off. The lamina propria is found beneath the mucosal epithelium, and connective tissue is the primary constituent. Gut-associated lymphoid tissue (GALT) is found within the lamina propria. Enteral circulation consists of a vast network of capillaries within the villi, which supports the high metabolic demand of intestinal tissue, and lacteals, which begin within the villi and converge to form larger lymphatic vessels. GI contents are absorbed through either capillaries that enter the portal circulation or intestinal lymphatics, which ultimately empty into the vena cava.

**Inherent Protective Mechanisms**

Inherent protective mechanisms are structural and functional components of the GI tract that provide protection from potential pathogens and excessive antigenic exposure. Structural components include epithelial tight junctions, the microvillus membrane, and a surface mucous layer. Functional components include peristalsis and secretions such as gastric acid and proteolytic enzymes.

**Mucosal Immunity**

There is more immune activity within GALT than in any other part of the body. GALT is found along the entire length of the GI tract and is composed of distinct regions of lymphoid tissue, such as Peyer’s patches, that are readily visible on histopathologic examination. Components of an individual unit of GALT include the dome, follicle, and parafollicular region. The dome is composed of M cells, which are specialized enterocytes that act as antigen-presenting cells (APCs) and transport antigen to other types of APCs, such as macrophages and dendritic cells. M cells likely play an important role in sampling antigens that pass along the GI tract. The GALT follicles contain B lymphocytes, while the parafollicular region contains T lymphocytes, most of which are naïve (i.e., they have not been activated by antigen). Antigen from the gut is processed and presented to lymphocytes by APCs (Figure 1). A naïve lymphocyte becomes activated after recognizing a specific antigenic sequence, called an epitope, and then receiving a complex series of activation signals from APCs and helper T cells (CD4+ lymphocytes). Activated lymphocytes move through mesenteric lymph nodes into circulation via lymphatic drainage and return to the lamina propria. This journey from the lymphoid follicle to the lamina propria is known as lymphocyte homing and is dictated by molecular markers known as addressins (Figure 2).

There are numerous subsets of T lymphocytes, such as γ−σ and α−β. Most γ−σ T lymphocytes are negative for CD4 and CD8. Although their functions are incompletely understood, one role they likely play is the elimination of stressed or infected GI epithelium. The α−β subset of T cells contains CD8+ lymphocytes (cytotoxic T cells) and CD4+ lymphocytes (helper T cells). CD8+ lymphocytes

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**Table 1. Selected Canine Chronic Idiopathic Enteropathies and Commonly Affected Breeds**

<table>
<thead>
<tr>
<th>Enteropathy</th>
<th>Breed(s) Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory bowel diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphocytic–plasmacytic enterocolitis</td>
<td>Many</td>
</tr>
<tr>
<td>Eosinophilic enterocolitis</td>
<td>Many</td>
</tr>
<tr>
<td>Regional enteritis</td>
<td>German shepherds, others</td>
</tr>
<tr>
<td>Immunoproliferative enteropathy</td>
<td>Basenjis</td>
</tr>
<tr>
<td>Protein-losing enteropathy and nephropathy</td>
<td>Soft-coated wheaten terriers, others</td>
</tr>
<tr>
<td>Gluten-sensitive enteropathy</td>
<td>Irish setters</td>
</tr>
<tr>
<td><strong>Lymphangiectasia</strong></td>
<td>Lundehunds, small terrier breeds, others</td>
</tr>
<tr>
<td><strong>Antibiotic-responsive diarrheas</strong></td>
<td></td>
</tr>
<tr>
<td>Histiocytic–ulcerative colitis</td>
<td>Boxers, others</td>
</tr>
<tr>
<td>Shar-pei enteropathy</td>
<td>Shar-pei</td>
</tr>
<tr>
<td>Antibiotic-responsive diarrhea</td>
<td>German shepherds, others</td>
</tr>
</tbody>
</table>

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T lymphocytes recognize antigen presented by major histocompatibility complex (MHC) I on the target cell surface and can destroy that cell. CD4+ T lymphocytes recognize antigen presented in conjunction with MHC II by APCs and help promote memory and effector responses. Intestinal epithelium presents antigen mostly via MHC I, whereas M cells present antigen mostly via MHC II. CD4+ T lymphocytes most likely play an important role in promoting tolerance to food antigens and normal GI flora. CD4+ T lymphocytes also play a central role in the development of intestinal inflammation. Twenty-five percent of T cells within a given lymphoid follicle are CD8+, and the remaining 75% are CD4+, illustrating the pivotal role CD4+ cells play in mucosal immunity.

Therefore, therapy is often aimed at modulating the CD4+ subset. A certain subset of CD4+ lymphocytes, known as T regulatory cells, has become recognized for its role in promoting tolerance to GI antigens. Immunologic studies in mice have demonstrated the development of various forms of autoimmune disease, including IBD, when mice are deficient in T regulatory cells.

