Inflammatory Bowel Disease in Humans, Pets, and Horses

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Abstract

Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of the gastrointestinal tract. In humans, two major types exist: Crohn's disease and ulcerative colitis. Similarly, also pets can suffer from IBD having predominantly lymphocytic-plasmacytic enteritis/colitis, but also eosinophilic enteritis/colitis is common. Accumulating evidence suggest the induction of an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host as well as a dysregulation of the intestinal microbiota.

Symptoms of IBD are similar in humans and pets and may include diarrhea, vomiting, weight loss, anemia, as well as extraintestinal manifestations affecting the eye (uveitis), skin (rash), and joints (arthritis). Diagnosis of IBD requires a number of tests with endoscopy being the best tool to determine IBD. Biopsies of the mucosa are taken for differential diagnosis of IBD. As the pathogenesis of IBD is still unresolved, but implicates genetic factors, microbes, diet, and an aberrant immune response, so far treatment regiments only aim to control the disease activity by immunosuppressive medications like glucocorticoids. However, novel treatment options are underway that aim to reset the microbiota and showing promising efficacy.

There are thus many similarities in the clinical picture of IBD affecting humans, horses, and dogs, which not only give us great insight in the pathogenesis of IBD, but enable the pursuit of novel treatment options.

4.1 Introduction

Inflammatory bowel disease (IBD) describes conditions with a chronic or recurring immune response and inflammation of the gastrointestinal tract. The two most common entities of IBD in humans are ulcerative colitis (UC) and Crohn's disease (CD). IBD is caused by a combination of environmental, immune, and bacterial factors in genetically susceptible individuals (Fig. 4.1).

Peak onset of IBD in humans is usually between 15 and 30 years of age, but can occur at any age. There seems to be no gender bias for the occurrence of IBD as men and women are equally affected.

Inflammatory bowel disease resulted in 34,000 human deaths in 2010 (GBD 2013 Mortality and Causes of Death Collaborators 2015) and slightly reduces life expectancy.

4.1.1 Genes and Environment

In humans, the familial risk to develop IBD is tenfold higher and strongly suggests that these disorders have a genetic cause (Orholm et al. 1991).

Both genetic and environmental factors may influence the prevalence of IBD in the general population, as well as the degree of familial aggregation of IBD. The

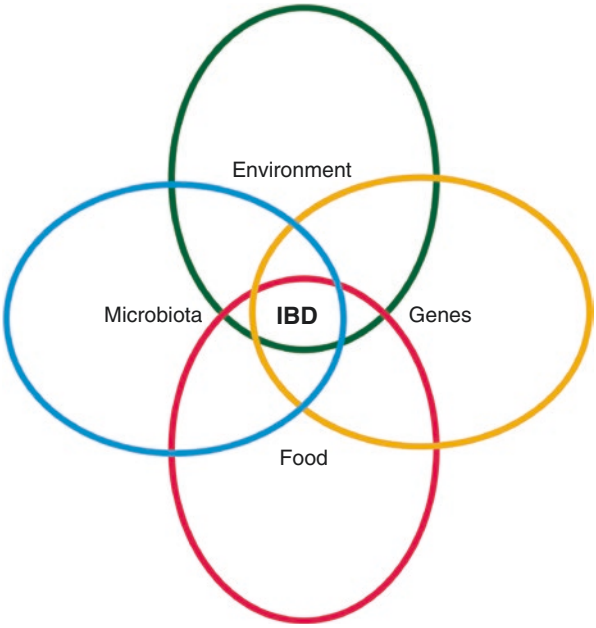

Fig. 4.1 The IBD pathogenesis is driven by the genetic background, environment, microbial flora, and the immune system

relative importance of these factors in causing familial aggregation may differ between low- and high-prevalence areas.

Worldwide, an increasing incidence and prevalence of IBD is observed with similar high-prevalence rates reported for Europe and North America. Based on the estimates, approximately 0.6 % of the Canadian population suffers from IBD, with UC being more prevalent than CD (Molodecky et al. 2012). Caucasians and people of Jewish descent also seem to have an increased risk, though it also seems to depend on the westernized lifestyle, as individuals emigrating from low-prevalent regions to higher prevalent countries (e.g., England) acquire increased risk for developing IBD (Molodecky et al. 2012).

Genome-wide association studies identified susceptibility loci that – triggered by environmental factors – result in a disturbed innate (e.g., disturbed mucosal barrier structure and function, impaired recognition of microbes) and adaptive (e.g., imbalance in regulatory and effector T cells) immune response toward a diminished diversity of commensal microbiota (Baumgart and Sandborn 2012).

There exist differences in genetic backgrounds for IBD, e.g., the NOD2 mutation is associated with CD in Western countries, but not in Japan, China, or Korea. Despite the discrepancies in genetics, familial aggregation is still observed to a similar degree in Asian and Western countries. Genes associated with IBD are involved in mucosal immunity and include roles in barrier function and microbe recognition (Park et al. 2006). In canine IBD patients, certain breeds as Soft-coated Wheaten Terriers, Lundehunds, or German Shepherds seem to be overrepresented in veterinary

literature (Littman et al. 2000) suggesting that also here the genetic background increases the risk of IBD. Recent genetic studies support this concept as certain polymorphisms in the Toll-like receptor-4 (TLR4) and TLR5 genes were significantly associated with inflammatory bowel disease in German shepherd dogs (Kathrani et al. 2010). In horses, genetic studies are ongoing. Granulomatous enteritis, a form of IBD with histological similarities to human Crohn's disease, shows a familial predisposition in Standardbred and Thoroughbred horses suggesting a genetic component (Lindberg 1984). No data exist regarding the prevalence of eosinophilic IBD in horses, although their incidence rate seems to rise. Also human patients have been reported to be afflicted in very rare cases with eosinophilic esophagitis, gastroenteritis, or colitis (Cianferoni and Spergel 2015). A possible relationship to a decreased level of intestinal parasitic infections is under discussion. The prevalence of lymphocytic-plasmacytic enterocolitis in horses was stated as 0.02 % (Kemper et al. 2000), but van der Kolk et al. (2012) noticed much higher prevalence especially in dressage horses. Though genetics set the ground for human and animal IBD, environmental and psychological factors are able to modulate and trigger the disease (Fig. 4.1).

