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Topical Review

Exocrine Pancreatic Insufficiency in the Dog: Breed Associations, Nutritional Considerations, and Long-term Outcome

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A B S T R A C T

Canine exocrine pancreatic insufficiency (EPI) is an alimentary tract disorder causing malabsorption and debilitations in affected individuals. This article covers predisposing factors to EPI and response to therapy. Although relatively easy to diagnose, knowledge of breed predispositions (and also of those breeds where the disease is less common) can guide the clinician. Numerous studies have examined therapy for EPI, and a key finding is the variability in response among affected dogs. This implies that close monitoring and individual tailoring of therapy is needed to maximize the chance of success. Important factors affecting outcome are the choice of enzyme preparation, presence of hypocobalaminemia, and the response to the first 2 to 3 months of therapy.

Canine exocrine pancreatic insufficiency (EPI) is an alimentary tract disorder characterized by inadequate production of digestive enzymes from pancreatic acinar cells, leading to the characteristic clinical signs of polyphagia, weight loss, and increased fecal volume.[1-4] This article will first examine signalment factors associated with canine EPI and show how knowledge of such factors can provide an insight into etiopathogenesis. It will next consider therapeutic and nutritional options commonly used by primary care veterinarians, and will finally examine factors associated with favorable response to therapy and long-term remission.

Signalment and Canine EPI

As with any medical disorder, knowledge of associations between certain signalment factors and canine EPI is useful to the clinician. In this respect, when a particular breed is known to be predisposed, diagnostic tests can be prioritized to confirm or eliminate that possibility at the earliest opportunity. Similarly, if a disease were known to be uncommon in particular groups of dog, unnecessary investigations can be avoided with the effect of saving time and expense. In addition to assisting with clinical decision making, knowledge of such associations can also help shed light on possible etiopathogenesis of a disease, and highlight where this may differ among breeds, ages, and genders. The common associations (and lack of associations) between canine EPI and various signalment factors will now be discussed.

Breed Associations

Studies examining breed association and canine EPI have been conducted in North America and Europe. In such studies, a number of breeds have been identified as being at risk for the development of EPI, including Cavalier King Charles Spaniels (CKCS), Chows, Cocker Spaniels, German Shepherd Dogs (GSD), Rough-coated Collies (RCC), and West Highland White Terriers. In one study, EPI in related English setters in Italy has been described, although the exact mechanism was not known.[5] Although these dogs had a congenital form of EPI (absence of acinar cells), the exact mechanism was not known and has never been seen in other dogs of this breed or in other breeds. Therefore, of all the predisposed breeds, the association between GSDs and EPI is well known, with this breed representing ~60% of all cases of EPI.[6,7] In addition, both CKCS and RCC are known to be overrepresented in studies from both North America[7] and Europe.[6]

In a recent European study, a predisposition in Chows was recognized, a finding that had not been identified before.[6] This association may have been identified in this study, but not others, because it was larger in size (~13,000 dogs assessed), such that associations could be identified in even the most uncommon breeds. Indeed, only 38 Chows were tested, but approximately two thirds of those tested were positive. The reasons for such a great prevalence in this breed are not known.

As important as knowledge of predispositions is a need to recognize where the disease may be underrepresented, and one study has examined such "negative" associations.[6] Observed prevalence in Boxers, Great Danes, Golden retrievers, Labrador retrievers, Rottweilers, and Weimaraners was significantly less, most notably in Boxers in which, of 524 individuals tested, none had EPI. However, EPI has been documented in Boxers in North America,[7] although that study did not specifically examine the issue of underrepresen-

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tation of breeds. Nonetheless, genetic differences may account for the difference in prevalence in EPI in dogs from different continents.

Gender

In most studies conducted to date, female dogs are overrepresented compared with male dogs. Although this female association is typical of most breeds, including Chows, CKCS, and GSD, it is less clear cut for RCC where it has been shown in some[8,9] but not all[6] studies.