Plasma cells, which are derived from B lymphocytes, localize in the lamina propria and produce mainly IgA subclass 2. The primary function of IgA is to bind antigen on mucosal surfaces, such as respiratory and GI epithelium. IgA subclass 2 is more resistant than other types of immunoglobulins to proteolytic enzymes produced by enteric flora. An immunoglobulin receptor allows mucosal epithelium to bind and transport IgA into the mucous layer of the intestinal lumen. IgA is secreted by intestinal epithelium as a dimer joined by a short secretory chain (Figure 3). IgG is also found in high concentration within the intestinal lumen.

**Table 2. Differentiation of Chronic Small Bowel from Large Bowel Diarrhea**

<table>
<thead>
<tr>
<th>Clinical Finding/Parameter</th>
<th>Small Bowel Diarrhea</th>
<th>Large Bowel Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Vomiting</td>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Frequency of defecation</td>
<td>Normal or increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Blood in feces</td>
<td>Sometimes melena</td>
<td>Occasional hematochezia</td>
</tr>
<tr>
<td>Mucus in feces</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Volume of feces</td>
<td>Sometimes increased</td>
<td>Normal or decreased</td>
</tr>
</tbody>
</table>

**CANINE IDIOPATHIC INFLAMMATORY BOWEL DISEASES AND ENTEROPATHIES**

**Lymphocytic–Plasmacytic Enterocolitis**

Lymphocytic–plasmacytic enterocolitis (LPE) is the most common form of IBD. A breed predilection has not been confirmed, although purebred dogs seem to be overrepresented in the veterinary literature. Varying degrees of vomiting, weight loss, and diarrhea are observed clinically. Although most clinical signs are referable to small intestinal disease, any part of the GI tract can be affected. Intestinal inflammation with altered lymphatic function can cause GI protein loss, resulting in panhypoproteinemia (i.e., PLE). The diagnosis of LPE is based on interpreting intestinal biopsy specimens and ruling out other causes of GI inflammation. Histopathologic grading of IBD severity is based on the amount of lymphocytic and plasmacytic infiltration within the lamina propria, along with the amount and severity of intestinal villus changes. There is an effort to standardize histopathologic grading; however, evaluation is still somewhat subjective. An increase in the number of inflammatory cells in the lamina propria is the primary change in animals with LPE, and the alterations in villus architecture are probably secondary to inflammatory infiltration. The pathophysiology of this disease is incompletely understood. An increased number of IgG- and IgA-producing plasma cells and T lymphocytes have been identified in dogs with LPE compared with control dogs. The presence of lymphocytes and plasma cells most likely represents a common immunologic response to a variety of enteral antigens, including bacterial, dietary, and endogenous antigens.

Because the causes of intestinal inflammation can be multifactorial, veterinarians should carefully consider the different factors that may be involved. If an infectious cause (e.g., histiocytic–ulcerative colitis) is suspected, appropriate antibiotic therapy is warranted. Antibiotic therapy may also prove to be beneficial in some cases of IBD, presumably because certain antimicrobials (e.g., metronidazole [10 to 15 mg/kg q12h], tylosin [20 to 40 mg/kg q12h]) are thought to globally
reduce and/or alter bacterial populations in favor of less pathogenic species. Most reports of dogs and cats with IBD that is responsive to antimicrobials are anecdotal, but there is evidence from studies using rodent models and human studies demonstrating that antimicrobial administration is an important adjunct therapy for IBD.

Dietary therapy using a hypoallergenic diet is considered an important component of treating idiopathic LPE. Although the duration of response to a dietary trial varies, most dogs exhibit improvement within 2 to 4 weeks. Common dietary antigens in commercial dog foods, including wheat gluten, soy, lactose, beef, and chicken proteins, have been suspected of playing a role in disease pathogenesis. Strict hypoallergenic diets include novel protein diets (prescription exclusion diets) and hydrolyzed protein diets. Novel protein diets simply contain a protein source to which the animal has not been exposed. Hydrolyzed proteins have undergone enzymatichydrolysis to low-molecular-weight proteins, which are theoretically less antigenic.

Numerous commercial novel and hydrolyzed protein prescription diets are available to veterinarians. Commercial manufacturers should be contacted directly for a complete list of their prescription diets and components. We recommend starting with one of these diets because they are nutritionally complete and balanced as well as convenient to feed. However, while GI inflammation resolves, the GI tract may become sensitized to the protein source in the initial therapeutic diet. Therefore, if novel protein diets are used, it is recommended to switch to a second hypoallergenic diet after 6 to 8 weeks of successful therapy. Over the course of months to years, some dogs may develop sensitivity to several different diets, requiring a switch to a different hypoallergenic diet to resolve clinical signs. Dietary therapy alone may be successful in dogs with less severe clinical disease or evidence of mild inflammation from GI biopsy findings.