4.1.1.1 Food and IBD

What animals and humans consume also exerts an influence on the development of IBD. Whereas high intakes of total fats, polyunsaturated fatty acids, omega-6 fatty acids, and meat are associated with increased risk of human IBD in general, high vegetable intake is associated with a decreased risk of UC, and intake of fibers and fruits is associated with a reduced risk of CD (Hou et al. 2011). Specialized dietary formulations (elemental, semi-elemental, and polymeric diets) have been studied in the treatment of pediatric CD, and although the exact mechanism is not fully understood, they reduce disease activity and symptoms (Levine and Wine 2013). There exists also a link between vitamin D and IBD, with low vitamin D levels associated with an exacerbation of the disease (Vatn and Sandvik 2015). Also a high-iron content in drinking water has been associated with an increased risk of developing IBD in Norway (Aamodt et al. 2008).

4.1.1.2 Smoking

Active and passive smoking significantly increase the risk to develop CD, even though apparently neither nicotine nor carbon monoxide is the cause (Baumgart and Sandborn 2012). In contrast, in UC smoking is protective and, after the onset of the disease smoking improves its course. Smoking cessation on the other hand aggravates UC (Lakatos et al. 2007).

4.1.1.3 Stress

Stress seems to increase the risk of symptoms in humans. Indeed, a high perception of stress correlates with an increase in symptoms. Although many individuals with active inflammation have active symptoms, there are also many individuals with active symptoms and no inflammation (Bernstein 2015). Also in cats and dogs, physical or psychological stress are likely to contribute in the etiology of IBD. As such, abnormal personality traits and potential environmental stress factors have been reported in 14 of 37 dogs (37.8 %), diagnosed with chronic idiopathic large bowel diarrhea (Leib 2000).

4.1.2 Immunobiology and the Microbiota

There exists an intricate balance between microflora, the intestinal barrier, and the immune system in the gut. Factors changing one of these three key players will have influence on the other two. Hence, changing the microflora does have an influence on the gut permeability and differentiation of intestinal epithelial cells and also changes the immune repertoire.

The microflora differs among human, dog, and horse (Kararli 1995). In humans, the stomach, duodenum, and proximal jejunum are predominantly colonized by aerobic organisms that include Streptococci and Lactobacilli with occasional *Candida* spp. (Balfour Sartor 2007). This changes in the distal ileum, where commensal bacteria take up an anaerobic predominance that more closely mimics the colon than the upper part of the small bowel. Dominant colonic organisms in humans include *Clostridium* spp., *Bacteroides*, and *Bifidobacterium* (Balfour Sartor 2007). Thus in human, *Firmicutes* and Proteobacteria phyla predominate in the duodenum, whereas in the distal colon *Firmicutes* and *Bacteroidetes* are the predominated phyla. Only few organisms are found in the upper gastrointestinal tract in humans. Indeed typical concentration of bacteria in the stomach, duodenum, and jejunum is 10^3–10^4 bacteria/ml content, which increases in the ileum to 10^8 bacteria/ml content. In the human colon, approximately 10^{11} bacteria/ml are measured; thus, approximately 3.9×10^{13} bacteria reside in the "standard" human colon (Sender et al. 2016). In contrast, in dogs a substantial microflora exists throughout the gastrointestinal tract with *Enterobacteriales* more common in the small bowel and *Clostridiales*, *Fusobacteriales*, *Bacteroidales*, and *Lactobacillales* present in the small intestine and the colon (Suchodolski et al. 2008). Thus, contrary to humans, horses, and chicken, *Fusobacteria* appear to be one of the major bacterial group (Suchodolski et al. 2008).

Commensal bacteria do not only help in digestion, but also promote epithelial cell growth and differentiation. Importantly, they also shape the immune repertoire, and as such germ-free mice are immunodeficient (Sansonetti 2004).

IBD seems to result from an impaired interaction of the intestinal commensal microbiota that is normally in a state of symbiotic mutualism with the human, canine, feline, or equine hosts. As such it is not an autoimmune disease, but rather seems to be an immunodeficient state (Bianco et al. 2015).

A number of specific pathogens have been incriminated in the development of IBD, though none have been confirmed as causal; rather, microbial antigens that are normally present in the intestinal lumen seem to drive inflammation in the gut (Abraham and Cho 2009).

4.1.2.1 Mucosal Immune System

In the intestine, innate immunity includes the epithelial barrier and phagocytic cells within the lamina propria (e.g., macrophages, dendritic cells, and neutrophils). The key population of the adaptive immunity arm is represented by T lymphocytes.

4.1.2.2 Epithelial Barrier

A single polarized epithelial layer covered by mucus film secreted from goblet cells represents the first-line defense of the mucosal immune system. Decreased expression of mucin as well as increased permeability and defective regulation of the tight junctions (Baumgart and Sandborn 2012) as well as defective sensing of microbial products is observed in IBD (Dahan et al. 2008). These abnormalities may be due to a primary defect in barrier function or may be the outcome of inflammation.

Macrophages and Dendritic cells

Macrophages in the gut mucosa display an anergic signature (are non-reactive) and do not produce inflammatory cytokines, but retain phagocytic and bactericidal activity. In IBD, however, a large number of macrophages recruited from the blood infiltrate the intestinal mucosa and secrete inflammatory cytokines (Smith et al. 2011; Kuhl et al. 2015).