Age

Onset of EPI typically arises in young adult animals (median age 3 years),[2-4,6,10] although cases range from growing dogs (3 months and up) to those in late adulthood and even geriatric (e.g., 17 years age).[6] Interestingly, median age of onset varies among breeds, with cases in GSDs and RCC occurring, on average, at a younger age (median 3 years) than CKCS (median age 7 years). Of all breeds affected, dogs of the Chow groups are youngest (median age 18 months). This may imply differences in pathogenesis among different breeds (see below).

Differences in Signalment and Differences in Pathogenesis of EPI in Different Dog Populations

As mentioned above, various breeds are predisposed to EPI, but can be separated into 2 distinct groups depending on age of onset. Age of onset can provide clues to the likely pathologic mechanisms: in breeds with early-onset disease an immune-mediated mechanism is possible or the disease may be congenital, whereas breeds in which EPI manifests later might develop the disease through other mechanisms including chronic pancreatitis.

Onset of EPI occurs at a relatively young age in GSD and RCC, and pancreatic acinar atrophy (PAA) is reportedly the most common cause. The disease may, in fact, have an immune-mediated pathogenesis, as evidenced by the presence of lymphoplasmacytic infiltrates in the pancreas of dogs of these breeds with subclinical EPI.[8,9] This age of onset is similar to that seen for other immune-mediated glandular diseases such as steroid-responsive meningitis and immune-mediated polyarthritis.[11] Although some studies have suggested that the disease is inherited in an autosomal recessive manner in both breeds,[8,9,12-16] this is at odds with the female predisposition. Furthermore, other studies have questioned the proposed autosomal recessive inheritance mechanisms and a single causal gene has not been identified despite numerous attempts,[17] and the fact that recent studies have questioned the pattern of autosomal recessive inheritance.[18] Further work is therefore required to ascertain the exact etiopathogenesis. Chows also tend to be diagnosed with EPI at a relatively young age, again arguing for a similar mechanism in this breed. However, no work has been conducted on pathogenesis in this breed and, alternative mechanisms, including congenital disorders such as pancreatic hypoplasia, would also be possible.[3]

In contrast to the GSD and RCC breeds, EPI cases develop later in life for the CKCS breed,[6] implying that a different pathogenetic mechanism might be responsible in such cases. Other than PAA, proposed pathologic mechanisms leading to onset of EPI include chronic pancreatitis (CP), pancreatic hypoplasia, and pancreatic neoplasia.[2,3] Of all such possibilities, CP is most likely because CKCS are reportedly predisposed and, therefore, ongoing uncontrolled pancreatic inflammation is the reason that they develop EPI. CP is also a common cause of EPI in cats and human beings, and most frequently arises in middle age onward, a pattern mirroring what is seen for dogs.[19-21] Because CP can be notoriously difficult to diagnose,[22,23] it is, perhaps, not surprising, that EPI cases do not commonly have a history of gastrointestinal disease before onset in this breed.[24]

Of all breeds known to be underrepresented, the most interesting is the Boxer, especially in light of the fact that a decreased prevalence for diabetes mellitus is also reported in this breed.[25] The decreased observed prevalence for both an exocrine and an endocrine pancreatic disease condition in Boxers is remarkable, although the underlying mechanism requires further study. One possible explanation is that the exocrine and endocrine pancreas of the Boxer is more able to withstand injury than that of other breeds; this could result from decreased predisposition to immune damage, decreased cell death during disease or more robust intrinsic regenerative mechanisms. Candidate proteins could include the regenerating (*reg*) proteins. In humans and rodents, *reg* proteins are secreted in pancreatic juice and may be protective of both exocrine and endocrine tissue.[26] Furthermore, in humans, overexpression of *reg* has been noted in some forms of cancer,[26] noteworthy, because Boxers are a breed prone to neoplasia.[24,27] However, to date, *reg* proteins have not been identified in any breed of dog, and further study is required to determine whether they, or other proteins, may have a role to play in protection from pancreatic injury or neoplasia in this species.

Finally, the reason for the gender association is not yet known but, as mentioned above, has enabled reappraisal of the possible genetic mechanisms underlying EPI.