Immunosuppressive agents should be considered for use in dogs with more severe clinical signs, moderate to severe inflammation that is evident on histopathologic examination of the GI tract, or PLE associated with

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Figure 1. Gut-associated lymphoid tissue. Components of an individual GALT unit include the dome, follicle, and parafollicular region. The dome is composed of M cells, which sample antigen from the GI lumen. The antigen is transported to APCs, such as macrophages and dendritic cells. APCs can also extend finger-like projections between epithelial tight junctions and into the GI lumen to sample antigen directly (not shown). APCs present antigen to naïve T and B lymphocytes. The follicle contains B lymphocytes and some plasma cells, whereas most of the T lymphocytes are located in the parafollicular region.
IBD. Guidelines for immunosuppressive therapy follow.  

**Prednisone** (1–3 mg/kg/day PO) is commonly used at a tapering dose. The exact dose and duration of prednisone are based on individual response to therapy. For dogs with concurrent PLE, immunosuppressive doses should be continued until protein (albumin and globulin) concentrations stabilize, ideally within the normal range. As a general guide, prednisone doses can be tapered by 25% of the initial dose every 2 to 3 weeks as clinical signs and protein concentrations resolve.

Like other glucocorticoids, prednisone exerts multiple immunosuppressive and immunomodulatory effects.Steroid-induced lymphopenia is caused by sequestration of lymphocytes and decreased release from the bone marrow. T- and B-cell circulation decreases. Antigen processing and presentation by APCs to T cells are also inhibited. Lymphocyte sensitivity to inflammatory mediators is decreased. Because of these combined immunosuppressive effects, particularly the effect on T lymphocytes, prednisone (or another, similar glucocorticoid) is often used to reduce intestinal lymphocyte infiltration. Iatrogenic hyperadrenocorticism is a common side effect of prednisone administration at the recommended dose. Clients should be informed that polyuria and polydipsia will likely occur and that serious complications, such as thromboembolic disease, opportunistic infections, and muscle wasting, are possible.

**Azathioprine** (50 mg/m² or 1 to 2 mg/kg PO q24h, initially) is a purine antimetabolite that is thought to exert most of its immunosuppressive effects via induction of T-cell apoptosis. T cells are thought to play a pivotal role in intestinal inflammation. Azathioprine can be used to treat canine IBD if prednisone alone is ineffective or iatrogenic hyperadrenocorticism becomes a problem. The dose is usually reduced by 50% after 2 to 6 weeks of therapy. Major side effects of azathioprine reportedly include bone marrow toxicosis and hepatotoxicosis.

**Budesonide** is a glucocorticoid that can be used to induce remission, with a success rate similar to that of...
An immunoglobulin molecule is composed of two heavy and two light chains that contain variable and constant regions. The constant region contains binding sites for complement and can interact with binding sites on cells such as macrophages. The variable region recognizes and binds specific antigenic sequences. Secretory IgA is unique because the constant regions of two IgA molecules are joined by a J chain during transport to the mucosal surface.

Figure 3. Secretory IgA. An immunoglobulin molecule is composed of two heavy and two light chains that contain variable and constant regions. The constant region contains binding sites for complement and can interact with binding sites on cells such as macrophages. The variable region recognizes and binds specific antigenic sequences. Secretory IgA is unique because the constant regions of two IgA molecules are joined by a J chain during transport to the mucosal surface.

Prednisone, in people with certain types of IBD. The mechanism of action is similar to that of other glucocorticoids (see section on prednisone). Budesonide differs from other glucocorticoids because it reportedly has potent topical antiinflammatory activity on the GI mucosa and minimal systemic side effects in dogs. However, significant suppression of the hypothalamic–adrenocortical axis still occurs, making iatrogenic adrenal insufficiency possible following rapid drug withdrawal. Budesonide should be considered for use in dogs experiencing intolerable side effects from traditional glucocorticoid therapy. When budesonide therapy is initiated in humans, the manufacturer recommends concomitant tapering of other glucocorticoids to avoid steroid withdrawal. Until more pharmacokinetic and clinical information is available for dogs, we cannot recommend routine use of budesonide.

Mycophenolate mofetil is an immunosuppressant used in humans to treat various conditions and prevent organ transplant rejection. Mycophenolate is metabolized to mycophenolic acid, which inhibits an enzyme involved in DNA synthesis that primarily affects rapidly dividing cells. Mycophenolate prevents B- and T-lymphocyte proliferation, reduces lymphocyte accumulation at sites of inflammation, and reduces levels of interferon-α. Therefore, mycophenolate therapy can reduce intestinal lymphocyte infiltration and division of lymphocytes within the lamina propria. It has been used as an adjunctive immunosuppressive agent in combination with other drugs, such as glucocorticoids, to treat a variety of autoimmune conditions. Mycophenolate use in veterinary referral centers is fairly common. To our knowledge, however, no clinical trials have evaluated the use of mycophenolate to treat LPE. Although mycophenolate appears to be an effective immunosuppressive agent, its main side effects in humans and dogs are vomiting and diarrhea. Unfortunately, mycophenolate has been shown to induce significant histologic changes in the gut of humans and dogs. We discourage routine use of mycophenolate until more detailed clinical and pharmacokinetic information is available.