4.1.2.3 T cells

T helper cell type 1 (Th1)-mediated immune responses are typically evoked in response to intracellular pathogen presented by antigen-presenting cells, with granuloma representing the hallmark of a Th1 response (Siegmund and Zeitz 2011). Th2 cells promote atopy, the induction of IgE responses, and eosinophil and mast cell activation. Th17 cells seem to specifically promote local tissue destruction. Last, there are also regulatory T cell populations that are responsible for the immunologically suppressive milieu in the intestinal mucosa.

The hallmark of active IBD in humans is a pronounced infiltration of innate immune cells (neutrophils, macrophages, dendritic cells, and natural killer T cells) and adaptive immune cells (B and T cells). The adaptive immune system in human IBD is now thought to mediate and perpetuate, but probably not start, intestinal inflammation. The disorder is characterized by an imbalance of effector T cells and regulatory T cells. Similarly as in humans, greater expression of Interleukin-17mRNA and Toll-like receptor 4 has been reported in horses with chronic active simple proctitis suggesting that Th17 cells are involved in active IBD in this species as well (Olofsson et al. 2015).

4.1.2.4 Eosinophils

Eosinophils are granulocytes that are associated with host defense against parasitic helminths, contribute in the pathology of allergic conditions, and also do play a role in immune regulation (Muniz et al. 2012). Eosinophils in human have been associated with fibrosis and strictures in humans with Crohn's disease (Masterson et al. 2015). In dogs, eosinophilic infiltration of the intestinal mucosa is considered as a subtype of IBD, whereas in cats the transition to a hypereosinophilic syndrome is less defined (Guilford 1996a, b). In horses, eosinophilic infiltrations are commonly detected in the rectal mucosa and submucosa of clinically normal horses suggesting that the presence of eosinophils in biopsies is no

proof of eosinophilic enteritis (Sloet van Oldruitenborgh-Oosterbaan and Grinwis 2014).

The IBD-associated dysbiosis might be due to the host's genotype that influences the composition of the microbiota, but also infections, antibiotics, drugs, and the diet are known contributors of a dysbiosis. Once this regulatory balance is disturbed, activation of leucocytes can lead to production and release of increased amounts of inflammatory molecules, which may lead to the development of chronic intestinal inflammation. Also in dogs and cats the enteric flora has an important impact on the etiogenesis of IBD. As such, significantly more mucosa-associated *Enterobacteriaceae* were reported in cats affected by IBD compared to healthy cats (Janeczko et al. 2008), and in dogs the number of clones belonging to the family of *Clostridiaceae* positively correlated with the clinical severity score (Xenoulis et al. 2008).

4.2 IBD in Humans

4.2.1 Clinical Picture

Primarily two types of chronic intestinal disorders exist in humans: Crohn's disease (CD) and ulcerative colitis (UC). Though similar symptoms like persistent diarrhea, abdominal pain, and cramping can be observed in both, they differ greatly in appearances and pathophysiology.

4.2.1.1 Crohn's Disease Versus Ulcerative Colitis

CD can affect any part of the gastrointestinal tract from the mouth to the anus, even though mostly the terminal ileum and the colon are affected, often discontinuously (Table 4.1). In contrast, inflammation in UC is continuously and restricted to the colon and rectum, seldom the anus (Fig. 4.2a, b). Also in CD, the inflammation is often transmural, and hence intestinal granulomas (Fig. 4.2b), strictures, and fistulas are common. Hence, chronic inflammation can make the inside of the intestine in CD so narrow that nothing can pass through. This is known as bowel obstruction, and it hinders digesting food and gas in the passage. The symptoms include severe cramping, nausea, vomiting, and a swollen belly. Bowel obstructions are treated in the hospital. If the obstruction does not clear on its own, surgery may be required. The transmural intestinal inflammation in CD may also generate deep ulcers with a pocket of pus, called an abscess.

Symptoms include fever, pain, and swelling. If an ulcer breaks through to an adjacent organ, it creates a tunnel called a fistula. A fistula between the colon and the vagina can allow bacteria into the vagina. A fistula to the bladder can cause chronic urinary tract infections. One that reaches the skin can create external sores. Fistulas and some abscesses are often treated with surgery.

In UC inflammation is restricted to the epithelial lining of the gut (Table 4.1 and Fig. 4.2a). While in UC pain associated food avoidance may lead to weight loss, in CD nutrient deficiencies are more common as it affects the small intestine, which is

Table 4.1 Important differences in Crohn's disease and ulcerative colitis

	Crohn's disease	Ulcerative colitis
Clinical picture	Affects any part of gastrointestinal tract from the mouth to the anus, mostly *terminal ileum*, rectum seldom, anus involvement common *Discontinuously*	Is restricted to the colon and *rectum*, seldom the anus *Continuously*
	Affects all bowel wall layers ("transmural lesions"), granuloma common → bowel perforation *Patchy* areas of inflammation *Nutrient deficiency*	Restricted to the mucosa (epithelial lining of the gut), granuloma seldom *Colon cancer risk*
Signs & symptoms	Diarrhea, abdominal pain, weight loss due to food avoidance and *malabsorption*	Diarrhea, abdominal pain Weight loss due to food avoidance
	Strictures, *perforations*	Rectal bleeding → *anemia*
Genes and environment	Runs in families, siblings 30 times more likely to develop CD than the general population 30 genes associated, most known NOD2 = CARD15 Associated with *Mycobacterium* and other pathogenic bacteria Higher risk for smokers	Aggregation in families, identical twins with concordance rate of 10 %, dizygotic twins with 3 % Ethnic differences 12 regions in genome are slightly linked Lower risk for smokers
	Majority of genes associated with IBD are involved in mucosal immunity, including roles in barrier function and microbe recognition	

responsible for nutrient absorption. The symptoms of IBD range from mild to severe and may return periodically over time. Most people have flare-ups folowed by longer asymptomatic periods, so-called remissions. Remissions can last for months or even years.