Nutritional and Therapeutic Considerations

Pancreatic Enzyme Replacement

Various therapies are used for dogs with EPI, but by far the most important is pancreatic enzyme replacement, although cases have reportedly been maintained for prolonged periods without supplementation.[28,29] A range of products have been recommended including enteric-coated preparations (including tablets, capsules, and granules), uncoated enzyme powder, and raw pancreas. In a recent study assessing prescribing habits of UK veterinarians, approximately two thirds gave uncoated preparations, whereas most of the rest gave a coated preparation and only a minority (< 1%) gave raw pancreas.[28] The findings of this study contrasted with those of an earlier UK study, whereby only one third gave uncoated preparations.[10] There has been considerable debate about efficacy of such products, with earlier work suggesting that dogs given uncoated enzymes had a better response to therapy,[10] but more recent work has not shown such a difference.[28] In light of this, a recent blinded randomized controlled trial (RCT) was conducted by the author and colleagues, comparing efficacy of an enzyme supplement with and without an enteric coating. Although signs of diarrhea, flatulence, and appetite change were not noticeably different, use of an enteric coating improved weight gain compared with the uncoated product (unpublished observations of the author). This suggests that, despite the initial work, the use of products with an enteric coating may convey a treatment advantage for canine EPI. Of course, different enteric-coated products may vary in efficacy, such that these findings are not necessarily applicable to other preparations. Further, the improved efficacy could be overcome by using a higher dose of uncoated enzyme, although this could lead to a delayed response and increase the cost of long-term therapy, and both factors can be reasons for euthanasia of dogs with EPI (see below).

Dietary Modification

The historical approach for dietary manipulation in canine EPI is to switch to a fat-restricted diet on the basis that fat digestion is dependent on pancreatic lipase, and normal digestion cannot be achieved even with enzyme replacement therapy.[29-31] Further, in an experimental model of EPI, such a strategy can improve fat assimilation.[32] It is also suggested to improve resolution of clinical signs, thereby improving patient demeanor.[30] However, such a strategy suffers from the problem that, on such a calorie-restricted ration, it may be difficult

to achieve optimal weight gain. Instead, feeding a fat-supplemented diet, in combination with enzyme replacement therapy, optimizes fat absorption in an experimental model of canine EPI,[33] and feeding a 19% fat diet (on a dry matter basis) improves weight gain and fecal quality in dogs.[34] Such a strategy is similar to recommendations for human patients with EPI (caused by chronic pancreatitis), in whom fat-supplemented diets are fed to maximize weight gain, whereas low-fat diets are used to control clinical signs only as a last resort.[35,36] Prospective studies, including dietary crossover trials, have been conducted assessing efficacy of dietary intervention in dogs.[37,38] Although using small numbers and short-term duration of the intervention, these have not demonstrated a clear benefit of any specific diet; in fact, different dietary strategies (low fat, normal fat and high fiber, low residue) appeared to suit different dogs, suggesting that, in clinical practice, empirical alterations based on individual response is most sensible. Further work has examined the effect of different triglycerides (TGs) on serum lipid variables and subjective well-being.[39] Although medium-chain TGs increased the serum concentrations of cholesterol and some fat-soluble vitamins, compared with long-chain TGs, there was no difference in well-being.

For long-term outcome, objective results (e.g., findings of RCTs) regarding efficacy of different dietary strategies is not available. However, one epidemiological study on treatment habits of veterinarians for canine EPI demonstrated that, although the use of both fat-supplemented and fat-restricted diets was commonplace, there was no difference in response to therapy when patient outcomes were compared.[28]

A further consideration is the incorporation of dietary fiber in the chosen. Although one short-term feeding study suggested that the clinical signs of some dogs with EPI improved best when feeding a high-fiber diet,[38] the effects of such a strategy have not been assessed long term. In the author's opinion, caution should be exercised when using diets with an increased dietary fiber content for management of dogs with EPI. This is because, although there is a (limited) capacity for digestion of fermentable fiber by large intestinal bacteria, it does not dramatically contribute to dietary energy content. In fact, dietary fiber can decrease nutrient assimilation in dogs,[40] thereby adversely affecting digestibility of other macronutrients, and this could be counterproductive for a cachectic EPI patient. A further issue regarding high-fiber diets is that it can confuse clinicians who are attempting to chose a low-fat diet by examining nutrient composition, expressed either on a "dry matter" or "as fed" basis. Given the limited contribution to diet, when macronutrient composition is more appropriately considered on an "energy" basis (e.g., per 1000 kcal), a diet that is fiber supplemented and apparently fat restricted turns out to have a normal or even high fat content.