Cyclosporine A is occasionally used to treat severe IBD that has not responded to conventional therapy or to induce rapid immunosuppression. Cyclosporine A inhibits T-cell proliferation by blocking interleukin-2 transcription. Lymphocytes and other rapidly dividing cells also become arrested in the G0–G1 phase of the cell cycle. Primarily T cells appear to be affected by cyclosporine A administration; however, B- and plasma-cell function is also likely inhibited. Because cyclosporine A appears to cause potent disruption of T-cell function, it is a logical choice to treat cases of LPE refractory to other forms of immunosuppressive therapy. The effectiveness of cyclosporine A in treating human IBD is still questionable. However, a reduction in clinical signs and T-cell numbers in duodenal biopsy specimens was noted following cyclosporine A therapy in a recent study of dogs with IBD refractory to steroid therapy.

Other therapies, such as salicylates or adjunctive therapies (e.g., probiotics, prebiotics), may be beneficial in some cases of LPE. Salicylates, including sulfasalazine, olsalazine, and mesalamine, are used primarily to treat large bowel inflammation in dogs. Sulfasalazine (10 to 30 mg/kg PO q8h) is the most common form and consists of 5-aminosalicylate linked to sulfapyridine. Large bowel microflora cleave the linkage between the 5-aminosalicylate and the sulfapyridine. Doses can be decreased by 25% to 30% every 2 to 3 weeks as clinical signs resolve. Keratoconjunctivitis sicca is the most common side effect in dogs; therefore, veterinarians should periodically assess tear production when using these drugs. Other reactions to the sulfa or salicylate portion of these drugs are also possible.
**Probiotics** are live microorganisms that can be added to the diet to modulate intestinal flora. Probiotics are used to treat various forms of IBD in humans, and many randomized, double-blind trials have exhibited their benefit.\(^1\)\(^8\) Organisms such as *Lactobacillus* and *Saccharomyces* are nonpathogenic and can be administered with food to animals.\(^3\),\(^3\),\(^2\) There are little clinical data\(^3\) evaluating the use of probiotics to treat diarrhea in veterinary patients. However, a high-quality canine probiotic formulation produced by a reputable manufacturer would be a logical choice for probiotic therapy in dogs. Possible mechanisms of action include reduction in the growth of pathogenic species and the intestinal mucosal inflammatory response.\(^3\),\(^3\),\(^4\),\(^5\)

**Prebiotics** are poorly absorbed carbohydrates or oligosaccharides (e.g., bran, psyllium, inulin, fructooligosaccharides) that stimulate the growth of bacterial organisms such as *Bifidobacterium* and *Lactobacillus*. These organisms produce short-chain fatty acids, which are essential for mucosal metabolism and health within the large bowel.\(^3\) Their use in human medicine is currently under investigation; however, prebiotics are relatively safe and cost-effective, making them a good addition to long-term therapy.\(^1\)\(^8\)

**Eosinophilic Enterocolitis**

Eosinophilic enterocolitis (EE) is less common than LPE in dogs.\(^3\)\(^6\) It is clinically indistinguishable from LPE, although eosinophilia is sometimes found on a complete blood count. Eosinophilic infiltration can occur anywhere along the GI tract, causing a constellation of clinical signs. Eosinophilic intestinal disease has been reported in mixed-breed and a variety of purebred dogs.\(^3\),\(^4\),\(^2\) Rottweilers and German shepherds may be predisposed to EE.\(^3\) One report\(^3\)\(^8\) suggests that most affected dogs are younger than 5 years of age. However, the exact sex and age distributions are uncertain. As with any workup for GI disease, parasitism should be ruled out. Empiric deworming is strongly recommended before intestinal biopsy specimens are obtained. In a dog with GI signs and peripheral eosinophilia, hypoadrenocorticism and hypeeosinophilic syndrome should also be considered in the differential diagnosis.

The histopathologic criteria of EE have varied somewhat in the veterinary literature, and as with LPE, there is an effort to standardize histopathologic grading schemes to achieve more uniformity. In general, histopathologic examination shows eosinophils as a significant proportion of the inflammatory infiltrate or as the predominant infiltrating cell within the lamina propria with varying degrees of villus architecture change. Lesions may be distributed more focally than in LPE; however, the GI tract can be diffusely affected.\(^3\),\(^3\) Proliferative lesions resembling obstructive tumors have also been reported\(^3\)\(^8\) in EE. The large bowel may be more affected by these proliferative lesions. The presence of eosinophilic infiltration implies hypersensitivity, and dietary antigens are thought to play a predominant role in this disease. Therapy for EE is identical to that for LPE.