In UC, about 5–10 % of patients have symptoms all the time. The constant chronic inflammatory status of people affected with UC also makes them more susceptible for developing colon cancer. The risk is even greater when inflammation affects the entire colon.

Extraintestinal symptoms of IBD include inflammatory responses affecting the eye (uveitis), skin (rash), joints (arthritis), and bile ducts (cholangitis). IBD also increases the risk of deep venous thrombosis and autoimmune hemolytic anemia. Also clubbing, a deformity of the ends of the fingers, may be a result of IBD (Danese et al. 2005).

4.2.2 Pathophysiology

For the development of IBD, bacteria are decisive, and this is emphasized from animal studies in which IBD-susceptible mice (e.g., IL-10 knockout mice) do not develop IBD in the absence of a microbiota. Moreover, it is known that the diversity

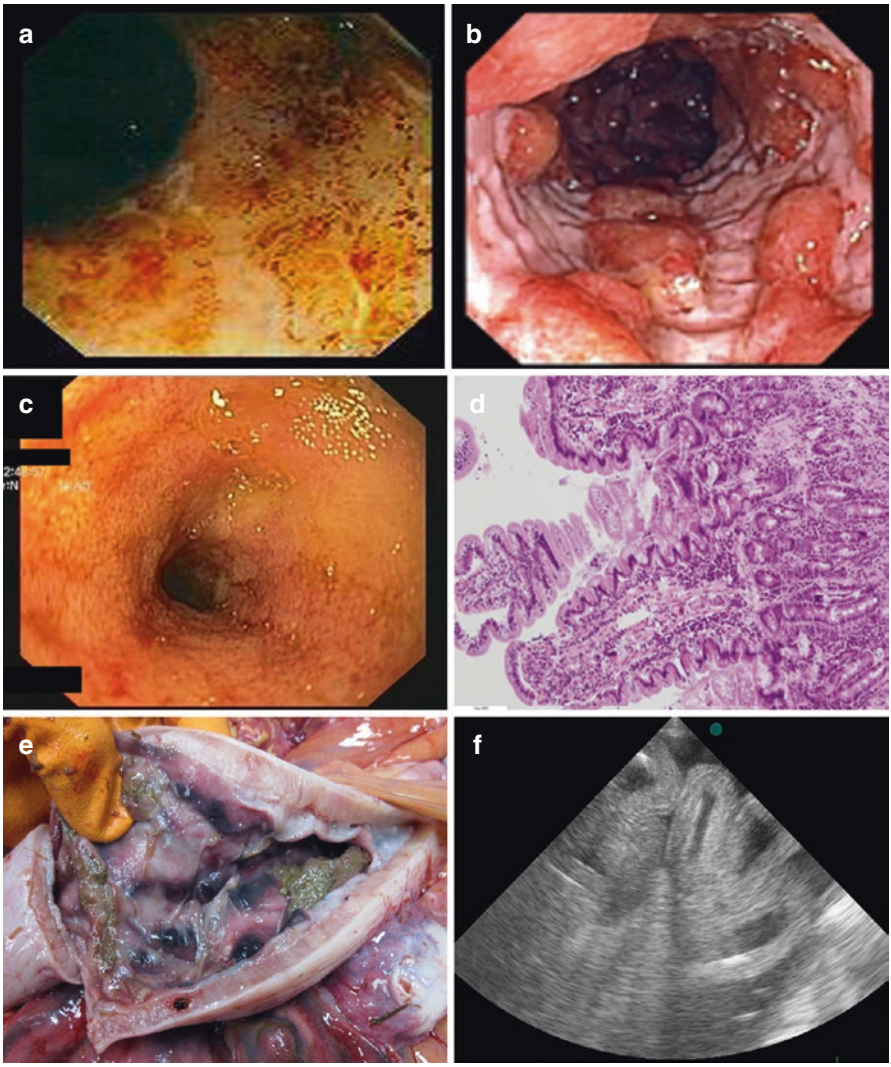

Fig. 4.2 Representative images from IBD lesions in different species. (**a**) Endoscopy in human ulcerative colitis with superficial ulceration, erythema, and friability of the mucosa. The internal surface of the colon appears blotchy and broken in places; (**b**) endoscopic image of human Crohn's disease showing a patchy, deep transmural inflammation (©David M Martin MD; www.EndoAtlas.com); (**c**) endoscopic appearance of the duodenum of canine IBD (note the flattened and glossy surface due to loss of folds of the absorptive mucosa as a result of inflammation); (**d**) histological appearance of canine IBD in courtesy of Barbara Richter (note the increased number of lymphocytes and plasma cells in the lamina propria of the duodenum as well as a low-grade infiltration with intraepithelial lymphocytes); (**e**) thickened jejunal wall and enlarged mucosal folds in a horse with LPE (equine lymphocytic-plasmacytic enterocolitis); (**f**) ultrasonographic appearance of thickened small intestinal walls in a horse with IBD

of the commensal microbiota is significantly reduced in IBD patient compared to control subjects with the phyla *Firmicutes* and *Bacteroidetes* being in particular affected (Frank et al. 2007). Also infections have been linked with the onset and exacerbation of IBD (Garcia Rodriguez et al. 2006).