Cobalamin Supplementation

Hypocobalaminemia is especially common in dogs with EPI and, in one recent study, was identified in > 80% of cases, with approximately one third having markedly reduced concentrations.[28] Despite this, one study revealed that only a minority (< 5%) of dogs with EPI and concurrent hypocobalaminemia received supplementation. This is especially concerning in light of the discovery that severe hypocobalaminemia (< 100 ng/L) is a negative prognostic indicator in canine EPI,[28] whereby it negatively impacts long-term survival.

Therefore, parenteral supplementation should be considered in all cases presenting with hypocobalaminemia.[41] The subcutaneous route is recommended because oral supplementation is unlikely to correct a deficiency in dogs with EPI. Furthermore, serum cobalamin should continue to be monitored in case supplementation is required in the future. There is some suggestion that circulating cobalamin concentrations can decline even in the face of otherwise effective therapy for EPI in dogs (David Williams, personal communication, April 2012).

Antibacterials

The use of antimicrobials is a common adjunctive strategy in dogs with EPI, and a recent UK study indicated that 44% of cases were given such therapy.[28] Agents most commonly used include oxytetracycline and metronidazole, with other agents such as amoxicillin-clavulanate, fluoroquinolones, trimethoprim/sulfonamide, and tylosin being used occasionally. Although there have been no objective studies, tylosin may be used more frequently in other countries where it is more readily available. The main justification for their use is the fact that secondary small intestinal bacterial overgrowth is thought to be common in dogs with EPI, possibly resulting from loss of bacteriostatic factors normally present in pancreatic juice and a greater availability of undigested substrate for bacterial growth.[42,43] However, although some studies have shown that the use of antibacterials may improve response,[44] others suggest pancreatic enzyme replacement therapy alone can reduce bacterial numbers in the small intestine.[43,44] In a recent study that examined outcomes in canine EPI patients, increased serum folate (possibly a marker of either qualitative or quantitative alterations in bacterial flora) was associated with a poor response to initial therapy, although long-term outcome was not affected.[28] Further, neither response to initial therapy nor survival were influenced by the use of antibacterials in this study. Nonetheless, again, more objective studies should be considered before firm conclusions can be made.

Histamine$_2$-receptor Antagonists

Another strategy frequently suggested for adjunctive management of canine EPI is the use of histamine$_2$-receptor (H_2-receptor) antagonists in order to block gastric acid secretion, thereby minimizing acid hydrolysis of pancreatic enzyme supplements and improving efficacy. However, experimental studies in dogs have suggested that this group of drugs is largely ineffective in raising gastric pH after administration, thereby questioning efficacy. Further, use of acid-blocking drugs would arguably only be beneficial when used in conjunction with either uncoated enzyme products or raw pancreas. Not surprisingly, therefore, many have questioned their necessity, instead suggesting that a simple increase in enzyme dose is a simpler and more cost-effective alternative.[1] Perhaps because of these concerns, H_2-receptor antagonists are uncommonly used (e.g., in < 10% of cases) in clinical cases, and there is no evidence for a beneficial effect of such medication.[28]

Other Therapy

Primary care veterinarians also use a range of other medications, on an ad hoc basis, in cases of canine EPI. Such drugs include glucocorticoids, probiotics, and antidiarrheal drugs. Glucocorticoids are often justified on the basis that concurrent chronic enteropathy may be present in some cases. However, such therapies are used too infrequently to enable accurate comments regarding efficacy to be made.