**Regional Enteritis**

Vomiting, diarrhea, weight loss, and fever can occur in dogs with regional enteritis. German shepherds appear to be overrepresented in veterinary reports. Affected dogs tend to be male and have an average age of 5 years.\(^4\),\(^1\)\(^2\) Thickened, obstructive lesions are found most often in the terminal ileum but may affect other areas of the large and small bowels. Lesions may be visualized by ultrasonography or contrast radiography. Obstructive lesions have been surgically removed.\(^4\) Histopathologic examination can reveal granulomatous infiltration and stenosis of the intestinal lumen.\(^4\),\(^1\)\(^2\) Other regions of the intestine can be normal. Trichuriasis should be considered a primary diagnostic differential for regional enteritis. Clinical and histopathologic findings similar to those for regional enteritis, in which *Trichuris vulpis* eggs have been visible within inflamed tissue, have been reported.\(^4\)

Historically, dogs have responded poorly to treatment. Resolution of inflammatory lesions was reported in one German shepherd treated with a combination of surgery, prednisone, and sulfasalazine.\(^4\)

**LYMPHANGIECTASIA**

Lymphangiectasia is caused by abnormal dilation of the mucosal and submucosal lymphatics within the GI
tract. In the veterinary literature, the terminology used to describe the various causes of lymphangiectasia can be confusing. The two basic classifications are primary and acquired lymphangiectasia.\(^4\) Primary lymphangiectasia is caused by abnormally formed lymphatics and is considered a congenital disorder. Intestinal lymphatic drainage is reduced or absent, leading to dilation of the abnormal lymphatic vessels and a massive loss of protein, fluid, and cells into the lumen of the intestine. Lipogranulomatous lymphangitis may also occur and exacerbate lymphatic dysfunction in cases of primary lymphangiectasia. Acquired lymphangiectasia results from lymphatic blockage or elevated venous pressure. Lymphatic blockage is caused by inflammatory or neoplastic infiltrates. Inflammation within the intestinal wall can be the primary lesion (e.g., IBD), and lymphatic inflammation and dilation ensue as inflammatory cells migrate via the lymphatics. Sometimes, there is minimal intestinal inflammation, and moderate or severe lipogranulomatous lymphangitis is visible within mesenteric lymphatics.\(^4\) In these cases, it is often unclear which abnormality was the initiating event—leaky lymphatic vessels, which result in lymphangitis and lipogranuloma formation, or lipogranuloma formation, which causes lymphatic obstruction. Occlusion of lymphatic flow secondary to neoplastic infiltration or, less commonly, abdominal or thoracic masses may occur. Portal hypertension resulting from cirrhosis, constrictive pericardial diseases, or right-sided heart failure can result in impaired lymphatic return and thus lymphatic dilation.\(^2\)

Any canine breed may be affected by primary or secondary lymphangiectasia. However, there may be a greater percentage of affected dogs among small terrier breeds and Lundehunds (see section on breed-specific enteropathies).\(^2\) Diarrhea seems to be the most consistent clinical finding in dogs with lymphangiectasia.\(^4\)–\(^7\) Small bowel diarrhea is more common; however, large bowel diarrhea or a combination of both may occur. Vomiting, weight loss, and ascites occur frequently but may not be present in all cases.\(^4\) Abnormal laboratory findings, including hypoalbuminemia, hypoglobulinemia, lymphopenia, hypocholesterolemia, and hypocalcemia, may not always be present. The severity of hypoalbuminemia roughly correlates with the severity of histopathologic lesions.\(^4\) Hypocalcemia consistently occurs in dogs with lymphangiectasia and appears to be multifactorial. The most obvious factor is an overall loss in bound calcium resulting from hypoalbuminemia. However, the ionized calcium level is also below the reference range in affected animals. This is thought to result from poor absorption of calcium, lipogranuloma formation within the lymphatics, and poor absorption of vitamin D from the gut.\(^4\),\(^5\)

A diagnosis of lymphangiectasia can be made following evaluation of intestinal biopsy specimens, which can be obtained endoscopically or surgically; each method has advantages and disadvantages. A potential disadva-

**Intestinal biopsy specimens are an important aid in diagnosing certain types of enteropathies. It is important to recognize that the manifestation of clinical disease does not always correlate with the degree of histopathologic lesions.**

The treatment of primary lymphangiectasia is targeted mainly toward reducing the amount of fat in the diet. Commercial fat-restricted diets are the logical choice in treating less severe cases. If the dog is anorectic or will not initially eat commercial diets, a home-cooked diet can be offered. One part skinless turkey breast plus two parts boiled, skinless white potato is highly palatable and fat restricted.\(^8\) If the dog responds to therapy, a more nutritionally complete home-cooked diet can be offered, or the dog can be transitioned to a commercial fat-restricted diet. The treatment of lymphangiectasia associated with
lipogranulomatous lymphangitis and secondary to IBD relies on reducing the amount of inflammatory infiltrate within the lymphatics in conjunction with offering a fat-restricted diet. Lymphangiectasia may resolve following successful treatment of the principal cause, such as LPE or EE (as already described). However, the long-term prognosis in many of these cases can be poor.