An impaired acute inflammatory response by macrophages that leads to defective bacterial clearance has been implied for Crohn's disease. In contrast, macrophages of UC patients exuberantly respond toward bacteria and are also reflected by the formation of granulomas in CD and not UC (Kuhl et al. 2015). In CD predominantly Th1 and Th17 cells that promote local tissue destruction are observed. UC is thought to represent a Th2-driven disease. Recent data suggest that natural killer T cells (NKT) are the source of Th2 cytokines like IL-13 and target epithelial cells to become dysfunctional (Heller et al. 2005). Consequently, UC may be more of a superficial epithelial injury disorder.

4.2.3 Diagnosis

The gold standard for all patients with IBD is endoscopy (Baumgart and Sandborn 2012). Diagnosis of IBD can be challenging, with colonoscopy being the most effective for diagnosis. Usually a blood test to test for anemia or infections and a fecal occult blood test, followed by endoscopy, are performed. But also X-ray and computerized tomography (CT) scan for severe symptoms are performed to rule out perforation. Biopsies of the mucosa are taken to differentiate from UC and CD.

Moreover, urine analysis and stool culture, liver function test, and electrolyte studies may be necessary.

4.2.4 Treatment of human IBD

Despite the importance of gut flora in the pathogenesis of IBD, therapy has focused on suppressing the immune system rather than removing the agent that might be responsible for the aberrant response, by reestablishment of a normal healthy gut flora. Treatment options are mainly reduced to lifestyle alterations, if contributing factors are known, medical management of the symptoms, and surgical interventions.

4.2.4.1 Anti-inflammatory and Immunosuppressive Medications

5-Aminosalicylates are the standard treatment for active UC, in which a combination of oral and rectal therapy is better than oral or rectal therapy alone.

Also corticosteroids are effective for inducing remission in CD and UC. However, over time the response rate decreases, so there is no role for corticosteroids in maintaining remission in either CD or UC. Moreover, long-term

use goes along with serious side effects and increases the risk of infection in general (Bernstein 2015).

In humans, a seminal advance was the introduction of treatment with an anti-TNFα monoclonal antibody, which targets an inflammatory cytokine and is particularly effective in Crohn's disease. However, anti-TNF agents are not effective in up to one-third of individuals and are quite expensive. Moreover, loss of response or intolerance to anti-TNF therapy is observed among initial responders at a rate of 10 % per year.

4.2.4.2 Antibiotics

Antibiotic therapy may induce remission in active UC and CD and prevent relapse in patients with quiescent CD and support the thesis that altering gut microbial flora modulates IBD activity (Khan et al. 2011). However, overuse always bears the risk of generating resistant strains.

4.2.4.3 Surgery

There is no surgical procedure that can cure CD; however, in UC surgical removal of the large intestine (colectomy) cures the disease and is necessary in case of carcinoma, perforation, and exsanguinating hemorrhage.

4.2.4.4 Nutrition

Gradual loss of blood from the gastrointestinal tract, as well as chronic inflammation, often leads to anemia and is treated with iron supplements.

Enteral nutrition can induce remission in active disease (Lahad and Weiss 2015). Although the exact mechanism as to how enteral nutrition can reduce disease activity and symptoms is not fully defined, impacting on the gut microbiome and secondary effect on the epithelial barrier and immune response to gut microbes is very plausible (Bernstein 2015).

4.2.4.5 Probiotics

In clinical studies, probiotics such as *Escherichia coli* Nissle 1917 show promising result in maintenance of remission in UC, but there is no evidence to support the use of probiotics in CD (Bernstein 2015).

4.2.4.6 Fecal transplantation

As intestinal dysbiosis is important in the underlying pathophysiology of IBD and *Clostridium difficile* can be successfully treated with fecal transplantation, studies are underway investigating this approach in IBD. In contrast to *C. difficile*, in which the intestinal microbiome balance has been acutely disrupted, in IBD the intestinal microbiome is altered with more permanence. Thus, a more prolonged fecal transplant treatment seems to be necessary. Still, several case series exist, in which a healthy commensal flora with fecal transplantation by enema was reestablished (Borody et al. 2003).

4.3 IBD in Dogs

4.3.1 Clinical Problem

As in human patients, clinical signs associated with canine inflammatory bowel disease are primarily gastrointestinal symptoms. They comprise vomiting, small and large bowel diarrhea, anorexia, weight loss, flatulence, and borborygmus (rumbling sound caused by the movement of gas in the intestines), but also abdominal pain and "colic"-like signs are possible. Small bowel diarrhea includes signs as weight loss, vomiting, and loose-watery or black stool (digested blood, melena). Large bowel diarrhea is signed by tenesmus (ineffectual and painful straining), fresh blood and/or mucus in the stool, and urgency, and these patients can also suffer from vomiting and weight loss. The owners often are awake during the night, hearing their pets licking their lips, they hear stomach rumble and they sometimes have to walk their dogs. Respiratory signs develop, if the disease is accompanied with protein loss (protein-losing enteropathy, PLE) and hypoproteinemia. Therefore, ascites or pleural effusion can accumulate in their body cavities. Also peripheral edema (tissue swelling) is possible. Specially, PLE dogs are at risk of thromboembolism based on the hypercoagulability (Goodwin et al. 2011).

Not only the suffering of the patients but also the social incompetence and the difficult and expensive therapy of IBD dogs make this disease a severe problem in veterinary medicine.

In human patients, IBD can be subdivided into Crohn's disease and ulcerative colitis (UC) (Odze 2003). The two forms of the disease differ in their clinical picture as Crohn's disease is a marked transmural granulomatous process, which can affect any part of the gastrointestinal tract from the mouth to anus, whereas UC is a more superficial process, restricted to the colon (Odze 2003). In dogs, the two major forms of IBD cannot be distinguished, and IBD is common in both, the small and the large intestine (Fig. 4.2c, d) (Guilford 1996b). In contrast to human medicine where the two disease subtypes express different cytokine patterns (Sanchez-Munoz et al. 2008), a definitive inflammatory response or cytokine pattern could not be established in dogs (Tamura et al. 2014; Luckschander et al. 2009).