Therapeutic Efficacy and Outcome in Dogs with EPI

Therapeutic options are well described for EPI, but the optimal treatment regimen is not yet known and may vary among individuals, and reasons for treatment failure are incompletely understood. This variability makes it difficult for the clinician to offer owners, with the necessity for lifelong, expensive treatment for their pet, accurate guidance on likely prognosis. Several studies have examined response to therapy in canine EPI.[10,28,41,45]

Response to Therapy

Although appetite and body condition improve in most dogs, clinical signs persist in many treated dogs.[28] Despite notable

weight gain, approximately one fourth of dogs remain underweight, whereas other clinical signs (most notably diarrhea) can remain a problem in just over 10% of cases. Diarrhea, vomiting, and polyphagia also persist in some cases. This suggests that current therapeutic strategies, or the way in which they are implemented, remain suboptimal for treatment of this condition. What follows, therefore, is a summary of recent information regarding outcomes of dogs with canine EPI, with the hope that an understanding of the negative prognostic indicators may help to improve the approach of primary care veterinarians.

Response to Initial Treatment in EPI. As alluded to above, not all dogs respond optimally to therapy. In a recent study, primary care veterinarians were asked to score subjectively the response of EPI cases to therapy.[28] A good response to initial therapy (RIT, e.g., within the first 2 to 3 months) was seen in approximately 60% of dogs given enzyme supplementation, whereas the remaining dogs showed either a partial (17%) or poor (23%) response. These findings appear to be typical because they mirrored the findings of an earlier study on EPI therapy.[10] When factors determining RIT are assessed, no strong predictors were seen, including signalment factors, presence of abnormal folate or cobalamin concentration, and the use of particular therapies.

Although one retrospective study suggested improved outcome in dogs with the use of uncoated enzyme supplements,[10] a more recent study suggested no effect.[28] As mentioned above, both studies have been superseded by a recent prospective RCT, whereby an enteric-coated enzyme formulation led to greater improvement in body weight and body condition, in the first 2 months of therapy (A. J. German, unpublished data).

This suggests that the variability in initial response may be related to factors outside the influence of the veterinarian. For instance, it may relate to failure of the owner to come to terms with the presence of a lifelong illness, cost concerns with therapy, or other unmeasured factors. In the absence of any more specific information, the author's recommendation would be to prioritize good owner counseling at this stage, and advise regular reassessments to enable treatment changes and pre-empt owner concerns. Involvement with an online support group staffed by owners or other affected dogs may also prove helpful.

Long-term Response

Although overall median survival time for treated dogs, reported in one study, was approximately 5 years,[28] this figure masks important differences among different groups of dog. Interestingly, in this study, the 2-year survival rate of 57% suggests that those surviving an initial period of therapy tend to go on to survive for a prolonged period. This supposition is confirmed by the fact that dogs with a good RIT (in the first 2 to 3 months of therapy), on average, survived almost 8 times as long as those with a poor initial RIT.

The only prognostic factor of significance was the presence of severe hypocobalaminemia (< 100/ng/L), with such dogs, on average, surviving approximately half as long as those with serum cobalamin ≥ 100 ng/L.[28] As with RIT, a number of factors appear to have limited effect on survival, including signalment, the nature of clinical signs present at diagnosis, and the use of various therapeutic interventions such as diet, and use of antibacterials and H_2-antagonists.[28] Although one retrospective study suggested improved outcome in dogs with the use of uncoated enzyme supplements,[9] a more recent study suggested no effect.[28] Interestingly, both studies have been superseded by a recent prospective RCT, whereby an enteric-coated enzyme formulation led to greater improvement in body weight and body condition, in the first 2 months of therapy (A. J. German, unpublished data). This may reflect that type of enzyme supplement, dietary modification (to any different type), use of a fat-restricted diet, treatment with antibiotics, and treatment with H_2-receptor antagonists did not have a significant effect on survival. Although the most recent objective data might suggest that the use of enteric-coated enzyme formulations convey a short-term advantage, it is unclear as to whether such an advantage is maintained long term. In this regard, retrospective data are conflicting, and longer studies are required.

Conclusion

Based on current evidence, the current recommendations for management of canine EPI would include the use of enteric-coated pancreatic enzyme supplementation (or a greater dose of uncoated product), a highly digestible diet (that need not be fat restricted), and parenteral cobalamin supplementation.[46] In the author's experience, although diet and enzyme replacement are rarely neglected, cobalamin supplementation often is, even in the face of demonstrable hypocobalaminemia. Because supplementation of B vitamins is inexpensive and safe, it should never be neglected as part of therapy.

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