**BREED-SPECIFIC ENTEROPATHIES**

**Immunoproliferative Enteropathy in Basenjis**

Male and female basenjis 3 years of age are most commonly affected by immunoproliferative enteropathy. Alopecia and hyperpigmentation of the skin, particularly the pinnae, are observed in many affected dogs.49 The disease is generally characterized by episodic diarrhea progressing to constant diarrhea over time.50 The initial bouts of diarrhea are often preceded by a stressful event. Low or low-normal thyroxine levels have been reported in affected dogs, but it is unclear whether hypothyroidism plays a role in the development of alopecia and hyperpigmentation, which has occurred in some dogs. Severe hypoalbuminemia (<1.0 g/dl) can occur.51,52 A unique feature of this disease is a progressive increase in serum globulin concentration due to increased IgA production.53 This is distinctly different from other forms of IBD in which PLE is characterized by panhypoproteinemia. Gastric and small intestinal thickening with loss of normal intestinal layering can be observed during ultrasonographic examination.54

Gastric mucosal hypertrophy, marked lymphocytic infiltration of the stomach, and hyperplasia of secretory cells are commonly noted during histopathologic examination. Lymphocytic–plasmacytic infiltration of the small intestine can also be noted. All regions of the small intestine can be affected, with the most severe lesions generally being found proximally.49,52 In several older basenjis, LPE has progressed to intestinal lymphoma.50 The pathophysiology of this disease is complex, including severe inflammatory cell infiltration and hypertrophy of the gastric wall, intestinal inflammatory cell infiltration with albumin loss, and circulating immunocomplex deposition. Renal deposition of circulating immunocomplexes can lead to glomerulonephritis, which has been reported in some affected basenjis.50,52 Deposition of immunocomplexes within the thyroid is thought to contribute to thyroid atrophy.

Tylosin, metronidazole, and trimethoprim–sulfonamide antibiotics have been used to treat suspected intestinal bacterial overgrowth. H2-receptor blockers or proton pump inhibitors may also be beneficial in alleviating signs associated with gastric irritation. Immunosuppressive doses of steroids have alleviated clinical signs in some basenjis. Unlike in other forms of IBD, limited-antigen dietary therapy is thought to be minimally beneficial, but a highly digestible diet should be initiated. One report49 suggested the following immunosuppressive regimen: prednisolone administered at a dose of 2.2 mg/kg/day PO (divided) for 5 days and then, if the patient responds, 1.1 mg/kg/day (divided). In this report,49 prednisolone (1.1 mg/kg PO) was continued for 6 months on alternate days and then gradually withdrawn. Initial improvement is generally noted following antibiotic and glucocorticoid therapy; however, relapse is common. Survival times are generally less than 2 years following the initial onset of diarrhea.50

**Protein-Losing Enteropathy and Nephropathy in Soft-Coated Wheaten Terriers**

Middle-aged, female soft-coated wheaten terriers are commonly affected by PLE and PLN.55 Vomiting and weight loss are typical presenting signs. PLE often precedes PLN. Glomerular immunocomplex deposition resulting from enteritis is thought to be the inciting cause of PLN.55 A serum biochemistry profile often shows evidence of panhypoproteinemia. Intestinal infiltration is typically lymphocytic–plasmacytic but can be eosinophilic or can involve a mixed population of inflammatory cells. Affected dogs seem to be extremely
sensitive to dietary antigens, although it is unclear whether the dietary sensitivities that develop are primary or secondary. One study demonstrated positive gastric mucosal reactions to extracts containing milk, lamb, wheat, and chicken. During a dietary trial, the same study also identified adverse reactions to corn, tofu, cottage cheese, milk, and farina (cream of wheat). Clinical signs included vomiting, diarrhea, and pruritus. A wheat gluten dietary trial in an earlier study demonstrated a significant decrease in serum globulin concentrations and mild increases in intestinal lymphocytes and plasma cells, which were collected via endoscopic biopsy. The treatment is similar to that of LPE, with dietary therapy being highly important. The canine fecal α1-protease inhibitor test can be used to detect early intestinal disease in soft-coated wheaten terriers. In soft-coated wheaten terriers with PLE, an E.R.D.-HealthScreen (Heska) test for microalbuminuria should be periodically conducted or a urine protein:creatinine ratio evaluated for evidence of concurrent PLN.

**Gluten-Sensitive Enteropathy**

Gluten-sensitive enteropathy has been reported in certain familial lines of Irish setters and is thought to occur as an autosomal recessive mode of inheritance. A similar condition in humans is known as celiac disease. Affected dogs are generally younger than 1 year. Clinical signs include diarrhea and poor body condition. Gluten, which is found in wheat products, contains a polypeptide known as gliadin. Intestinal histopathologic findings in affected Irish setters are similar to findings in patients with LPE. Increased intestinal permeability and decreased brush border enzymatic function have been demonstrated in affected dogs. In one study, pups that were fed a gluten-free diet from weaning showed superior intestinal function compared with a second group that was fed gluten from weaning. Because the intestines are more permeable in weanling pups, part of the disease pathogenesis may result from abnormal processing of dietary antigens, which then leads to an aberrant immune response. Dogs managed on gluten-free diets exhibited a decrease in clinical signs, reduction in the severity of histopathologic lesions, and improvement in intestinal enzymatic function.