Extraintestinal signs of IBD play an increased role in human medicine. A variety of signs are described including musculoskeletal, dermatologic, hepatobiliary, ocular, renal, and skin diseases. Also pulmonary manifestations, including nonspecific lymphocytic infiltrations, organizing pneumonia, and noncaseating granulomas, are described (Majewski and Piotrowski 2015). In dogs, extraintestinal signs are not that often recognized, compared to human medicine. The most common concomitant problems in IBD dogs were pruritic skin diseases and otitis externa (Foster et al. 2003; Guilford 1996b). Also immune-mediated diseases as thrombocytopenia (Ridgway et al. 2001) and nonerosive polyarthritis are described in a few number of dogs (Pedersen et al. 1976).

4.3.2 Comparing Therapies

There is general agreement among human and veterinary investigators that IBD is a multifactorial disease. The external environment, the patient's genetic background, the intestinal microflora, and the immune system are involved in the generation of IBD (Scaldaferri and Fiocchi 2007) (Fig. 4.1).

When the diagnosis of IBD is established, client education and owner compliance is the key for a successful management of the IBD-affected pet. The owner has to be informed that IBD is a chronic disease, which can only be controlled, but not cured, and that relapses of the disease are possible. Canine IBD patients need an individualized therapy based on the severity of the disease, on the type of intestinal wall infiltration, and also on the environment and owner's commitment. A distinct step-by-step therapy in consent with the owner seems to be the best approach.

4.3.2.1 Nutritional Therapy: Dietary Trial

In contrast to human IBD, dietary management is the cornerstone of canine IBD patients. The diet has to fulfill the most important criteria as:

- The patient's nutrient requirements should be fulfilled.
- The patient should accept the diet.
- The owner's compliance should be achieved (should be able to feed or cook the diet).
- The diet should be highly digestible and fat restricted.

A novel diet should be introduced to the IBD patient. This can be as simple as switch to a new manufacturer, but usually an antigenic modification is used. This can be either the introduction of a novel single protein and carbohydrate source or the use of a protein hydrolysate (Simpson and Jergens 2011). In a hydrolyzed diet, the protein structure is disrupted, hereby preventing immune recognition by an already sensitized patient, but also preventing sensitization of a native individual (Cave 2006). A positive response to dietary trial implicates a food-responsive enteropathy (FRD), including food intolerance and food allergy (Simpson and Jergens 2011). The dietary trial should be continued for 8–10 weeks, although most canine patients have a positive response during the first 2 weeks (Luckschander et al. 2006).

4.3.2.2 Antimicrobial Therapy

For an antimicrobial trial, typically metronidazole and tylosin are orally given. Both medications have immunomodulatory characteristics, and they influence the intestinal flora by their antibacterial properties (Hall 2011). If the dog has a positive response, it is called antibiotic responsive (ARD) or tylosin-responsive diarrhea (TRD) (Kilpinen et al. 2015). Although metronidazole has antiparasitic, antibacterial, and immunomodulatory characteristics, it should be used with caution due to

its described potentially carcinogenic properties, especially after long-term use (Bendesky et al. 2002).

4.3.2.3 Anti-inflammatory and Immunosuppressive Medications

Corticosteroids are the most often prescribed immunosuppressant drug in canine IBD (Craven et al. 2004). Unfortunately, side effects are common, especially in large breed dogs and demand combination therapy with, for example, azathioprine or local active glucocorticoids (Budesonide®), although side effects cannot be excluded (Dye et al. 2013). If there is a poor response, additional immunosuppression as cyclosporine can be considered. In contrast to human medicine, less information exists concerning the use of anti-TNF alpha agents in canine IBD. As in human medicine, sulfasalazine is used for his anti-inflammatory property on colonic mucosa, but based on the various side effects in dogs, caution is warranted.

4.3.2.4 Probiotics

Although probiotics seem to have effects on the gastrointestinal flora in IBD dogs, the clinical efficacy is not proven (Rossi et al. 2014; Allenspach et al. 2006).

4.3.2.5 Fecal transplantation

Only few information are available about the use of fecal transplantation in IBD pets (Roman 2015).

4.3.2.6 Cobalamin

As in humans, cobalamin (vitamin B12) is receptor-mediated absorbed in the ileum. In humans the intrinsic factor, which plays an important role in the absorption of cobalamin, derives from the gastric parietal cells. In contrast, it is mainly produced in the pancreas of dogs and cats. It has been shown that IBD dogs with hypo-cobalaminemia have a higher risk for euthanasia, which can be prevented by subcutaneous administration of cobalamin in the treatment of IBD (Allenspach et al. 2007).

4.4 Feline IBD

4.4.1 Clinical Problem

Cats differ from dogs and humans, because they are true carnivores. Cats have low levels of amylase in the saliva (McGeachin and Akin 1979); they also have lower levels of enzymes for the breakdown of carbohydrates.

Cats differ in the anatomy of their intestinal tract, as the intestine is shorter and the pancreatic duct enters into the common bile duct, before it opens into the proximal duodenum marked by the papilla duodeni. The proximity of the bile duct system, the pancreas, and the intestine might contribute that feline IBD is often accompanied by cholangitis and/or pancreatitis, feline inflammatory

disease (FID), or triaditis (Jergens 2012). The clinical signs of the affected organs as jaundice or fever overlap with the clinical signs of IBD. Feline IBD can affect any age of cats and any breeds, although middle-aged cats and Asian breeds as Siamese cats are predisposed (Jergens et al. 1992). Similar to dogs and different to human patients, feline IBD is a diverse disease, which can affect the small and the large bowel. Feline IBD patients often are presented with vague clinical signs as weight loss, lack of appetite, and vomiting, also with signs of small and large bowel diarrhea. Additionally, extraintestinal manifestations involving the kidney (Weiss et al. 1996) and the skin are described in cats (Guilford et al. 2001). As in human or canine IBD patients, the course of feline IBD is cyclical and is characterized by spontaneous remissions and exacerbations (Jergens et al. 1992; Guilford et al. 2001). Specially in strict indoor cats, the diarrhea and defecating outside of the litter box put an emotional pressure on the owners of IBD cats.

4.4.2 Comparing Therapy

4.4.2.1 Nutritional Therapy

As in canine IBD, nutritional therapy is proven to be effective in the treatment of feline IBD. In one study, more than 50 % of cats with idiopathic IBD improved with elimination diet (Janeczko et al. 2008). Moreover, cats in this study improved quicker to dietary intervention (2–3 days) compared to canine IBD patients (10–14 days) (Luckschander et al. 2009).

4.4.2.2 Antimicrobial Therapy

Tylosin and metronidazole have been successfully used as a single agent or in combination with immunosuppressive drugs in the treatment of feline IBD (Allenspach et al. 2006). Metronidazole should not be used as a long-term treatment due to the possible carcinogenic side effects (Craven et al. 2004).

4.4.2.3 Immunosuppressive Medications

Glucocorticoids as a single agent or in combination with antibacterial therapy are the most often used therapy in feline IBD. Due to cat's sensitivity to salicylates, sulfasalazine should not be used in cats. Compared to canine IBD, only anecdotal reports exist concerning the use of cyclosporine in feline IBD (Jergens 2012; Allenspach et al. 2006).

4.4.2.4 Probiotics

Little information about the use of probiotics in feline IBD is known.

4.4.2.5 Cobalamin

Similar to dogs, the intrinsic factor for cobalamin (vitamin B12) resorption is mainly produced in the pancreas of cats. Low serum cobalamin concentrations are therefore an indicator for pancreatic diseases, but also for severe ileal

diseases, and additionally a negative prognostic factor in feline IBD patients (Ruaux et al. 2005). Various studies report the high efficacy of the parenteral supplementation of cobalamin in chronic enteropathy cats (Ruaux 2013).

4.5 Equine IBD

4.5.1 Clinical Problem

IBD in horses describes a group of gastrointestinal disorders characterized by cellular infiltration of the mucosa and submucosa with eosinophils, plasma cells, lymphocytes, basophils, macrophages, or epithelioid cells. The classification of equine IBD is based on the main histological cell types and includes:

- Granulomatous enteritis (GE), where the predominant cells are macrophages, giant cells, lymphocytes, and plasma cells forming circumscribed granulomas in the mucosa or submucosa. This form closely resembles Crohn's disease in humans with marked villous atrophy, especially in the ileum (Lindberg 1984). Pathophysiologically, abnormal reactions to intestinal bacteria, dietary agents, or aluminum exposure are discussed, but there is also some evidence of possible involvement of *Mycobacterium avium* (Lindberg 1984; Mönki et al. 2015). Young standardbreds are overrepresented, showing a familial predisposition (Lindberg 1984).
- Lymphocytic-plasmacytic enteritis (LPE), which is characterized by excessive infiltration of lymphocytes and plasma cells in the lamina propria of the gastrointestinal tract (Fig. 4.2e, f). There is no known sex, breed, or age predilection, although a recent study reported an increased incidence in dressage horses with possible gluten sensitivity as etiological factor (van der Kolk et al. 2012). LPE is discussed as a possible precursor of intestinal lymphoma (Kalck 2009). A certain degree of lymphoplasmacytic infiltration is common in intestinal biopsies; therefore, the histological results should be revised carefully (Kerbyson and Knottenbelt 2015).

Eosinophilic enteritis can be further subdivided in diffuse eosinophilic enteritis/enterocolitis (DEE), idiopathic focal eosinophilic enteritis (IFEE), and the multisystemic eosinophilic epitheliotropic disease (MEED). In DEE, infiltrations with eosinophils and lymphocytes can be detected in the mucosa and submucosa of small and/or large intestine. IFEE presents with single or multiple, focal, circumferential constricting, or plaque-like lesions with wall thickening mainly in the small colon and the left dorsal colon, where it is also termed segmental eosinophilic colitis (Makinen et al. 2008). MEED is chronic condition of unknown etiology with eosinophilic infiltration of multiple organs and the skin. As in GE, young standardbreds are most commonly affected by MEED, but the disease can occur in any breed, sex, or age (Kalck 2009).

As in human patients, horses with IBD present with a wide range of gastrointestinal signs that include mainly weight loss and also lethargy, poor appetite, intermittent fever, ventral edema, and diarrhea or free fecal water, if the large intestine is

affected (Kalck 2009). Abdominal pain can occur in all forms of IBD based on neuronal inflammation within the small intestinal walls or due to excessive gas production in the large intestine as a result of excessive amounts of undigested carbohydrates reaching the cecum and colon (Kalck 2009). Therefore, IBD poses a predisposition for displacement or volvulus of the large colon. In contrast to other forms of IBD, horses with IFEE often present with acute, sometimes severe, colic requiring surgical treatment (Kerbyson and Knottenbelt 2015).

Extraintestinal signs are not very common in horses, but can include hepatic and pulmonary granulomas in GE, exfoliative dermatitis in MEED and GE, or signs of multiple organ involvement in MEED as renal insufficiency, peripheral lymphadenopathy, respiratory problems, or ulceration of the tongue and mouth (Kerbyson and Knottenbelt 2015). Some horses present with pruritic skin diseases that resemble human dermatitis herpetiformis and could be associated with gluten sensitivity (van der Kolk et al. 2012).