**Protein-Losing Enteropathy in Lundehunds**

The Lundehund is a small Norwegian breed similar to the spitz. Diarrhea and vomiting as well as edema and ascites, which result from panhypoproteinemia, can occur in Lundehunds with PLE. The age of diagnosis ranges from 20 months to 7 years. Males and females are both affected. A recent report regarding Lundehunds in North America showed evidence of PLE in almost half of the animals tested. Forty-nine percent of the dogs had abnormal fecal canine α1-protease inhibitor concentrations. Plasma cytic infiltration of the lamina propria with lacteal dilation can be observed on histologic examination. The associated lymphangiectasia has characteristics of primary and acquired lymphangiectasia. Electron microscopy of Lundehund intestine has revealed changes consistent with abnormally formed lymphatics. Histopathologic examination of affected Lundehunds has demonstrated inflammatory cell infiltrate in the intestinal lamina propria and lymphatics consistent with acquired lymphangiectasia. The severity of histopathologic lesions seems to decrease in the distal jejunum and ileum.

No specific treatment has been determined for affected Lundehunds. Because lymphangiectasia is the predominant finding in this disease, the treatment recommendations in the lymphangiectasia section of this article can be followed.

**ANTIBIOTIC-RESPONSIVE DIARRHEA**

**Histiocytic–Ulcerative Colitis**

Histiocytic–ulcerative colitis was originally reported in boxers (i.e., boxer colitis) but has also been diagnosed in French bulldogs, a mastiff, an Alaskan malamute, and a Doberman pinscher. Females are more commonly affected than males. Interestingly, six of seven boxers in one report exhibited brindle coat coloring. Large bowel diarrhea is the predominant clinical finding in...
these dogs; however, varying degrees of weight loss can occur. Abnormalities visible during histopathologic evaluation include mucosal ulceration and infiltration of the lamina propria with high numbers of periodic acid–Schiff–positive macrophages (histiocytes).69–71

This disease has historically responded poorly to conventional therapy, often resulting in euthanasia. Conventional treatment included administration of glucocorticoids, azathioprine, sulfasalazine, and antibiotics as well as fiber supplementation. Recent publications describing the use of enrofloxacin as the sole agent or in combination with other antibiotic therapy have reported complete resolution of diarrhea in all dogs with confirmed histiocytic–ulcerative colitis. Conventional therapies failed in several of the dogs, which remained free of clinical signs following enrofloxacin therapy. Although the duration of treatment varied from 2 to 21 months and enrofloxacin was used in combination with other drugs (i.e., metronidazole, amoxicillin) in several cases, there is convincing evidence that administration of enrofloxacin at standard dosages resolves canine histiocytic–ulcerative colitis.72,73 In most of the dogs, diarrhea resolved within 7 days, and histiocytic infiltration was reduced or resolved on subsequent histopathologic evaluation. A recent report by Van Kruiningen et al74 has identified the most likely infectious cause. Macrophages in the lamina propria, submucosa, and regional lymph nodes of affected boxers were examined for immunoreactivity to polyclonal Escherichia coli antibody. Ten of 10 samples exhibited immunoreactivity. The identification of E. coli antigen within macrophages, combined with the response to enrofloxacin therapy, indicates that E. coli is the most likely cause of histiocytic–ulcerative colitis.74

Enteropathy in Shar-Peis

A poorly characterized enteropathy affects shar–peis. Clinical signs include persistent diarrhea and weight loss. Small bowel diarrhea is most common; however, large bowel diarrhea can also occur.75 Shar–peis reportedly have various types of immunodeficiency. In at least one report,76 five of six shar–peis with IgG deficiency exhibited GI signs. It is tempting to speculate that immunodeficiency plays a central role in the development of the enteropathy. The diagnostic approach in affected dogs is similar to that in any other dog exhibiting signs of chronic diarrhea, and the cause may be multifactorial, including both IBD and alterations in bacterial flora (see sections on LPE and ARD).

Antibiotic-Responsive Enteropathy and Diarrhea

A recent trend in the veterinary literature is to rename or redefine the syndrome known as small intestinal bacterial overgrowth (SIBO) as ARD.77 This is because of a lack of consensus on what defines SIBO, and patients that are responsive to antibiotic therapy may not have bacterial overgrowth. For the purposes of this discussion, ARD and SIBO are included together. It is important to remember that ARD/SIBO may be secondary to other disease processes, such as exocrine pancreatic insufficiency or IBD.

Greater than 10^5 CFU/ml of aerobic bacteria or 10^4 CFU/ml of anaerobic bacteria cultured from duodenal juice was historically considered to be consistent with SIBO.76 The clinical relevance of these numbers is questionable because many healthy dogs have had much higher culture results.77 In addition, cobalamin (vitamin B12) and folate concentrations have not been found to reliably correlate with bacterial culture results or a response to antibiotic therapy.78,79

In dogs with ARD/SIBO, overall intestinal bacterial counts do not necessarily decrease following antibiotic therapy.77,78,80 The predominant current theory is that antibiotic therapy causes a change in the population dynamics of intestinal flora, tipping the balance toward bacterial species or subtypes less likely to be involved in the pathogenesis of diarrhea.