Typical abnormalities in clinical pathology are hypoalbuminemia due to a protein-losing enteropathy, hypoproteinemia, anemia, and abnormal carbohydrate absorption tests. With liver involvement, elevated levels of gamma-glutamyl transferase are common (Kalck 2009; Kaikkonen et al. 2014).

4.5.2 Comparing Therapies

The treatment of horses with IBD is often unrewarding, and the prognosis is generally reported as poor, although a recent study stated an overall survival rate of 65 % (Kaikkonen et al. 2014).

4.5.2.1 Nutritional therapy

Similarly to dogs and to a smaller degree also as in human patients, dietary management is very essential for equine IBD patients. The patients should receive a highly digestible, well-balanced feed in small, but frequent meals. Usually, protein requirements are increased, and the rations should contain at least 14 % crude protein (House and Warren 2016). High-fiber diets minimize the involvement of the most common affected small intestine and provide energy through increased production of volatile fatty acids in the large intestine (e.g., addition of beet pulp) (Kalck 2009). Supplemental fat (corn oil, rice bran) is used to increase the energy content of the diet (House and Warren 2016). It is also recommended to place the horse on a mono-diet to eliminate possible dietary antigens. The preferred ration consists of grass hay and oats that are considered to be gluten poor (van der Kolk et al. 2012). A case report demonstrated clinical improvement, reduction of antibody levels, and increases of duodenal villus length after 6 months on this diet (van der Kolk et al. 2012).

4.5.2.2 Immunosuppressive medications

As in dogs, corticosteroids are the most often used drugs in horses in order to decrease the intestinal inflammation. A prolonged and tapering course is necessary. Due to the poor absorptive capacity of the intestine leading to decreased absorption

of oral medications, parenteral routes of administration are preferred initially (Kalck 2009), although some authors reported a fair to moderate outcome with oral prednisolone (Kaikkonen et al. 2014). In this study, the overall survival rate was significantly higher in horses that responded to the initial treatment (Kaikkonen et al. 2014).

Anecdotal evidence speaks of azathioprine as a useful adjunct in the treatment of IBD (Divers 2010), but evidence-based proof of efficacy is lacking.

Sulfasalazine is sometimes used in horses with acute colitis for its anti-inflammatory effects in the large colon due to the inhibition of eicosanoid metabolites and the interaction of 5-aminosalicylic acid with oxygen-derived free radicals, but side effects as keratoconjunctivitis sicca or thrombocytopenia are possible (Divers 2010). As such, the application in equine IBD patients is not described.

4.5.2.3 Probiotics and fecal transplant

Despite widespread use and promising results in vitro, in vivo there is still no convincing evidence for successful use of probiotics (Schoster et al. 2014). Effects of fecal transfaunation in equine IBD are not described yet.

4.5.2.4 Antibiotics

Similarly to human medicine, antibiotics are not regularly recommended in equine IBD, although metronidazole can be considered for its antimicrobial and anti-inflammatory effects (Kalck 2009). Other authors consider treatment with macrolides and rifampin in horses with GE due to a possible etiological involvement of *Mycobacterium avium* (Mönki et al. 2015).

4.5.2.5 Antihelminthics

Administration of larvicidal antihelminthics is recommended even in cases with proper deworming regimes and negative fecal flotation tests due to the difficulties to diagnose larval cyathostomiasis and in face of a possible link between parasite-induced inflammation and the development of IBD (Kaikkonen et al. 2014).

4.6 Synopsis

Taken together, humans, dogs, horses, and cats do suffer from IBD with a very similar pathophysiology and disease course, strongly determined by their anatomy and genetic background.

It is striking to note, when comparing human and pets, that in particular dogs share a similar physiology and clinical picture. As in humans, an underlying immunodeficiency (genetic predisposition) with a misbalanced microbiota that is reinforced by environmental factors (nutrition, smoking habit) results in the disease. However, unlike in humans in whom IBD comprises two entities (UC and CD), in pets this is not observed as the inflammation usually include the small and the large intestine. IBD also differ in horses as it affects primarily the small intestine and not

the colon. This difference might be explained by their exclusive herbal diet. Moreover, the observed discrepancies between human and pets are very likely due to the differences in the microbiota distribution along the gut. In human very few organisms are residing in the upper bowel, whereas in dogs – though a gradient is also present – much more organisms reside in the upper regions of the small intestine. Also differences in the main bacterial strains exist in human and pets, e.g., *Fusobacteria* in dogs are underrepresented in humans. In contrast, IBD in cats differ, which can be explained by their meat diet and anatomical features predisposing them for concurrent inflammation of the liver, the pancreas, and the intestines (triaditis).

The observed differences however broaden our understanding on the pathophysiology of IBD, and this has implication in the therapy choice for human and pets, e.g. for the treatment the site of application (oral versus rectal by enema) might be relevant to reach the site of inflammation (oral for small bowel, enema for large bowel).

Though, standard therapy still usually includes the use of immunosuppressive medication to diminish the symptoms, causative treatments, that aim to re-establish a healthy gut microbiota, are underway. In particular, a sustained change in diet, food supplementations as well as fecal transplantation show promising efficacies in human, but also pets.

It has to be emphasized that IBD in pets, and in particular canine IBD, represent a natural model of IBD and thus studies with canine patients are highly indicative for a therapeutic success as they do not rely on an artificial system. As so far biologics are usually tested and approved for human use and secondarily are transferred to the veterinarian patients, comparison of the similar pathophysiology suggest that the exchange of therapeutic strategies may be done bi-directionally in the future.

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