German shepherds are overrepresented in reports of ARD/SIBO. Low serum and mucosal concentrations of IgA have been demonstrated in German shepherds compared with other breeds.81,82 One factor that may explain the difference between clinically affected and unaffected German shepherds is differences in cellular immune responses between the two groups. A second and possibly more important factor is the overall balance of intestinal flora and its role in the development of diarrhea. The validity of testing fecal IgA has recently been questioned.83 This report cites variation in immunoglobulin measurements in a single defecation between individuals of the same breed and between different breeds as well as a lack of adequate controls as limitations in determining normal and abnormal fecal immunoglobulin concentrations. Therefore, the role that IgA deficiency plays in German shepherds with chronic enteropathies is still unknown. German shepherds are also predisposed to IBD. ARD/SIBO may be part of the spectrum of IBD in this breed rather than a syndrome of bacterial overgrowth due to immunodeficiency.
CONCLUSION

The predominance of purebred dogs affected by many of these enteropathies stresses the importance of the genetic or immunologic component in the development of disease. The immunologic reaction can be uncontrolled, inappropriate, or poorly responsive. Equally important is antigenic exposure. The role of some dietary antigens, such as gluten, can be clearly defined, but the role of most dietary antigens remains poorly defined. The role of bacterial antigenic exposure also remains unclear. Is *E. coli* the only causative organism, or are multiple organisms involved in the development of histiocytic–ulcerative colitis? What role do bacterial antigens and/or bacterial populations play in the pathogenesis of ARD/SIBO and IBD? Does mucosal IgA deficiency cause ARD/SIBO and/or IBD in German shepherds? Although there is still much to be learned regarding the syndromes discussed in this article, many dogs benefit from therapies aimed at reducing the antigenic load and modulating the inflammatory response within the GI tract. Therapies, including dietary manipulation, antibiotics, and immunosuppressive drugs, may be successful alone or in combination in treating a variety of chronic idiopathic enteropathies in dogs.

REFERENCES


(continues on p. 306)
Mucosal Immunity and Chronic Idiopathic Enteropathies in Dogs (continued from p. 302)

### ARTICLE #2 CE TEST

This article qualifies for 2 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. **Subscribers may purchase individual CE tests or sign up for our annual CE program.** Those who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. CE subscribers can take CE tests online and get real-time scores at [CompendiumVet.com](http://CompendiumVet.com).

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
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<tbody>
<tr>
<td>1. GALT is found within the ________ of the intestine.</td>
<td>a. serosa c. lamina propria b. lamina dura d. Peyer’s patch</td>
</tr>
<tr>
<td>2. CD4+ T cells recognize antigen presented by</td>
<td>a. MHC II. c. MHC I. b. CD8+ T cells. d. neutrophils.</td>
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<tr>
<td>3. IgA is secreted as ________ by intestinal epithelium.</td>
<td>a. chimera c. a J chain b. a dimer d. pentamer</td>
</tr>
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<td>4. The most common form of IBD in dogs is</td>
<td>a. regional enteritis. c. LPE. b. gastroenteritis. d. EE.</td>
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<td>6. Primary lymphangiectasia is characterized by</td>
<td>a. right-sided heart failure. b. restrictive pericarditis. c. abnormally formed lymphatics. d. lymphatic drainage of intestinal inflammatory infiltrates.</td>
</tr>
<tr>
<td>7. Which statement regarding immunoproliferative enteropathy in basenjis is correct?</td>
<td>a. Survival times are generally less than 2 years following the initial onset of diarrhea. b. Survival times are generally less than 6 months following the initial onset of diarrhea. c. Limited antigen dietary therapy is imperative to control diarrhea. d. Histopathologic examination results of the stomach and intestine are often unremarkable.</td>
</tr>
<tr>
<td>8. Which statement regarding PLE and/or PLN in soft-coated wheaten terriers is correct?</td>
<td>a. PLN is often the inciting cause of PLE. b. The diagnoses are most commonly made in dogs younger than 1 year. c. Amyloidosis is thought to be the primary cause of glomerular injury. d. Enteritis with glomerular immune deposition is thought to be the inciting cause of PLN.</td>
</tr>
<tr>
<td>9. The currently recommended treatment of histiocytic-ulcerative colitis is</td>
<td>a. prednisone therapy at tapering doses for several months. b. a strict hypoallergenic diet. c. metronidazole pulse therapy. d. administration of enrofloxacin at standard doses for several months.</td>
</tr>
<tr>
<td>10. Which breed is overrepresented in reports of intestinal bacterial overgrowth and ARD?</td>
<td>a. golden retriever b. Labrador retriever c. Australian shepherd d. German shepherd</td>
</tr>
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